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

FDA PUBLIC HEARING

WEDNESDAY, JUNE 29, 2011

8:00 a.m. to 3:15 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

Silver Spring, Maryland

MEETING ROSTER

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C O N T E N T S

P R O C E E D I N G S

(8:00 a.m.)

Opening Remarks by Presiding Officer

DR. MIDTHUN: Good morning and welcome to this, the second day of the Avastin hearing. There will be a few changes to the schedule today that I will note as we proceed throughout the day. But now we will proceed to the portion of the hearing where Genentech will make its presentation, and they have two hours allocated for that. Thank you.

Affirmative Presentation by Genentech

DR. BARRON: Good morning. Thank you, Dr. Midthun, committee members, FDA representatives and guests. My name is Hal Barron. I'm the executive vice president of global product development and the chief medical officer for Genentech Roche. I want to thank Dr. Hamburg for granting us this hearing today.

Yesterday we heard moving testimonies from the public as well as comments from CDER on their interpretation of the studies evaluating Avastin in patients with metastatic breast cancer. As we

begin our presentation, I want to be clear about why we requested the hearing.

We are here today for one purpose, to explain why we believe that women with metastatic breast cancer are better off if Avastin, in combination with paclitaxel, remains an approved treatment option. We recognize the complexity of this situation and respect that both parties have come to divergent conclusions on this important issue.

It's important to highlight that CDER and Genentech agree on two fundamental principles: First, that the magnitude of improvement in progression-free survival observed in E2100 represents clinical benefit. This reflects CDER's progressive thinking that PFS of a certain magnitude represents benefit in and of itself. CDER's position on PFS will likely result in more clinical trials and more timely access of new medicines for patients with metastatic breast cancer. We are not here to debate that issue.

We also agree with CDER that the accelerated

approval process must be preserved, particularly CDER's authority to quickly withdraw products which are identified to have new safety concerns or products which fall to confirm any benefit in subsequent studies, or when sponsors fail to conduct the agreed upon confirmatory trials in a timely manner.

However, we disagree on four key points which each of our speakers will address in detail today. The first point is that Avastin's safety profile has been broadly misunderstood based on how CDER has presented the data. Avastin has an acceptable risk profile for the indication for which it is approved.

Second, E2100 was a well-conducted clinical trial with robust results that are clearly clinically meaningful.

Third, the AVADO and RIBBON 1 studies met their prespecified primary endpoint with hazard ratios less than 0.7, and as such do not invalidate the findings of E2100.

Fourth, the regulations around accelerated

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

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

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

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

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

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

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

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

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

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

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

The conclusion drawn by CDER that the

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

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

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

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

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

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

development.

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

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

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

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

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

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

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

When it comes to which agents, prior use of

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

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

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

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

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

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

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

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

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

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

explore with you.

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

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

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

confusion, and I therefore would like to walk you through the analysis in detail.

As we know, attributing deaths to a specific cause is always difficult and subjective, whether by investigator or CDER. However, CDER's assessment was concerning because there were imbalances in the sources of information for the two treatment groups. Per ECOG and NCI standards, only events for the paclitaxel plus Avastin arms were to be entered in NCI AdEERS, the Adverse Event Expedited Reporting System database. That is, events occurring in the paclitaxel-alone arm were not collected because the safety profile of this agent was considered well known.

CDER conducted their post hoc assessment by using AdEERS as a source. Their analysis comparing the two treatment arms is based, at least in part, on information collected for just one treatment arm and taking this approach likely introduces bias. And this potential bias becomes apparent when looking at treatment-related deaths across all the studies. Note that for the AVADO and the two

RIBBON 1 cohorts, the chemotherapy arms had treatment-related deaths on par with the chemotherapy, and yet the analysis for the paclitaxel-alone arm in E2100 stands apart.

Nevertheless, we agreed to and have used CDER's E2100 analysis in our product label and in our pooled incidence figures. Despite this, the rates for treatment-related deaths across the MBC experience, 1.8 percent and 1.8 percent, are identical with standard dose Avastin.

Now, although these data seem straightforward, CDER's July 2010 ODAC presentation and the subsequent press reports have led to confusion about treatment-related mortality. For example, this is an excerpt from ODAC's discussion, and I quote. "I still do not get a clear picture. Looking at the FDA presentation, there was almost about 1 to 1 and a half percent increase in treatment-related mortality which was maybe related to Avastin with the different chemotherapy arms, whereas in your data, I did not see that. I mean, disease control versus 1 percent or 1 and a half

percent chance of dying from the complication from their therapy, therapeutic index becomes somewhat different."

This interpretation went beyond the ODAC as revealed in this excerpt from the National Cancer Institute bulletin reporting on the July 2010 meeting. Speaking of AVADO and RIBBON 1, "In both trials, women in the bevacizumab groups had an increased risk of death. In an analysis of the data prepared by FDA, 0.8 percent of the women in AVADO and 1.2 percent of the women in RIBBON 1 who received bevacizumab died from side effects thought to be related to the drug."

Where did this misunderstanding come from? CDER defined a subset of treatment-related deaths as Avastin-related according to specific AE terms which have been associated with Avastin, such as arterial thromboembolism or congestive heart failure. However, and this is a key point, the terms were applied only to the Avastin arms, even though these same adverse events also occurred with chemotherapy alone. In this way, CDER's

classification of Avastin-related deaths was imbalanced because it was applied to the Avastin arms only. It was not applied to the chemotherapy arms even though deaths occurred due to these AEs such as arterial and venous thromboembolism.

Further, CDER emphasized Avastin-related deaths over treatment-related deaths in their communication to ODAC and the public. This characterization led to a misunderstanding that there was a higher treatment-related death rate in the first-line MBC studies.

When we look at treatment-related deaths due to these select AEs, we note the familiar Avastin-related death rate of 0.8 to 1.2 percent in the AVADO and RIBBON 1 studies that have been repeatedly highlighted and publicized. However, and please take note, if these same AE terms are applied equally to the chemotherapy arms, a similar incidence of so-called Avastin-related deaths is observed across the AVADO and RIBBON 1 studies.

In summary, if you remember one slide about deaths, let it be this one. There were fewer total

deaths, fewer MBC deaths, and a similar rate of non-breast cancer deaths in the E2100 study and also in the pooled safety analysis for standard dose Avastin plus chemotherapy. These are the facts regarding deaths in the MBC safety population.

We'll now move to adverse events. The tables shows grade 3 to 5 select adverse events, which were collected evenly across all the MBC studies in the pooled analysis of standard dose Avastin. Among the select adverse events, there was a 13.3 percent increase with Avastin plus chemotherapy compared to chemotherapy alone. Hypertension and proteinuria account for much of the increase such that excluding these two more common AEs, when they were the only cause of grade 3 or higher event, results in an overall incidence of 5.6 percent for other AEs.

Hypertension and proteinuria, which are related to Avastin's mechanism of action, VEGF inhibition, are well described, and guidelines for monitoring and management are available in the

package insert.

To refresh your memory, the grading systems for hypertension and proteinuria are described. Note the E2100 study used an older version of toxicity grading such that any treatment for hypertension is considered grade 3, whereas in the other studies, grade 3 was scored for the use of more than one drug. Grade 4 hypertension indicates life-threatening consequences. Grade 3 proteinuria is based on a laboratory measurement of the urine whereas grade 4 proteinuria is a clinical problem known as the nephrotic syndrome. I will speak to each of these adverse events in turn.

Hypertension is very common in our society. More than 50 million Americans have hypertension warranting treatment, nearly 1 in 3 over the age of 18. Half of our population over age 60 is hypertensive. Two-thirds require more than one drug to manage. That would be similar to the definition of grade 3 used in the AVADO and RIBBON 1 studies as described on the previous slide. Guidelines for treatment are well

established, and doctors are knowledgeable.

Hypertension is a common side effect of Avastin exposure. Monitoring and management are indicated and provided in the package insert. Reversibility is expected, although the subject has been incompletely studied. It has been primarily confirmed by the experience of clinicians. Because the use of Avastin and other VEGF pathway inhibitors is widespread, a National Cancer Institute task force has recently provided management guidelines.

The NCI angiogenesis task force published their recommendations in 2010. I'd like to call your attention to three features of this article. First, the authors point out that the goals and approach to blood pressure management in metastatic cancer patients is different compared to a typical hypertensive population due to their reduced life expectancy. Second, hypertension is considered reversible such that discontinuation or dose reduction can be used as a means of control. Third, because blood pressure elevation is a

reversible mechanism-based effect, physicians are advised to anticipate the need to discontinue or reduce anti-hypertensives when treatment ends.

What has been the experience with hypertension in MBC? There were no deaths due to hypertension. Grade 4 toxicity was 0.4 percent; that is, five patients in the total experience of 1,427. In addition, treatment discontinuation due to hypertension was low at 1.7 percent.

Now, let’s move to proteinuria. In addition, VEGF leads to changes in the kidney architecture akin to this artistic rendition that result in leakage of the protein albumin in the urine. At the microscopic level, these changes are similar to those seen in the preeclampsia of pregnancy, a VEGF inhibition-related disorder that resolves with delivery of the placenta.

In clinical experience, proteinuria typically resolves with Avastin discontinuation, which is in the management guidelines, and proteinuria has not been associated with an increase in creatinine. Preclinical and clinical

evidence indicates that massive proteinuria occurs in people with preexisting kidney disease, such as after nephrectomy where repair and resolution may take longer. These facts strongly suggest that data from renal cell cancer, which is in our product label and has been called out by CDER in the summary argument, may be a special case.

In the MBC experience, there were no deaths due to proteinuria in any of the studies. Grade 4 toxicity, the clinical nephrotic syndrome, occurred in 0.4 percent or five of the 1,427 patients. The proportion who discontinued treatment due to proteinuria was low at 1.1 percent. We have not observed an association between proteinuria and reduction in glomerular filtration as determined by serum creatinine in any of the MBC studies.

Now, next I will present a series of three slides on the time course of proteinuria from the adjuvant colorectal cancer study, CO8, conducted by the NSABP and supported by Genentech. This large 2700-patient study provides a prospective evaluation of proteinuria as part of our

postmarketing commitment for Avastin and was highlighted in CDER's summary argument.

This slide shows the incidence of proteinuria at any time during the study for chemotherapy or chemotherapy-plus Avastin. The data are displayed by any grade and specific grade. As expected, more proteinuria was seen with Avastin, mainly grade 1, but 2.6 percent had grade 3 or 4 proteinuria. One of the 1,338 patients on the Avastin arm had the clinical nephrotic syndrome. We were somewhat surprised by the incidence of grade 1 proteinuria in the chemotherapy arm.

I'm now highlighting the 463 control patients and the 728 Avastin patients to discuss the status of their proteinuria at the last study visit on the next slide.

The data on this slide illustrate two major findings. First, you see that proteinuria has resolved to grade 1 or zero in more than 96 percent of patients in either treatment arm. Second, you see that grade 2 to 4 proteinuria, which, if not

resolved, could lead to renal impairment in a proportion of patients over a period of years, is very similar in both arms. In sum, 32 of 2700 patients in the CO8 trial had grade 2 to 4 proteinuria at last study visit, and the actual number of affected patients, 16 and 16, is identical for the chemotherapy and the chemotherapy plus Avastin arms.

Just a few weeks ago at the ASCO annual meeting, the CO8 investigators presented their data on the incidence of grade 3 to 4 hypertension and proteinuria between three and nine months after one year of Avastin treatment. These data are from their public presentation. The incidence of hypertension and proteinuria during the study were consistent with the product label.

Please note the investigators' report that essentially no differences were observed between the treatment arms for either grade 3 and higher hypertension or proteinuria within 12 months of the completion of Avastin. Together, the large body of evidence from the CO8 trials confirms the

experience of physicians and from several of the patients we heard from yesterday that clinically significant hypertension and proteinuria, VEGF-related side effects of Avastin, are largely reversible upon treatment discontinuation.

Returning to MBC, this is a summary of the select adverse events with standard dose Avastin in the pooled analysis. The total is increased from 23.1 to 36.4 percent. The 13.3 percent increase is mainly 7.7 percent due to hypertension and proteinuria exclusively. Key to note is that 75 percent of the serious AEs are grade 3.

Among the 5.6 percent increase due to other causes, the absolute increases for bleeding, congestive heart failure, and arterial thromboembolism range from 1.2 to 1.6 percent. The incidence of other select AEs is less than 1 percent in both treatment arms.

Yesterday from CDER, we heard an anecdote of fatal GI perforation occurring in the Avastin arm of the AVADO study. Notably, the rate of grade 3 to 5 perforation was actually 0.5 percent higher in

the placebo arm of this study. If we look at the pooled analysis, GI perforations occurred in 0.3 percent on the chemotherapy arms and 0.5 percent on the chemotherapy plus Avastin arms. The incidence of venous thromboembolism was higher on the chemotherapy arms in the MBC experience.

How does this safety profile compare to available treatments for MBC? Multiple serious toxicities are well established for single agent chemotherapies used in first-line MBC. These include kidney, liver, cardiac, respiratory and other toxicities. And when used in combination as for the approved use of gemcitabine plus paclitaxel, there's an increase in adverse events due to both additional and especially overlapping toxicity such as grade 3 and higher increases in neutropenia at 35.4 percent as well as thrombocytopenia, dyspnea, anemia and transaminitis.

In summary, Avastin has been shown to have acceptable risks for the indication for which it was approved. There were fewer total deaths on the

Avastin arms and fewer MBC deaths on the Avastin arms. The non-breast cancer deaths and treatment-related deaths are similar. With regard to grade 3 and higher AEs, these were primarily grade 3 with 7.7 percent increase exclusive to hypertension and proteinuria with reversibility anticipated. A 5.6 percent increase in grade 3 or higher other events was seen.

Avastin has serious side effects, as described in the product label, but it is not more or uniquely toxic compared to other MBC treatments.

Let's turn to efficacy. The next series of slides will establish that Avastin plus paclitaxel is effective in first-line MBC. Importantly, the E2100 study is not invalidated by the results of AVADO and RIBBON 1.

We have three areas of scientific disagreement with CDER regarding efficacy. First, we find that E2100 study to be well-conducted with robust results. Second, AVADO and RIBBON 1 are both positive studies. They do not invalidate the E2100 study, and external experts endorse this

position. Third, the chemotherapy partner may contribute to the greater magnitude of effect observed with weekly paclitaxel and Avastin in E2100, and this can be studied in a confirmatory trial.

E2100 is a randomized, controlled Phase 3 trial that enrolled over 700 patients predominantly from the United States. As such, the study reflects the demographics, comorbidities and standards of practice associated with MBC in this country. E2100 was sponsored by the National Cancer Institute and led by the Eastern Cooperative Oncology Group, one of the largest and most experienced cancer research organizations in the United States. The results of E2100 have been subjected to multiple sensitivity analyses and independent review by CDER.

E2100 was one of many cooperative group studies that have met FDA standard for regulatory approval from 1990 to 2008. These studies have influenced the standard of care in multiple tumor types in this country.

Funded by the U.S. government, E2100 has had a global influence. Avastin plus paclitaxel was first approved in Europe in 2007. Currently, this combination is available to women with first-line metastatic breast cancer in 84 countries around the world.

Now, let's look at the E2100 study design. As this diagram shows, MBC patients were eligible if they had not received prior treatment with chemotherapy in the metastatic setting. The study was large, 722 patients were randomly assigned to treatment with paclitaxel 90 milligrams per meter squared weekly times three in four-week cycles alone or combined with Avastin at the standard dose. Therapy was continued until disease progression. The primary endpoint was progression-free survival.

The E2100 study had 85 percent power to detect a 33 percent increase in PFS from the projected six months to eight months with 685 patients and 546 events.

Shown here are the primary study results

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

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

Overall survival is depicted on this slide.

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

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

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

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

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

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

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

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

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

Reviewing the same data as CDER, the European Commission came to the opposite conclusion. They retained approval for Avastin plus paclitaxel in February 2011. This ruling followed the advice of the Committee for Medicine Products for Human Use, CHMP, which made these statements in December 2010. "The available data have convincingly shown bevacizumab to prolong progression-free survival of breast cancer patients without a negative effect on the overall survival." And, "The benefits of Avastin with paclitaxel outweigh its risks, and the combination remains a valuable treatment option."

The CHMP did not consider the AVADO and RIBBON 1 studies to invalidate E2100. Rather, they stated, "Avastin has been convincingly shown to prolong PFS without a negative effect on OS, and the new study data support this conclusion."

Another influential scientific body determined that the E2100 results were not invalidated by AVADO and RIBBON 1. The National Comprehensive Cancer Network, NCCN, unanimously

affirmed Avastin plus paclitaxel for first-line MBC in October 2010. As can be seen on the list on the right, NCCN represents the nation's top cancer centers for treatment and research. The NCCN guidelines, which are highly influential in the practice of oncology, are updated by an evidence-based process that involves explicit review of scientific evidence by expert physicians.

The NCCN breast cancer panel members specialize in breast cancer. They have their primary, if not exclusive, practice in breast cancer, and they are active breast cancer researchers and educators. Twenty-seven panel members participated in the Version 2.2011 recommendation.

The NCCN panel reviewed the same studies as CDER, meeting in person or by phone on three occasions to discuss Avastin plus paclitaxel in MBC in the five months leading to FDA's withdrawal proposal. This resulted in a unanimous decision to affirm a recommendation for Avastin with paclitaxel as a preferred partner.

Now let's turn to the data across the first line MBC studies. Here are the forest plots for the E2100 AVADO and RIBBON 1 studies, showing a consistent PFS improvement with Avastin. Each was a positive study that exceeded its primary PFS endpoint with target hazard ratios of .7 to .75 in favor of Avastin and had been agreed upon as supplemental biologic license applications to support conversion. If you look at the hazard ratios for AVADO and RIBBON 1, you note that they bracket the .65 hazard ratio for gemcitabine plus paclitaxel, which is fully approved in first line MBC.

As we stated in July 2010, the hazard ratios in these studies are not statistically different. The medians, which may not reliably reflect treatment effect, look far more different from one another. The hazard ratios in these studies ranged from 0.48 to 0.69. This could be due to chance or could reflect a difference in chemotherapy partner or exposure in combination with Avastin.

If we now understand that the measure of

magnitude is median PFS and that the E2100 result must be replicated, then it is important to maintain the treatment conditions exactly as feasible and incorporate paclitaxel as the chemotherapy partner.

The next series of slides relates to statements and actions related to chemotherapy partner for Avastin and the available scientific data on the subject. Both the European and NCCN decisions indicate that chemotherapy matters, as illustrated in this table. The importance of chemotherapy partner is highlighted by the different actions taken in Europe with regard to the taxanes, reaffirming paclitaxel but choosing to withdraw docetaxel upon further review based on clinical study data. The EMA also issued a positive opinion for full approval for capecitabine with its hazard ratio of 0.69 and median PFS of 2.9 months based on the RIBBON 1 data.

CDER has previously expressed the view that treatment results may vary by chemotherapy in several communications to Genentech. At the 2006

Type B meeting, FDA recommended that Genentech consider separate studies with the individual chemotherapy agents in the Avastin MBC study because their treatment affect will vary according to the chemotherapy regimen used. Of course, the Avastin indication for MBC was limited to paclitaxel as the sole chemotherapy partner.

In the laboratory, multiple models show an enhanced anti-tumor effect with Avastin combined with chemotherapy. In these models, the taxanes have equal or greater efficacy than other chemotherapy agents. A consistent finding has been that longer exposure of Avastin plus chemotherapy increases efficacy. In the clinic, many practitioners favor weekly paclitaxel because it is well tolerated. In addition, greater efficacy has been seen in some Phase 3 studies comparing weekly to intermittent schedules of paclitaxel in early and metastatic breast cancer. In contrast, docetaxel duration is limited by toxicity.

In a recent meta-analysis, longer duration of chemotherapy led to greater efficacy. Most

pertinent to today's discussion, in the Avastin MBC trials, greater efficacy was observed with paclitaxel in the E2100 study.

Is it biologically plausible that paclitaxel is a preferred partner for Avastin? Let me go through some of the data from our MBC trials demonstrating greater exposure for paclitaxel compared with docetaxel.

We observed a longer treatment duration with paclitaxel, the white dotted line, compared to docetaxel in the AVADO, golden line, and RIBBON 1, blue dotted line, studies, 8.4 versus 5.5 and 4.7 months. The proportion of patients on treatment at 12 months was 30 percent for paclitaxel versus zero percent and 8.5 percent. These observations are admittedly difficult to separate from treatment effect.

However, we also find that there was less discontinuation due to toxicity prior to disease progression with paclitaxel compared to docetaxel in RIBBON 1 at 27 weeks or longer, 27 percent versus 59 percent. Paclitaxel was associated with

greater dose intensity prior to disease progression compared to docetaxel in the two studies.

Weekly paclitaxel provides more frequent exposure, and this has been linked to greater antiangiogenic activity in the preclinical setting. Together, these data are consistent with less overlapping toxicity and greater tolerability of paclitaxel in the clinic. The clinical data suggest that weekly paclitaxel plus Avastin is more effective because combined exposure is greater, and this can be confirmed with an additional study.

Placing the efficacy data together, we find that E2100 is a well-conducted trial with robust results that are not invalidated by AVADO and RIBBON 1. Accelerated approval was granted with the definitive AVADO PFS data. Europe and NCCN reaffirmed the paclitaxel results, and AVADO and RIBBON 1 are positive studies. Multiple lines of evidence indicate that chemotherapy exposure partner may matter.

Now let’s go back to the clinic. For the assessment of benefit risk in this indication, I

present the pooled safety, representing the totality of the MBC experience and the E2100 efficacy data in a way that would allow physicians, patients, and health authorities to assess and contrast each element in clinical decision-making.

With regard to deaths, there were fewer overall MBC deaths with Avastin, and treatment-related mortality is equal in the pooled analysis. There's a 13.3 percent increase in select grade 3 or higher AEs, 7.7 percent exclusively due to hypertension and proteinuria, and 5.6 percent due to other causes in the pooled safety analysis.

The efficacy data for E2100 are listed on the right. For survival, there's a 7.4 percent increase at one year and 4.9 percent increase at two years. For PFS, there's a 24.5 percent increase at six months and a 20.6 percent increase at 12 months. A 28 percent increase, more than a doubling, was observed in response rate.

These data demonstrate a favorable benefit risk for paclitaxel plus Avastin. But we also seek to do better by defining a biomarker for patients

who may achieve greater benefit. Dr. Reimann will discuss this further in his talk, but I will introduce the subject.

Angiogenesis in tumors involves a complex interaction between tumor, stroma, and many pro and antiangiogenic factors as captured by this figure. This complexity creates considerable challenges for biomarker discovery.

Since 2002, Genentech and Roche evaluated more than 100 potential markers in clinical specimens of plasma, tumor, and host DNA across seven tumor types. Data from more than 10 phase 3 trials with adequate sample collections began to read out in 2010 and will continue through 2012. Naturally, VEGF pathway markers have been a major focus in this work based on the mechanism of action of Avastin.

This slide summarizes the current status of our biomarker research, focused on predicting which patients will benefit from Avastin and which patients may be at greater risk for adverse events. Our narrowed candidate list is displayed according

to the type of tissue assayed. Based upon extensive work to date, the key candidates are highlighted in yellow.

For breast cancer, based on data from the AVADO trial and other tumor types, the leading predictive biomarker candidate is VEGF-A, the target of Avastin, and Dr. Reimann will detail the methods and analyses leading to this selection.

In closing, based upon acceptable safety risks and demonstrated efficacy, we interpret the benefit risk for Avastin plus paclitaxel in MBC to be favorable, and expert scientific bodies agree with this interpretation. In the context of an incurable disease and the available treatments, which we believe constitute an unmet need, and certainly this is what we heard from the testimonies yesterday, it is best for patients to continue to have this treatment option.

This is the argument for maintaining accelerated approval while a new confirmatory trial, one that replicates E2100 with the paclitaxel partner and includes a biomarker

hypothesis to better define clinical benefit, is conducted.

I thank you for your attention and invite Dr. Reimann to the podium.

DR. REIMANN: Good morning. I'm James Reimann, global head of oncology biostatistics at Genentech Roche. Today I'll be addressing two topics, the robustness of the E2100 PFS results and the design of the proposed confirmatory study of Avastin combined with paclitaxel.

We start with robustness of E2100 PFS results by which I mean that the E2100 results were not unduly affected by designs -- concerns about study conduct or analysis methods. At the ODAC in 2007 and again more recently, CDER has raised several concerns about E2100 related to the open label design, missing data, variability in tumor assessment, and a more recent question about whether the E2100 data could represent a random high.

I will walk you through our careful assessment of these concerns which show that they

are not unusual in breast cancer studies and that there was no evidence of bias.

Second, I will review the design and timelines of the proposed confirmatory study of Avastin in combination with paclitaxel.

First, robustness. We have carefully assessed the E2100 PFS data with regard to the four concerns shown on the left. I'll address each of these concerns with two critical questions in mind. The first question is whether the concern is out of line with well-accepted breast cancer studies. I will do this by considering the phase 3 studies of various medicines for breast cancer. The second question, at the right, is whether this concern led to any evidence of bias.

To start with point 1, let's look at the open label nature of E2100. In contrast to many other disease areas, open label studies are common in oncology. In fact, 78 percent of ongoing phase 3 studies in metastatic breast cancer found on clinicaltrials.gov are open label. As a result, open label studies have commonly served as the

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

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

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

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

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

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

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

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

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

Importantly, the rate of missing data in

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

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

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

by treatment arm. This was included in the progression-free survival definition in the study analysis plan that was reviewed and agreed to CDER prior to the primary study analysis.

We saw that the amount of missing data in the independent review in E2100 was comparable to an approved breast cancer medication and balanced by study arm.

Point 3, variability in scan interpretation. First, let me explain how independent review was performed in E2100 using what is called a two-reader format. Six hundred and forty-nine patients had scans for independent review, and two radiologists, which I'll call Reader 1 and Reader 2, assessed these scans in accordance with the RECIST criteria and came up with their conclusions. The IRF checked whether these two readers agreed on progression status and date and objective response status and date. In the event of agreement, those results were used for analysis, which occurred in 55 percent of cases. For those not agreed on, a third radiologist reviewed the

data.

I will focus on the cases where there was disagreement in progression status and progression date, which was observed in 34 percent of patients and features in CDER's ODAC briefing books and presentations.

Now, it is difficult to assess whether this amount of disagreement, 34 percent, is expected because this level of detail is not normally disclosed in study manuscripts and has not been publicly disclosed for other breast cancer medications. But one way that we can assess it is by looking at the opinion of the adjudicator.

The third radiologist assessed the reads by the two primary radiologists, and in 98 percent of cases, agreed with one of the primary readers. This means in 98 percent of cases, they decided that both the choice of lesions and the assessments from one of the primary readers were appropriate and should stand as the final read.

CDER was aware back in 2007 that there was not great experience on this issue, as quoted here.

"CDER continues to gain experience regarding the reliability of radiographically-determined disease progression, and at this time does not have sufficient experience to say whether the 34 percent rate of discordance between two radiologists is unusual."

Given the lack of available data, a group of prominent statistical researchers at NIH looked into this further and published their findings in 2010. They assessed possible bias and variability in the hazard ratio by performing a simulation study. What they found was that the amount of bias is extremely small, and, importantly and unexpectedly, this bias favors the control arm, not the experimental arm. They also used the data from E2100 IRF publication in JCO as an example, and they found with the amount of differing assessment in E2100, they would have expected a bias of between .01 and .02 in the estimated hazard ratio in favor of the control arm.

So, in summary, although inter-reader differences at the IRF do have some variability,

this would tend to bias against the novel medicine.

A second issue raised by CDER was differences between the investigator and independent reviews in E2100. Now, these differences are expected because of different choices in lesions and images, use of nonradiographic data, and perceptions about new lesions, which can be small. We now have published examples of expected discrepancy rates in many studies with the results from a number of breast cancer studies shown at the right.

The agreement rates on progression status and date for E2100 were virtually identical to that observed for the pivotal studies of Tykerb and Ixempra. And these pivotal studies used a two-reader independent review very similar to that used in E2100. And both of these studies received full approval based on their progression-free survival results.

In addition, the discrepancy rates in E2100 were identical by study arm. The agreement rates were 76 versus 76 percent and 49 versus 49 percent.

So again we find these differences are expected, and there is no evidence of bias.

Last, we address an issue that CDER raised just last December, that the E2100 results could represent a random high. Reading from CDER's December decision memo, "It is possible that the magnitude of effect observed in E2100, based on the interim analysis, represents a random high and that the true effect is more consistent with a smaller effect seen in the other trials." We examined this issue carefully, and we found no evidence of bias.

There is an extensive literature about bias in estimates arising from interim analyses dating back to early work by Scott Emerson and Tom Fleming in the early '90s. As shown by the following quotes, the impact for a well-designed study that reports results with more than 50 percent of events is very small. "Estimates from a trial stopped early for efficacy have negligible bias. Such estimates on average are therefore correct. For trials with a well-designed interim monitoring plan, stopping at 50 percent or greater information

has a negligible impact on estimation."

We confirmed this in E2100 by calculating adjusted estimates of the hazard ratio using commonly used adjustment methods. We found negligible bias in E2100 in the hazard ratio in the third or fourth decimal place, which would not change any results you see in these slides.

In addition, the estimated PFS hazard ratio in E2100 was very precise because this study had the narrowest confidence interval around the hazard ratio estimate of all of the studies of Avastin and first-line metastatic breast cancer. So it is incorrect to assert that E2100 and the results may have been less accurate due to interim data.

So in summary, we have carefully assessed each of the points raised by CDER during the 2007 ODAC and again more recently. In each case, we find that these points are present in the pivotal studies of breast cancer medications. In fact, all four of these issues were present to a similar degree in the pivotal study of Tykerb, which received full approval based on its progression-

free survival results. More importantly, we found no evidence of bias arising from any of these points.

The concerns raised by CDER were addressed by Genentech in a detailed submission in December 2007, two months before the issuing of the accelerated approval decision. Quotes from CDER in Dr. Pazdur's office director's memo that accompanied this approval are here. "The current application demonstrates a robust effect on PFS and response rate. Prespecified sensitivity analyses corroborate the maintenance of a treatment effect in handling missing data. Recent applications have had missing data similar to that observed in the current Avastin application, and because of the close agreement between the two assessments, investigator, and IRF, systemic bias seems unlikely."

Based on the findings that I've shown you today, we agree with their assessment and stand behind the robustness in substantial magnitude of the E2100 PFS results.

Now we change gears. Given Issue 3 before this hearing, the question remains what a study to confirm the magnitude of benefit of Avastin in combination with paclitaxel would look like. I will review the confirmatory study design and timeline, feedback received from CDER in February of this year, and the data supporting the biomarker component of the study. The study schema is shown here.

This study is intended to confirm the magnitude of benefit in E2100 and closely matches the design of E2100. The study population is 480 patients with HER2-negative metastatic breast cancer who have not received prior chemotherapy. Randomization will be stratified by plasma VEGF-A level, prior adjuvant therapy use, and hormonal receptor status.

The treatment regimens are identical to E2100 with standard weekly paclitaxel and Avastin or placebo continued until progression and with no crossover. The study has two primary endpoints, progression-free survival in all patients and

progression-free survival in patients with high plasma VEGF-A, which I will elaborate further.

The first and most important objective, shown on the left, is to confirm the magnitude of effect seen in E2100 in the overall study population which could lead to full approval in the overall population. The second objective, on the right, is to validate a method of selecting patients with greater clinical benefit on Avastin using plasma VEGF-A. I will first focus on the overall population objective.

For the primary analysis of PFS in all patients, we are targeting 326 PFS events which gives 85 percent and 99 percent power to detect a hazard ratio of .67 or .5. This study will have a smaller number of patients and a smaller number of events than E2100 because we are targeting a greater treatment effect.

We expect that this study will predominantly be enrolled outside the United States. The preliminary feasibility assessment is based on prior studies of Avastin in first-line metastatic

breast cancer, the experience of our global CRO, and a country-specific survey of interest in this study. We intend to start this study as soon as possible and to provide results to FDA as soon as possible.

We believe that this can best be done through an interim analysis of PFS for the purpose of regulatory futility. By regulatory futility, I mean an early analysis of the data to see whether the benefit seen in E2100 is likely to be confirmed. If the futility boundary is crossed, this analysis could trigger an early voluntary withdrawal of the accelerated approval by Genentech.

We propose that this analysis be conducted at 220 PFS events, three and a half years after the start of the study with a final PFS analysis following one year later. A more detailed feasibility assessment is ongoing, and we'll give results very shortly, to determine the best locations for the study and to further refine the enrollment rates and the timeline.

Let me tell you a bit about the regulatory history of the study to better understand the timeline and the FDA feedback we received. So going from left to right, in July 2010, ODAC voted that AVADO and RIBBON 1 were not considered to have confirmed E2100. One month later, Genentech submitted a proposal to CDER for a new confirmatory study of Avastin combined with paclitaxel. CDER granted a Type B meeting to discuss the high level Phase 3 design, which was held in February of this year and to which I will return in a moment.

Coming up, CDER has asked us to meet with CDRH, the Center for Devices and Radiologic Health, to discuss the VEGF-A test prior to starting a special protocol assessment with CDER, abbreviated here at SPA, in the fall. We are planning for the first patient to be enrolled in Q1 next year.

A central question at the Type B meeting was whether the new study would support full approval of Avastin in combination with paclitaxel. The key quotes from the meeting are shown here.

CDER clearly states that repeating the

magnitude of PFS benefit from E2100 combined with no detriment to overall survival would support full approval of Avastin in this setting. So we now have clarity from CDER on a path to full approval. Nevertheless, we have heard from some members of ODAC and some members of the wider oncology community, including yesterday, that new breast cancer medicines need to prolong overall survival.

To respond to your perspective, let's review what overall survival data as seen with available medicines in first-line metastatic breast cancer and what it takes to optimally power studies to detect an overall survival benefit in this setting.

There are only two non-hormonal medicines approved by FDA since 1980 for the first line treatment of HER2-negative or HER2 unspecified metastatic breast cancer, Avastin in 2008 accelerated approval and Gemzar full approval, 2004. Neither of these medicines have demonstrated a statistically significantly improved overall survival.

What about Gemzar, which was cited by CDER

in the 2007 and 2010 ODACs and in their December memos? So let's look at the data.

The pivotal study of Gemzar included 529 patients who received either paclitaxel alone or in combination with Gemzar. This open label study had co-primary endpoints of overall survival and time to progression, with overall survival tested at the .03 level, which means you need to see a p value smaller than .03 to be statistically significant.

This study showed significantly improved time to progression, shown here, and the company approached CDER about a possible submission. CDER allowed the company to perform two unplanned interim survival analyses to support a possible submission. The results of the second interim analyses of survival are shown here.

The p value of .049 did not meet the cutoff of .03 specified in the protocol. And, in fact, CDER found p values of greater than .05 in multiple sensitivity analyses. The conclusion of the CDER reviewers was that this data did not show a significant survival benefit but rather represented

a strong trend. Gemzar did receive full approval based on these data, but CDER did not allow the survival data, the survival numbers, to be included in product labeling.

When the protocol-specified final analysis was performed, as shown here, it was again not significant with a p value of .12, and these results are today included in the product label. This study demonstrates that a 2.3-month improvement in median survival accompanied by a trend in overall survival was considered clinical benefit in this setting.

Put side by side, we see that the E2100 data compare favorably to Gemzar, helping us to understand that the E2100 data also demonstrates a meaningful clinical effect. In the larger E2100 study shown at the right, the magnitude of PFS improvement is greater, both as a hazard ratio and as a difference in medians.

The interim overall survival results that were provided in the initial sBLA of Avastin in breast cancer, shown in the middle row, were very

similar to the interim overall survival results for Gemzar. And the final overall survival results prespecified in each study protocol were very similar with regard to hazard ratio and degree of statistical confidence.

So after benchmarking the E2100 results against the gemcitabine, we are confident that a clinically meaningful benefit will be demonstrated in a confirmatory study.

So talking about overall survival benefits, everybody here, FDA, ODAC, Genentech, patients, we are all working to prolong survival in patients with metastatic breast cancer. Now, this may come from a large and profound effect in a single study with a single agent, or this may come from a combined PFS effect across multiple agents in first-, second- and third-line setting. But it will not come if we do not do the studies, and the studies are too large and too unfeasible. And it is our position that a strict requirement for new medicines to demonstrate significantly improved overall survival would greatly impact feasibility

of studies in this setting. This is because in the first-line setting, it is very difficult to optimally power studies to see overall survival benefit.

Why is this? The key reason is because survival after first line progression is especially long in breast cancer. We know from multiple long-term studies that overall survival has been getting longer in metastatic breast cancer. This is likely due to the combined effects of better diagnosis, new medicines such as the taxanes, and better supportive care.

Importantly, two-thirds or more of a patient's survival time is after their progression on first-line treatment. During this time, patients typically receive multiple subsequent therapies which are not controlled by study protocols and can differ between treatment arms. These therapies add variability, certainly, but also possible bias.

Because of this long survival, a similar absolute benefit in PFS and overall survival

measured in months translates into a much smaller relative benefit in overall survival measured by the hazard ratio. For example, a four-month improvement in median PFS from 6 to 10 months is a 67 percent improvement, while a four-month improvement in median overall survival from 24 to 28 months is a 17 percent improvement.

This dilution of the overall survival hazard ratio compared to the PFS hazard ratio has been noted in several publications; and because studies are powered based on hazard ratios, not based on medians, it means we need much larger clinical studies to optimally power for overall survival benefits in first-line metastatic breast cancer. This means that typical studies in the front-line setting, which are enrolling about 500 to 800 patients, are not optimally powered for overall survival.

This is an important point. Although they may be fully powered for a large overall survival benefit such as eight months, they are underpowered to observe benefits on the order of three to four

months, which may still be clinically meaningful and clinically interesting.

In summary, a strict requirement to demonstrate statistically significant overall survival in first-line metastatic breast cancer would greatly impact feasibility of studies. And CDER has exercised regulatory flexibility on this issue in the past, approving agents in the refractory setting based on progression-free survival. And in the first-line setting, we agree with CDER that a large magnitude of PFS benefit with no impairment to overall survival is clinical benefit.

Let’s return to the biomarker component of the confirmatory study. First, let’s review the analysis of plasma markers in AVADO. Biomarkers were assessed in an optional sub-study with separate patient consent. Fifty-four percent of patients had a baseline plasma sample, and, importantly, patient prognostic factors did not differ between patients who did and did not have samples.

Plasma markers were selected based on their role in angiogenesis and metastasis. For the primary analysis, the marker cutoff was prespecified to be the median value. Additional analyses were performed on marker quartiles to further explore the relationship between VEGF-A levels and efficacy. Standard Cox regression methods were used to control for baseline characteristics.

What we found in AVADO was that high levels of plasma VEGF-A were predictive of a larger benefit of Avastin with a hazard ratio of .87 in the VEGF low group and .49 in the VEGF high group. The interaction test was borderline significant at .08. To explore the cutoff value by quartiles, we looked at the results and saw the benefit increased from .87 in the lowest quartile up to .40 in the highest quartile.

Other findings were that high VEGF-A was strongly prognostic for poor outcome in both PFS and OS, and this was unrelated to other baseline characteristics. High VEGF-A was not found to be

predictive for overall survival in AVADO, although this analysis has the caveat that there were a smaller number of overall survival events in the biomarker sub-study.

Next steps include development of a commercially plasma VEGF-A assay and prospective validation within the confirmatory study. We continue to pursue the plasma VEGF-A hypothesis in other tumor types. To date, we have supporting data in some tumor types but not in others.

So to summarize the confirmatory study, we have designed a study of Avastin plus paclitaxel specifically designed to confirm the substantial magnitude of benefit seen in E2100 in all patients. Current enrollment projections indicate that this study is feasible, both by taking advantage of global enrollment and by investigator interest in the biomarker question.

We are planning an interim analysis of PFS, which could trigger an early voluntary withdrawal of the accelerated approval by Genentech if the magnitude of benefit of E2100 is not likely to be

confirmed by the futility boundary.

We met with CDER in February to discuss the design, and their feedback was very clear. CDER said that confirming the magnitude of PFS seen in E2100 with no detrimental in OS would support full approval of Avastin in metastatic breast cancer. This study also provides the opportunity to validate the emerging hypothesis that high VEGF-A is predictive of larger clinical benefit, an area in which both FDA and ODAC have expressed interest.

My overall conclusions are shown here. First, we are confident in the strong and meaningful PFS benefits in E2100. The issues raised by CDER in 2001 and again more recently were reviewed carefully. We found that these concerns were not unique to E2100. They are seen in the pivotal studies of approved breast cancer medications, and there was no evidence of bias.

Second, AVADO and RIBBON 1 do not invalidate E2100. They were well-conducted. They were completed promptly. They met their primary endpoints with high statistical confidence. They

did use a different chemotherapy backbone and schedule than E2100.

But what has changed and why we are here today is that now we have clarity from CDER on what is needed to convert Avastin to full approval, by confirming the magnitude of benefit from E2100. With that change, it's Genentech's position that the proper course forward is to perform a confirmatory study with weekly paclitaxel. We have agreement with CDER on the design of the study and what it must show.

Thank you for your attention, and now I invite Dr. Joyce O'Shaughnessy to the podium.

DR. O'SHAUGHNESSY: Dr. Midthun, ODAC and CDER colleagues, ladies and gentlemen, I appreciate the opportunity to share with you my perspectives on the clinical utility of Avastin-paclitaxel as first-line treatment for metastatic breast cancer.

I hold the Celebrating Women Endowed Chair in Breast Cancer Research at Baylor University Medical Center, and I am co-chair of the U.S. Oncology Breast Cancer Research Program. In

addition to my involvement in breast cancer clinical research, I am a practicing medical oncologist who is focused solely on the care of breast cancer patients.

I am here with Genentech, who has paid for my time and travel to this meeting. I have been involved in developing and enrolling patients onto Avastin breast cancer clinical trials since 2000. I have come to speak to you today because, as a breast cancer specialist, I am very aware of where we still have gaping unmet medical needs that cause significant suffering. But first, it is important to understand that there are three main types of HER2-negative metastatic breast cancer.

Slow-growing, indolent, estrogen-receptor ER, positive breast cancer is often without symptoms and is probably best treated not with a combination but with sequential single-agent chemotherapy when hormonal therapy is no longer effective.

Aggressive ER-positive breast cancer often causes debilitating bone pain or threatens liver or

lung function.

Triple negative breast cancer is highly symptomatic in most patients, has a median survival of only 12 to 18 months, and few known effective treatment options. Triple negative metastatic breast cancer and aggressive ER-positive disease are best treated with combination chemotherapy, or Avastin-paclitaxel.

In my practice, the Avastin-paclitaxel combination plays an important role in alleviating the symptoms that occur with aggressive metastatic breast cancer. Just last week alone, having carefully considered all of the available options, I recommended to three patients who have metastatic triple negative breast cancer and who are in need of rapid relief from severe bone pain, chest wall and arm pain, and liver pain that they begin treatment with Avastin-paclitaxel.

As co-chair of the U.S. Oncology Breast Cancer Committee, I oversee the development and conduct of breast cancer clinical trials within the U.S. oncology network. In this capacity, I have

been involved in the evaluation of several new agents and regimens that have helped shape the current standards of care for patients with early and metastatic breast cancer, some of which I have listed on this slide.

I have also had a longstanding interest in clinical trial endpoints for metastatic breast cancer. Twenty years ago, I served as the coordinator for a joint FDA and NCI working group that published a commentary on demonstrating safety and efficacy of investigational anti-cancer agents in clinical trials. Twelve years after this publication, a follow-up report stated that between 1990 and 2002, endpoints other than survival were the approval basis for 68 percent of regular approvals and for 100 percent of applications granted accelerated approval by FDA.

So what are key treatment goals and endpoints? The accepted treatment goals for metastatic breast cancer and to prolong and/or to improve or preserve patients' overall functioning and performance status by decreasing or preventing

tumor-related symptoms for as long as possible with the least possible treatment-related toxicity in clinical trials and in the clinic. The goals of decreasing or preventing tumor-related symptoms and prolonging disease control are accomplished by improving response rates and progression-free survival. A very important aspect of managing metastatic breast cancer is to alleviate and prevent the symptoms that impair function with the least possible treatment-related toxicity.

This slide shows the key efficacy results for the four most commonly used combination therapies for aggressive metastatic breast cancer: Avastin-paclitaxel, gemcitabine-paclitaxel, docetaxel-capecitabine, and ixabepilone-capecitabine.

Avastin-paclitaxel provides a higher rate and a longer duration of disease control, as is seen by the improved response rate and the longer progression-free survival in E2100. The magnitude of the PFS and response rate benefit with Avastin-paclitaxel compares favorably to the two to

three-month improvement in PFS and the 12- to 15 percent improvement in response rates seen with these approved combination chemotherapy regimens used in clinical practice as first-line treatment.

Importantly, and my main message to you as a practicing clinician, is that the higher response rate and longer progression-free survival do provide meaningful clinical benefit to patients with rapidly progressive symptomatic or heavily tumor-burdened metastatic breast cancer.

Triple negative breast cancer is an especially grave form of metastatic breast cancer, and very few clinical trials have shown defined treatment benefit in this group. Looking at the triple negative data from E2100, there is a 21 percent increase in response rate and a five-month improvement in progression-free survival with Avastin-paclitaxel.

There is also a trend towards improved survival in this group. On the right, the pooled data from all the first-line Avastin trials in my mind corroborate a definite clinical benefit in

this triple negative population that has great unmet need.

Importantly, in my experience, Avastin-paclitaxel is a well-tolerated combination regimen. In contrast to combination chemotherapy, the toxicities associated with Avastin-paclitaxel are generally not treatment-limiting. Oncologists must, of course, consider a patient's underlying risk for developing the uncommon but serious toxicities that can occur with Avastin-paclitaxel in order to avoid a potentially serious side effect.

As we heard from several of the women who testified yesterday, the most common Avastin-related toxicity, hypertension, and the less common toxicity, proteinuria, are typically without symptoms, manageable, and, in my experience, reversible. This tolerability allows patients to have the sustained progression-free survival benefit that can be achieved by combining two agents. This is difficult to accomplish with a combination of two chemotherapy drugs due to the

need for dose reductions and the eventual need to stop one or both agents due to cumulative toxicity.

Avastin and paclitaxel is compatible with a good quality of life for my patients. To illustrate this point, shown here is a summary of the toxicities that can lead to dose reductions for the main four combination regimens. I have bolded for you the toxicities that had double-digit increases when the combination regimen was compared with single-agent taxane or capecitabine.

The three combination chemotherapy regimens lead to increases in neutropenia, which is a lowering of the white blood cell count; neuropathy, which is numbness and tingling in the hands and feet; hand-foot syndrome, which is redness and pain in the hands and feet; and stomatitis, which causes mouth sores. These toxicities are in contrast to those seen on the left with Avastin-paclitaxel, which generally don't limit the delivery of therapy.

In conclusion, Avastin-paclitaxel is an important treatment option in my practice. The

longer progression-free survival and higher response rate do provide meaningful clinical benefit to my patients with symptomatic or rapidly advancing disease who require combination therapy. The toxicities associated with Avastin-paclitaxel are generally not treatment-limiting, which allows for the delivery of sustained combination therapy.

Loss of access to Avastin-paclitaxel would most acutely impact metastatic triple negative patients who have few effective treatment options, as well as patients with aggressive symptomatic ER-positive breast cancer. It is on behalf of the women in my practice who have aggressive metastatic breast cancer and those who I unfortunately will meet in the future who are best treated with tolerable and effective combination therapy that I have come to speak to you today.

As you will hear in a few minutes as well from Dr. Barron, I call on the FDA to work with the sponsor to keep Avastin-paclitaxel available as an approved option, even if it means limiting the indication to patients with metastatic triple

negative and aggressive ER-positive breast cancer whom their oncologists believe need combination therapy while the confirmatory trial is being done.

Thank you very much for allowing me to share my experience with you, and I would now like to introduce Michael Labson from Covington & Burling.

MR. LABSON: My focus today as an attorney specializing in food and drug regulation will be on why the legal provisions governing accelerated approval call for retaining Avastin as an approved treatment option. I will review the statute, regulations, prior guidance from CDER, and the Department of Health and Human Services. I will also do a fuller walk-through of the regulatory history of Avastin because it explains why we are here and why we disagree with the statement yesterday that we are seeking multiple bites at the apple.

This slide shows the key legal provisions that govern accelerated approval. The overarching purpose, as set out in the statute, the reason we have accelerated approval, is to facilitate the

availability of treatments in areas of unmet medical need. Metastatic breast cancer is an area of high unmet medical need.

The approval provision states that FDA may approve a medicine based upon an effect on a clinical endpoint or on a surrogate endpoint reasonably likely to predict clinical benefit. FDA's regulations specify further that the clinical endpoint may be an effect other than survival or irreversible morbidity where there remain unanswered questions about a medicine's effect on ultimate outcomes.

Avastin's approval for breast cancer is based on progression-free survival, as you heard yesterday, an endpoint CDER agrees is meaningful in this setting without a showing of overall survival or improvement in quality of life.

For withdrawal, the law states that FDA may withdraw approval if a post-approval study fails to verify clinical benefit or other evidence demonstrates that a treatment is not safe or effective. CDER's view on withdrawal is that

Avastin had its chance. We had the chance to submit post-approval studies to confirm benefit, and did not make that showing.

That rigid approach is not required under the law, and it is not consistent with the law's purposes, to provide access to a medicine that addresses serious unmet medical need where there is a meaningful showing of benefit but questions remaining regarding the magnitude of that benefit.

The data and the regulatory history for Avastin call for the exercise of the flexibility that the law provides to maintain accelerated approval. Let's look first at the regulatory option CDER had for Avastin in 2008. At that time, CDER had data from E2100, top-line AVADO data, mature PFS results, and immature OS data. CDER also had later-line capecitabine data from the 2119g study.

After heavily vetting the E2100 study, CDER concluded the data were reliable and supported approval. In particular, CDER accepted PFS as a meaningful endpoint, accepted Avastin's safety

profile, and determined that Avastin provided clinical benefit with favorable benefit-risk.

CDER had three regulatory options: full approval, accelerated approval, or no approval. And as CDER has explained and the review documents show, CDER utilized accelerated approval to address CDER's uncertainty about the scopes of Avastin's effects. The accelerated approval provisions worked in a flexible manner, as the law intends, to provide a treatment option to patients with significant unmet medical need and with post-approval studies to address the open questions that existed at that time.

Today we see the additional data, the mature OS data for AVADO and data from RIBBON 1. There are also the data from RIBBON-2 showing a PFS effect outside the first-line setting. AVADO and RIBBON 1 met their PFS endpoints, but with a lesser magnitude of effect for Avastin with non-paclitaxel chemotherapy. Safety is unchanged, as you heard from CDER yesterday. The question is, do these data on Avastin with other chemotherapy agents

refute the substantial effect on PFS for Avastin with paclitaxel from E2100?

One view is that the data on Avastin with paclitaxel stand distinct and benefit is confirmed. That is the view of the European Medicines Agency, numerous other health authorities, and the National Comprehensive Cancer Network. Until 2010, Genentech also thought that benefit was confirmed under the standard set by CDER based on the positive showing in AVADO and RIBBON 1. I will come back to this point further in a few minutes.

CDER's view is at the other extreme, that although the studies showed a robust effect and involved different chemotherapy agents than E2100, the results negate the showing of benefit from E2100. That view leads to withdrawal. Indeed, we heard yesterday that CDER has not even considered any other options.

But there is a middle ground, drawing on the discretion CDER acknowledged yesterday. Based on the showing of benefit, if there are open questions about the nature of Avastin's effect in metastatic

breast cancer, and particularly its effect with paclitaxel, the appropriate course is to retain accelerated approval subject to a new study designed directly to confirm the magnitude of benefit for Avastin with paclitaxel. This is the course Genentech has proposed.

The law provides this flexibility, and this middle course best meets the purposes of accelerated approval, to facilitate needed treatment options for a severe disease pending further study to confirm the level of benefit already shown in E2100. CDER and HHS have both previously emphasized this precise point.

At the 2003 ODAC on the accelerated approval program, Dr. Robert Temple explained, “When a drug has proved active, you don’t lightly remove it because a trial failed. You try to do other studies. You think about why the studies failed.”

At the same ODAC, Dr. Pazdur emphasized that the regulations provide flexibility on withdrawal decisions, and that withdrawal may not be appropriate where a confirmatory study does not

confirm clinical benefit. As Dr. Pazdur explained, "The withdrawal provision in the regulation gives us judgment so we don't to have a reflex situation; you fail, therefore you must come off."

Here CDER agrees that the post-approval studies met their endpoints and show that Avastin is active in metastatic breast cancer with no new safety new signals. On these facts, Dr. Temple's and Dr. Pazdur's cautions to exercise regulatory judgment and not to move automatically to withdrawal are particularly on point.

CDER's comments from the 2003 ODAC have been echoed by the Department of Health and Human Services, HHS, FDA's parent agency, also emphasizing that FDA should proceed with caution in considering withdrawals of accelerated approval. In 2009, in official comments to the Government Accountability Office, HHS explained, "When trials do not appear to confirm clinical benefit, FDA must carefully assess each case and the consequences of all regulatory options, including their potential impact on patients."

HHS further stated, “Failure to confirm clinical benefit in a completed trial may reflect unforeseen limitations in trial design rather than clear evidence of lack of effectiveness.” Here the post-approval trial showed effectiveness in a disease with extremely limited treatment options. The impact on patients from withdrawal would be great.

The unforeseen limitation was the difference in magnitude by chemotherapy partner, particularly when focusing heavily on the medians, and relatedly, CDER’s evolving emphasis on replicating the magnitude of improvement in median PFS from E2100.

Because accelerated approval is intended to keep a medicine available where there is a meaningful showing of benefit but some remaining uncertainty, we strongly disagree with CDER’s assertion that allowing a new confirmatory study here undermines the accelerated approval program. As the comments from HHS, Dr. Temple, and Dr. Pazdur caution, a rigid approach to withdrawal

does not best serve patients.

Here the regulatory history of Avastin shows that one of the unforeseen limitations of AVADO and RIBBON 1 is that the trials would be expected not just to show a PFS benefit but to replicate the 5.5-month change in median PFS from E2100. That is not the guidance Genentech received when identifying AVADO and RIBBON 1 as appropriate confirmatory trials.

In 2008, when CDER granted accelerated approval, it understood that AVADO and RIBBON 1 would not replicate the PFS results from E2100. This slide shows the office director's review memo supporting approval in 2008. As indicated, CDER specifically requested the preliminary results of AVADO before taking regulatory action.

The definitive PFS data were available, and the office director noted that there was an improvement in PFS based on data for the standard Avastin dose, showing a hazard ratio for PFS of 0.64, a 36 percent reduction in the risk of disease progression or death, an improvement in median PFS

of 0.8 months, and an 18.6 percent improvement in objective response rate. There is no mention of overall survival or an overall survival trend.

CDER thus knew, in approving Avastin for metastatic breast cancer and accepting AVADO as a post-approval trial, that AVADO would show benefit, but would not replicate the magnitude of benefit -- the magnitude of median PFS effect from E2100. And we heard yesterday that CDER never communicated to Genentech that AVADO was not adequate to confirm benefit.

For RIBBON 1, in a January 10, 2006 meeting, CDER acknowledged that, “The treatment effect will vary according to the chemotherapy regimen used. The test will be whether there is a treatment effect for each chemotherapy pairing.”

CDER recognized that the different chemotherapy regimens will yield different effects. CDER accepted the study design with target hazard ratios of 0.7 and 0.75 for the two study arms, and did not say that RIBBON 1 would only be considered to show clinical benefit with a level of effect on

median PFS near 5.5 months.

Here's the key Type B meeting from February 2009, before the AVADO and RIBBON 1 supplements are submitted. In advance of that meeting, Genentech provided CDER the top-line AVADO and RIBBON 1 results. With this information in hand, CDER stated in official meeting minutes, "FDA confirmed that the basis for conversion to full approval will be demonstrated improvement in progression-free survival and evidence that survival is not impaired."

There is no statement that AVADO and RIBBON 1 failed to confirm benefit, even though CDER had received the median PFS results from the studies. There is also no reference to the need for Genentech to replicate a change in median PFS near 5.5 months, as in E2100, to confirm benefit.

It is not until the July 2010 ODAC and the NOH that CDER states that the magnitude of median PFS change from E2100 must be replicated or there must be an effect on overall survival. But Genentech did not have this guidance when

identifying AVADO and RIBBON 1 as confirmatory trials. In fact, we heard yesterday that CDER felt it was unable at that time to give specific guidance on the required magnitude of benefit.

This explains where we now are. CDER's thinking changed over time, and we thus have post-approval studies that, in hindsight, are limited in their designs to meet CDER's expectation of reproducing the magnitude of median PFS benefit from E2100.

This regulatory history shows that Genentech is not trying to undermine the accelerated approval program by gaining inappropriate multiple bites at the apple. Rather, Genentech is trying to respond to its understanding of CDER's evolving thinking on how to establish clinical benefit for Avastin in this setting.

Maintaining approval subject to a new study is an opportunity to conduct a confirmatory trial squarely addressed at confirming the magnitude of benefit for Avastin with paclitaxel, with the required showing for full approval now clearly

established.

The need to consider the option of a new study rather than withdrawal is especially great under our facts. All of the first-line studies met their agreed-upon PFS endpoints. The data from the secondary endpoints also showed consistent effects. The greatest effect we have is for Avastin with paclitaxel, and CDER accepts it is robust and clinically meaningful. CDER's open questions are the magnitude of benefit and the role of the chemotherapy partner. These questions can be addressed through further study.

Safety. Safety is well-characterized and presented in the approved prescribing information. CDER agrees there are no new safety signals. And as you have heard from Dr. Horning and Dr. O'Shaughnessy, the overall safety profile is in line with other treatment options.

Genentech completed the post-approval studies with rigor and diligence. An unmet medical need persists. In over three decades, looking at non-hormonal HER2 status unspecified medicines, FDA

has approved only one other treatment for first-line metastatic breast cancer, Gemzar, with a 2.3 month improvement in disease progression, no proven survival benefit, and toxicity. As you heard yesterday, there are no MBC treatments approved with labeling for quality of life, and no survival benefit has been approved for first-line treatments outside hormone-positive, HER2-positive disease.

We are not aware of any other instance where FDA has sought to withdraw accelerated approval on such facts, and it is not the right outcome here. Withdrawal would remove a therapeutic option with demonstrated efficacy, and it would narrow the viability of the accelerated approval pathway for sponsors by establishing an inflexible approach to the consideration of post-approval studies.

These facts provide the answers to the issues the presiding officer has stated will be presented in this proceeding. Issue 1 asks whether AVADO and RIBBON 1 failed to verify clinical benefit for Avastin with paclitaxel. The answer is

no, because they showed a statistically significant benefit and a robust effect seen especially in the hazard ratios.

Issue 2(a) asks whether the totality of the data show that Avastin with paclitaxel does not provide benefit. No. The data show clear effectiveness in the first-line setting, particularly with paclitaxel.

Issue 2B asks whether the data fail to establish safety and favorable benefit-risk. No. The safety profile is well-characterized and has not changed. It is a profile that CDER accepts across a range of other approved indications for Avastin. The most common adverse events are generally manageable. Other serious adverse events are rare.

Issue 3 asks, if the data have not confirmed the safety and effectiveness for Avastin with paclitaxel, should accelerated approval be maintained subject to the conduct of an additional study? The answer is yes. Maintaining Avastin as an approved option is called for by law, supported

by the data, and in the best interest of patients.

This final issue is in large measure the fundamental question for these proceedings. The EMA, other health authorities, the NCCN, and many oncologists, patients, and cancer organizations, on the same studies, have concluded that the data validate that Avastin is a valuable treatment options. Others are not convinced. But the issue here is whether there should be a sweeping regulatory action that withdraws Avastin as an approved option for all in an area where the options are already too few, or whether physicians and patients should be left to make informed individual decisions, with appropriate prescribing information, while further work is done.

The law provides a path forward between the two poles of full approval, as in Europe, or full withdrawal, as CDER has proposed. Retain accelerated approval and require a true confirmatory trial designed to meet the expectations CDER has now clearly set out.

Thank you for your attention. Dr. Hal

Barron will now provide our concluding remarks.

DR. BARRON: Thank you very much.

Before we end, I want to make a couple of comments on what we have heard over the past day and a half and how we have come to see the issues at hand. Hopefully this is helpful for you, Dr. Midthun.

We have seen many slides with many, many numbers; hazard ratios, response rates, confidence intervals, p values, et cetera. But what we cannot lose sight of, though, is the many women behind these numbers.

We have heard moving testimonials from numerous women who have described their enormous hardship from being diagnosed with this devastating and incurable disease, how grateful they are for the simple pleasures in life, and how significant their unmet need truly is.

In the subsequent presentation, CDER made it clear that despite the fact that both confirmatory studies demonstrated an improvement in the prespecified primary endpoint of PFS and that there

were no new safety signals observed, this isn't enough to allow accelerated approval to be maintained while we confirm the magnitude of effects seen in E2100 and a subsequent study.

What became clear at the end of CDER's presentation is why we have come to divergent conclusions. CDER stated that the first-line metastatic breast cancer indication does not represent an unmet need. CDER even went further to state that if these women did have an unmet need, as do women in later stages of their disease, the criteria for clinical benefit would have been "more lenient."

We respectfully but strongly disagree. These women have a significant unmet need and deserve the option to be treated with Avastin in combination with paclitaxel. This is the key issue for Dr. Midthun and Dr. Hamburg to decide.

We are willing to work with the FDA, as Dr. O'Shaughnessy alluded to, to find a solution, such as a modified or restricted label. Our primary objective is to preserve, in an appropriate

manner, options for women with metastatic breast cancer.

Thank you for your attention and for allowing us this opportunity to provide our perspective.

DR. MIDTHUN: Thank you very much.

We will now break for half an hour, and return at 10:30.

(Whereupon, a recess was taken.)

Questions by CDER

DR. MIDTHUN: All right. We will now go to the next portion of our session, which will be the opportunity for the CDER panel to present questions to the Genentech presenters, and there will be one hour for that.

MS. CARTWRIGHT: Thank you, and good morning. We'd like to begin with your proposed withdrawal standard.

May I have slide 128, please?

This is Genentech's proposed withdrawal standard. "Withdrawal is not appropriate unless the data establish that there is no longer a

reasonable likelihood of clinical benefit, and no meaningful way to characterize the potential benefit further."

Can you tell us of anyplace where FDA has stated the withdrawal standard in this way?

MR. LABSON: Well, our point here is simply that where the data that you have from the original trials and the post-approval trials show a benefit but there's uncertainty, that the purpose of the accelerated approval law is met by keeping the medicine as a treatment option.

That's sort of the fundamental purpose of the statute, and that still exists when you're looking at the data after the post-approval trials are confirmed. And that's consistent with the statements and interpretation we see from the 2003 ODAC and from the HHS comments about needing to approach withdrawal carefully based on the particular facts at hand.

MS. CARTWRIGHT: But that is not the withdrawal standard in the statute or the regulations?

MR. LABSON: It is how we think the withdrawal -- what the withdrawal standard means and how it's interpreted. It provides that -- we agree that the withdrawal provisions, an important part of the scheme, and it provides that FDA may withdraw approval if post-approval trials don't confirm benefit. But that has to be judged based on the facts that you have and in light of the purposes of the law, to make treatments available in areas of unmet medical need.

MS. CARTWRIGHT: Doesn't this standard actually shift the burden to FDA to prove that there is no longer a reasonable likelihood of clinical benefit, rather than placing the burden on the sponsor to establish that the product is safe and effective?

MR. LABSON: No. We would agree the burden is to show that there's a benefit, with uncertainty. That's why you're still under accelerated approval and not regular approval.

MS. CARTWRIGHT: You also stated in your May submission that if the confirmatory study fails to

meet the standards CDER set in the February 2011 Type B meeting, withdrawal could then be appropriately considered.

What results of your proposed study would constitute a failure under your proposed withdrawal standard?

DR. REIMANN: Yes. As you heard in our presentation, we are proposing an interim analysis of progression-free survival specifically for the purpose of regulatory futility. By that, I mean, if the results at that time indicate that it is unlikely that the magnitude of effect seen in E2100 will be confirmed -- and will you please bring up the slide -- then we will propose -- sorry. I just want to get the slide up here. Let me talk you through the slide from the top.

The purpose of the interim analysis is to rule out a large magnitude of PFS benefits similar to that seen in E2100, and we heard from Dr. Pazdur on this yesterday. It is important that the study would still continue to the final analysis, and that is because of the biomarker question. We

don’t want to inhibit the study from answering the important biomarker question. But the interim analysis results could trigger withdrawal based on futility boundary.

We have not yet discussed this boundary with FDA, and we think that’s an important discussion. When we met with FDA earlier this year to discuss the confirmatory study, CDER didn’t want to talk about the ongoing accelerated approval, so we haven’t yet had that opportunity. We see this futility boundary being based largely on the hazard ratio, but also informed by the absolute benefit.

MS. CARTWRIGHT: But once you had this interim analysis under your reading of the regulations and the approach to withdrawal, how many additional trials would you say would be necessary before you would agree that you’d failed to confirm benefit?

DR. REIMANN: This is the definitive additional trial.

MS. CARTWRIGHT: So where your slide says that it could lead to voluntary withdrawal, you’re

saying that it would. This would be the definitive trial?

DR. REIMANN: I think CDER appreciates that this would also be a discussion between CDER and the company because it could be a possibility that the different measures of magnitude do not entirely agree at the boundary, and the Data Monitoring Committee could have opinions on this matter as well.

MS. CARTWRIGHT: Thank you. Dr. Jenkins is going to ask you some questions now about the actual proposed study.

DR. JENKINS: You mentioned in your presentation that you're still conducting feasibility analyses for this trial. Can you share more information about that feasibility analysis as far as how long you think it's going to take to enroll this trial and when you expect to submit the final study report for this trial?

DR. REIMANN: Yes. The preliminary feasibility analysis has already been performed. That was based on our prior enrollment experience,

our global CRO, and an initial questionnaire that went out to the countries specific to this protocol. The more detailed feasibility analysis is currently ongoing and will deliver results in early July.

This more detailed feasibility assessment is looking at the standard of care in the different countries, the ability of the study sites to follow the protocol as specified, and, of course, their interest in the protocol. We also need to make sure that there is a proper handling of biological specimens by local laboratories to make sure the protocol is conducted as in the high level protocol summary we discussed with FDA early this year.

So in short, we will have the updated feasibility in early July to inform our discussions with CDER coming this fall.

DR. JENKINS: Are you planning to conduct this confirmatory trial in countries where the Avastin plus paclitaxel indication is approved by the regulatory agency in that country?

DR. REIMANN: We have approached

approximately 50 countries for participation in the study. Some of the countries, many of the countries, have Avastin plus paclitaxel approved. But I think here it's important to distinguish regulatory approval from access to patients. In many cases, the regional health authorities of the state health authorities do not provide access to patients. And so we believe this will be a very attractive study in many locations where the trial is being proposed, even in the United Kingdom.

DR. JENKINS: Do you plan to conduct the study in the United States?

DR. REIMANN: We will have study sites in the United States. Based on preliminary feasibility, we believe the study will predominately be enrolled outside of the United States.

DR. JENKINS: Okay. Under your proposal, the indication for paclitaxel would remain in the label under accelerated approval. So I'm wondering, in your feasibility assessment, you made the point this morning in your presentation that

Genentech stands behind the view that the progression-free survival benefit is 5.5 months, that the 1-year survival benefit is a 7 percent improvement, and that the two-year survival benefit is a 4 percent improvement over paclitaxel alone.

So I'm wondering if your feasibility assessment has included the likelihood of enrolling patients in this study in the United States or other countries where the indication is approved on the label. We've heard in the past that patients are reluctant to agree to be randomized to not receive what's an approved treatment for their serious and life-threatening condition. So if this indication remains in the label, can you help me understand the feasibility of conducting this trial in those countries?

DR. REIMANN: I think it's obvious to everybody at hand that we have this very public hearing today, and there is a lot of dispute about the data with FDA. But I'd like to ask Dr. Horning to comment.

DR. HORNING: Well, I would concur with what

Dr. Reimann just said, which is that there is scientific debate over the interpretation of the data, and there are varied opinions of physicians and patients, as we heard yesterday. And we feel that there will be a proportion of such patients and physicians in the United States who are currently at equipoise, or near equipoise, where there will be interest in participating in such a study. We also believe that the biomarker component raises the scientific interest of the study, and the interest of investigators as well as patients.

DR. JENKINS: Can you share more details about how you are planning the study? What effect are you planning to confirm with your analysis? So what's your planned analysis of this trial going to look like, in your -- what will a win look like, essentially, in your statistical analysis plan?

DR. REIMANN: I think we have to distinguish win from the protocol versus win with the FDA. And we heard, in fact, two different answers from CDER yesterday on what the study would need to show. We

heard a certain magnitude of median PFS or an improvement in hazard ratio; and then we heard a certain improvement in median PFS and an improvement in hazard ratio. These two things are quite different when sponsors consider the design of confirmatory study.

We believe in providing a well-conducted study with substantial evidence that will enable that decision to happen, and we realize that will be a discussion with CDER for the withdrawal. But we are committed to get the study started as soon as possible and to get data as soon as possible. And we anticipate the interim analysis will be conducted 3 and a half years after this coming Q1.

DR. JENKINS: Okay. I think we clarified yesterday in our presentation that our focus has been heavily driven by the magnitude of the median difference in progression-free survival. And I think we clarified that yesterday afternoon, that Dr. Pazdur misspoke when he said the median or the hazard ratio.

So are you planning -- do you expect this

trial will show a median difference in progression-free survival of the magnitude seen in E2100, which was approximately 5 and a half months? Is that what you're expecting to see?

DR. REIMANN: Yes. I think I would like to clarify, though, what we heard at the end of CDER's presentation yesterday, if I heard correctly in your redirect, that CDER thinks we should confirm exactly the median benefit and exactly the hazard ratio. And I think it's important here that we recognize that all clinical studies are conducted with variability.

So if truth in the new study is 5.5 months, then there's a 50 percent chance, just by variability alone, of being less than 5.5 months, and there's a 50 percent chance of it being greater than 5.5 months. If we then also have to exactly match a hazard ratio, you have a 50 percent chance of it being less and 50 percent chance of it being more.

So I think we need to get better clarity from what the agency needs as far as the exact

showing of benefit.

DR. JENKINS: But your expectation going in is that you will replicate the 5 and a half month progression-free survival seen in E2100?

DR. REIMANN: Yes, definitely. We are very confident in the substantial benefit seen in E2100. And what I personally expect to see is substantial improvement in objective response, in progression-free survival and 1-year survival. I think it's an interesting fact that if we do a study of this size, you would actually be powered to see a 1-year survival benefit of approximately 6 percent.

I know that's not the discussion today, but we believe we've designed a study that will provide substantial evidence to enable a regulatory decision. And the inclusion of the interim analysis will enable that to happen sooner.

DR. JENKINS: I'd like to go back to that interim analysis. Can you provide more detail about the criteria for futility that you plan to propose for the interim analysis? The slide you projected was very vague on what the actual

criteria would be. So where would Genentech see futility in confirming the benefit in that interim analysis that would lead you to voluntarily withdraw this indication?

DR. REIMANN: Well, clearly that's a discussion we need to have with CDER, and we haven't had that discussion yet. I would envision the futility boundary to be primarily based on a hazard ratio, which I believe has superior statistical properties for variability, but also be informed by the absolute benefit. That includes the median benefit, but also early benefits and later benefits.

I think you can appreciate that if the futility boundary is too loose, then we would terminate a study early that actually would replicate the management of benefit in E2100. So I think it's a matter of us looking at the numbers and sitting down together and working on it with a boundary that we can both feel comfortable with.

DR. JENKINS: And you can't share your proposal at today's meeting?

DR. REIMANN: Actually, we wanted to be informed by FDA's discussion of the magnitude of benefit that had to be demonstrated to inform our proposal.

DR. JENKINS: Thank you.

MS. CARTWRIGHT: You made some comments that CDR has been inconsistent with regard to magnitude. So we'd just like to go through a little bit of the regulatory history on that point.

Would you agree that on October 28, 2004, CDER told Genentech on a telephone conference that approval based on PFS would depend on the overall results and magnitude of PFS?

MR. LABSON: The issue isn't whether CDER said that magnitude would be considered, which I think is pretty straightforward. The point is that CDER never communicated that the standard would be a showing of median PFS of 5.5 months. And you can see that in the regulatory history; for example, having the AVADO results at the time that CDER accepted AVADO as a confirmatory trial and knowing that the median PFS, based on the data they had in

hand, was 0.8 months, although the hazard ratio was more in line with E2100.

MS. CARTWRIGHT: Well, speaking of the AVADO results, did CDER ever tell Genentech that those top-line AVADO results, which were communicated in just a couple of slides, would confirm clinical benefit for Avastin?

MR. LABSON: The key point is CDER accepted AVADO as a confirmatory trial, knowing what the data were.

MS. CARTWRIGHT: Well, at that time, wasn't CDER also presented with results that indicated there was a trend in overall survival in that top-line data?

DR. HORNING: Just to clarify, CDER requested and Genentech provided more than just a couple of slides. There were actually 22 slides that provided details of the clinical trial and the results.

At that time, the results that were available that you could hang your hat on, so to speak, were the response rates, which were called

out in the slides. And also the PFS, the progression-free survival, at that time was mature, with more than half the patients experiencing an event. As we have spoken about earlier, at that time, with the top-line definitive progression-free survival results, the hazard ratio was 0.64 and the median delta in PFS was 0.8 months.

There was also within that slide deck some very preliminary survival data, with about 20 percent or less events at that point in time. And it was called out in this office director's memo that immature survival data had also been viewed.

MS. CARTWRIGHT: And Genentech did direct CDER's attention to that immature survival data with the red circle that we saw on a slide yesterday?

DR. HORNING: Within the slide deck, there were several things that were called out, and the overall survival data were called out at that time. You can imagine that there would be interest in overall survival because of the necessity for

providing or demonstrating an improvement in progression-free survival with no impairment in overall survival.

So these preliminary data and the upper bounds of the confidence interval would suggest that it was very unlikely that you're going to see an impairment in overall survival in AVADO based upon the data that were provided at that point in time.

MS. CARTWRIGHT: And is Genentech aware of CDER making regulatory decisions based on top-line data, be it two slides or 22 slides?

MR. LABSON: Well, we have Dr. Pazdur's review memo from that time that said that CDER specifically requested the AVADO data before making regulatory action. Understand that CDER didn't review the full data set, but I think he also explained yesterday that he wanted to be sure, that CDER wanted to be sure, before approving that it wasn't going out on a limb where there would be a failed study.

So I think the assessment wasn't a full

review of the data, but saw the data to make the conclusion that AVADO was not a failed study but a study that showed benefit for Avastin in metastatic breast cancer.

MS. CARTWRIGHT: Right. And I think Dr. Pazdur also explained that was essential because we did have a failed study in this case with AB2119g. So thank you.

So talking about sort of the initial approval in 2008, we'd like to just ask a couple of questions about the ODAC meeting where the E2100 results were discussed. And if I could have slide 138.

This is a quote from Dr. Schenkein from Genentech, and he said at that time, "The data demonstrated robust and clinically meaningful PFS treatment effect. In fact, it represents the longest PFS seen to date with any treatment in this setting. A PFS of this magnitude represents clinical benefit for first-line treatment of metastatic breast cancer patients."

So isn't it true that Genentech, in

presenting the E2100 results, was really explaining that the magnitude of 5.5 months was the key?

DR. HORNING: I think at the time that this ODAC occurred and when the E2100 results were first presented, there was tremendous excitement in the community. I recall being in the audience at the ASCO meeting when the results were first presented. And indeed, the treatment effect that was seen in E2100 at that time was unparalleled. And I believe that you saw that in Dr. O'Shaughnessy's presentation this morning.

So you've selected a statement that relates to the meaningful PFS improvement as described in medians; and the PFS improvement as described in hazard ratio, with more than a 50 percent reduction in the risk of disease progression or death, I would submit is equally meaningful.

MS. CARTWRIGHT: And at that same meeting, Genentech had a consultant, Dr. Winer present, and he said, regarding the E2100 results, that for progression-free survival to equal benefit, this progression-free survival needs to be substantial

in magnitude, it needs to be established with confidence, and, ideally, it should be supported by other measures of efficacy, by survival, by quality of life, and by objective response rate. And that also was a part of Genentech's presentation at that ODAC meeting?

DR. HORNING: Yes. The response rate data that we have called out today, the 28 percent improvement in overall response rate, was a secondary measure that would be consistent with Dr. Winer's statement.

DR. JENKINS: I'd like to go to the chemotherapy partner hypothesis that Genentech is now proposing, that it's uniquely effective in combination with paclitaxel.

Can you share with us, when did that hypothesis really crystallize? As recently as ODAC, Genentech was advocating for a broad labeled indication for Avastin in combination with multiple chemotherapy agents. So when did your hypothesis that paclitaxel is the uniquely effective agent crystallize in your mind?

DR. HORNING: Well, I think from an historical perspective, the initial introduction of the hypothesis, if you will, that chemotherapy matters was brought up at the ODAC meeting in 2007 that we were just discussing, that was brought up by Dr. Kathy Miller from the University of Indiana. And it was looking at the 2119 and the E2100 results and discussing potential reasons. I think that also is very much in line with what you heard from Mr. Labson about trying to understand trials and looking deeper. So it had been ongoing for some period of time.

When we were presenting our data in July of 2010, we felt at that time that we were presenting the results of clinical trials that were positive and had met the standard for a demonstrated improvement in progression-free survival and no impairment in overall survival.

As a consequence of the ODAC discussion and our understanding of CDER's current thinking, we more closely evaluated the overall study results in this context. We see from the hazard ratios that

there is an effect of Avastin in each of our studies. We see that the effect is somewhat more pronounced in E2100. And at that point in time, we began to look at our data even more deeply with regard to some of the differences in the tolerability of paclitaxel in the clinic.

I will also say that during the ODAC transcript, that I made references to this as well. And if we could have the slide up. The statement was made with regard to different types of chemotherapy. And I had mentioned that there were always differences in the tolerability of the underlying chemotherapy, and that the time that patients are actually on treatment and receiving chemotherapy in combination with Avastin may be an important parameter that we are speaking about here.

DR. JENKINS: So at the time of the ODAC, is it true that you were seeking approval for an indication for use in combination with docetaxel as well, based on the 0.8 months median survival in AVADO?

DR. BARRON: Let me just add one point to the prior question. You used the term “uniquely.” I think you said “uniquely effective.” And I think the point of our presentation was to highlight the fact that the hazard ratios and the benefit observed in AVADO and RIBBON 1 was significant, and we acknowledged that the treatment effect appeared less in those two studies. But the benefit was observed in those two studies. The primary endpoint was significant. And so we are providing a hypothesis as to why there might be greater benefit with paclitaxel, but we wouldn’t describe it as uniquely effective such that the other regimens were inactive.

DR. JENKINS: It goes to the question of magnitude of PFS effect being clinically meaningful. I think we have agreed and you have agreed that the effect seen in E2100 is real and the safety profile has not changed, and that would be considered clinical benefit. At the time in July, you appeared to believe that the effect seen in combination with docetaxel was also evidence of

clinical benefit, as low as 0.8 months of median progression-free survival difference?

DR. HORNING: Well, our discussion in July 2010 at the ODAC was really to describe the treatment effect and the ways that it can be viewed scientifically. And when we look at the AVADO study, the hazard ratio was 0.62, which is a considerable treatment effect, certainly in line with approved agents in metastatic breast cancer.

I think in the AVADO trial this is a case where the median is underestimating the treatment effect. Nonetheless, we do recognize that the tolerability of docetaxel in combination with Avastin is less good than with paclitaxel, and we respect the judgment of those who've used the two in combination as well as the decision that was made in Europe.

DR. JENKINS: So you think the AVADO trial is an underestimate of the effect, in combination with docetaxel, but the E2100 is an accurate estimate of the effect with paclitaxel?

DR. REIMANN: No. I don't think we would

say that. I think the AVADO data, they are. They showed a hazard ratio of .62, and the difference in median PFS was .8 at the median.

If we could just put the slide up. I think it's very misleading when we always describe treatment effects in a time basis on medians because this is an example, I think, of where the medians are very close, showing .8 months. But actually, there are many points on the curve where the difference is bigger than .8 months. And this actually was seen with a data update that I know that FDA doesn't rely on.

But I think that we have other examples from studies in oncology. I think, as an example, of panitumumab in refractory colorectal cancer, which did receive approval, where the medians are quite notably almost on top of each other. And FDA used some regulatory flexibility, describing the benefit there as absolute improvement in PFS.

So I think this focus on medians is a little -- there's too much of it right now.

DR. JENKINS: Yes. I was just picking up on

the fact that Dr. Horning said that she thought that the AVADO median PFS was an underestimate of the true effect; and yet Genentech seems to think that the E2100 results for paclitaxel combination is the true effect at 5 and a half months.

I noted in your submission that you called out that there's never been a trial in first-line metastatic breast cancer that showed an effect of 5.5 months on median progression-free survival. That's one of the issues that's in debate here, is whether E2100 is an accurate representation of the true effect or was an overestimate, an outlier, and that the true effect is more in line with what you've seen in the other trials, including what we saw in Study 10, which Genentech submitted as part of your submission and referenced us to.

So just highlighting that, I'm wondering how it can be an underestimate in AVADO but an accurate estimate in E2100.

DR. REIMANN: Okay. There are a lot of questions there, so I'll address each one of them in turn.

First, I don't think it's proper to speculate about whether a study has an underestimate or an overestimate. You have the estimate. It has its confidence intervals. I think that's the way statisticians describe data, and that's the way we move forward in oncology.

With regard to E2100, if you could bring this slide up, I spent half of my presentation discussing E2100 in detail and why we are confident in the treatment benefit in E2100, not just that there was a benefit, but that it is of a substantial magnitude. And I know that FDA has a question about this, and that is what the purpose of the confirmatory study is for, to definitively answer this question once and for all. And so we've already provided that protocol to the FDA, and I think we have agreement on what that study would need to show.

But I do want to respond to your question about Study 10 because this did play a very large part in CDER's presentation. There were quite a few slides on this study, so I think it might be

helpful for the ODAC and for the presiding officer to know a little bit more about the study.

If you could please bring up the study schema.

The most important --

DR. JENKINS: I'm sorry. I think we want to move on to other questions --

DR. REIMANN: I'm sorry. I'm just trying to answer your question on Study 10.

DR. JENKINS: -- not use our time during this section. We know about study 10. I think that's in the package. I'll turn to one of my colleagues for other questions.

MS. CARTWRIGHT: We would like to ask a couple of other questions about your proposed study. You stated this morning that you will not complete the study for three and a half years after you begin enrollment, and you don't expect to begin accruing patients until next year.

So do we correctly understand that your new study would not be completed, assuming everything goes perfectly, until approximately 2016?

DR. REIMANN: You have the dates correct. Initial start of enrollment Q1, 2012. Interim analysis, three and a half years after that point. Final analysis, an additional year after that. We believe in the meantime, because of the substantial benefit that has been demonstrated in E2100, that it should be available to women with this indication.

DR. JENKINS: So if I could just follow up on that. So you're saying three and a half years after first enrollment to interim analysis, and another year after that to final analysis? Is that correct?

DR. REIMANN: Yes. That's exactly what I described in my presentation.

DR. JENKINS: And from that until final study report submitted to FDA for review?

DR. REIMANN: I think the important part about a voluntary withdrawal is that we wouldn't be anticipating a lengthy submission process of a preparation of a study report and a 10-month review period. I think this would be a very high level

discussion between senior management at Genentech and senior management at CDER to come to a decision.

DR. JENKINS: I'm just trying to understand when do you project you'll submit the final study report; three and a half years from first enrollment, another year, and then how much time. So are we talking essentially five years from first enrollment to get the final study report?

DR. REIMANN: I think a study report would be submitted approximately four months after the database lock, as per standard. But as I just said, the ability to make a regulatory decision would be in advance of that.

DR. BARRON: Let me just add one other point to that, that if we pass the futility mark, the probability is the trial is actually demonstrating what we expected to demonstrate, and therefore the delay is less of an issue. The reason we put the futility endpoint together is to ensure that if in fact the treatment effect is less, that we can inform the FDA and have withdrawal as quickly as

possible without jeopardizing the quality of the trial.

MS. CARTWRIGHT: So, again, just so we're clear, we're looking at approximately 2016/2017, and we could potentially be right back here having another proceeding to determine whether or not you've confirmed clinical benefit under your withdrawal rubric?

DR. REIMANN: I think it's important to reflect that in the accelerated approval legislation -- if we could bring the slide up -- there are multiple examples that are in time frames similar to this. If we look at the top of the slide, we have products that had been subject to regulatory action that were 10.4, 11, 10 years from initial accelerated approval. We have found products who are currently under accelerated approval and have not yet converted that have more than six and a half or more than seven and a half years; and then products who have been converted to full approval, we see a number of products here in the range of 6 to 12 years.

So, to be clear, this is not unprecedented, this time frame.

MR. LABSON: The other key point is now we have a clear statement from CDER about what will confirm or not confirm, and Genentech did not have that before. So now, with that standard clearly set, Genentech has been able to put together a proposal squarely aimed at that standard, and it will give us a direct answer. It's different than what we had before, where we didn't have clarity about what CDER was looking for, and therefore have studies that don't provide answers to the standard now being imposed.

MS. CARTWRIGHT: We'll just need a moment.

[Pause.]

MS. CARTWRIGHT: So when you say that Genentech was unclear on the standard, you were clear that you were supposed to confirm the magnitude of clinical benefit from E2100?

MR. LABSON: No. We're clear now. We weren't clear then. There's also how is magnitude being defined, hazard ratio focus or we're hearing

this heavy focus on the medians at this point. But I went through the regulatory history. I think it shows there would have been no way for Genentech to have understood that, where -- and, again, they gave AVADO to CDER, the results, and it doesn't match the E2100 results if you focus on the median. So they did not know that before.

DR. BARRON: I think it's important to point out that the AVADO and RIBBON trial were designed with the intent to be able to observe a hazard ratio between .7 and .75, and exceeding that threshold with a positive trial can be described as a magnitude of benefit.

What we're trying to explain is that we have been acting on the belief that hazard ratios were the best way to make cross-trial comparisons in terms of magnitude of treatment effect. And we believe that reflects the entire curve and more data points, and it's the evolved focus on medians that we're debating as new.

DR. JENKINS: I think we showed a slide yesterday of an advertiser from Genentech that

showed that the median progression-free survival from E2100 was a major part of your advertising campaign for that trial. So I'm curious; how can you say that focus on the median is now new?

MR. LABSON: Respectfully, I don't think that was a fair description of that one page out of a visual aid, which presented information on both the median and the hazard ratios with comparable prominence. I would note, too, that was a piece that was submitted in advance because we're under accelerated approval, to DDMAC and it was okayed for use.

DR. JENKINS: Well, I would note, I think all of our slides yesterday where we presented the results of the trials, we presented both the hazard ratio and the median progression-free survival numbers, as did that advertisement. So I'm just curious where the idea ever came from that confirmation of clinical benefit would only be based on the hazard ratio from the trials and not looking at both those pieces of information, factoring it into the benefit-risk analysis.

MR. LABSON: It's not that CDER wouldn't have been expected to look at all the data, including the medians. The point is that only a median of 5.5 months would be considered clinically meaningful. It just was never stated until the 2010 ODAC.

DR. JENKINS: So maybe one of the clinicians on the panel, Dr. Barron or Dr. Horning, can help me understand. If we're just looking at the hazard ratio, how do I put that into a benefit-risk assessment of looking at the toxicities of a drug, and I have a .5 hazard ratio, as one of our presenters noted yesterday, that could mean the difference between 1 week and 2 weeks or 12 weeks and 24 weeks, for example?

So how can I put a hazard ratio into perspective without looking at the magnitude of the median difference in progression-free survival?

DR. REIMANN: You can't. You need to look both at hazard ratios and absolute benefits. But I think it's important to look at absolute benefits in time, not just at the median point, but it's the

overall separation of the curves. It's early benefits, median benefits, and late benefits. And it's true that in CDER's presentations, you include both. But I think it's quite prominent in CDER's conclusions and summarization that the focus moves to the medians.

DR. JENKINS: Can we have up slide -- first I want to go back to the safety issues because you spent some time this morning on the safety issues.

Can we have backup slide 82? This is the boxed warning that's in the Avastin label currently. Do you agree that this is an accurate representation of the serious safety risk for Avastin, including gastrointestinal perforations, surgery, and wound healing complications, and hemorrhage?

DR. HORNING: Yes. As with most agents that are approved in breast cancer, Avastin has a black box warning.

DR. JENKINS: But you agree that these are serious and potentially life-threatening risks associated with the use of this drug that warrant a

boxed warning specifically for Avastin?

DR. HORNING: Yes. We have said that Avastin has serious side effects that are in line with other agents approved for metastatic breast cancer, including a black box warning.

DR. JENKINS: And did Genentech agree to this boxed warning language, or did FDA order you to implement this language for the safety risk?

DR. HORNING: We agreed.

DR. JENKINS: Thank you.

Can we have slide 100 from the FDA main presentation yesterday? Slide 100.

This is the absolute difference in the magnitude of PFS across the trials that have been submitted. Do you agree that these data accurately represent the median progression-free survival seen in these trials?

DR. HORNING: Yes. These are the median numbers that were taken from the Kaplan-Meier curves.

DR. JENKINS: Thank you. And also, slide -- from the main presentation yesterday of

Dr. Keegan, slide 125. This is a slide that was prepared by Genentech, an analysis that was presented by Genentech of the combined results of the survival data from all the first-line treatment trials. So this is E2100, AVADO, RIBBON 1.

Do you agree that this is the slide Genentech prepared?

DR. REIMANN: Yes. This is the slide Genentech prepared. And I think something you need to know is that the data maturity of the studies differed, and that in RIBBON 1 and AVADO, there were very few patients still at risk in the right-hand portion of this curve.

DR. JENKINS: So the hazard ratio for overall survival is accurate at 0.97, with a confidence interval from .86 to 1.08 and a p value of .56? That's accurate?

DR. REIMANN: That is correct. And we have updated data with also the most AVADO survival experience, which I could share if you like.

DR. JENKINS: So you would agree with the statement that there is no demonstrated overall

survival advantage for Avastin in first-line metastatic breast cancer?

DR. REIMANN: Yes. As an efficacy endpoint, there is no statistically demonstrable advantage in overall survival. When it comes to benefit-risk and you're trading off toxicities, then I think looking at early survival or 1-year survival is meaningful.

MS. CARTWRIGHT: Just a moment, please.

[Pause.]

MS. CARTWRIGHT: That concludes our questions. Thank you.

Questions by Advisory Committee and Presiding Officer

DR. MIDTHUN: Thank you very much.

Then we will move on to the next portion, which will be an opportunity for the advisory committee members and myself to ask questions of the Genentech panel.

So questions? Dr. Wilson?

[Pause.]

DR. MITHUN: Can you restart the timer,

please?

DR. WILSON: So I would like to ask several things. Obviously, as a member of ODAC, our focus is going to be on the safety and effectiveness of these various trials, and the regulatory aspect in terms of what happened when is really not going to be our focus.

I think that what I heard from the panel is that you would agree that the magnitude of the effect was an important endpoint, and that therefore is going to be the focus of your confirmatory trial. And so my focus really is going to be on E21 because I think the question isn't whether or not the "confirmatory trials" are clinically meaningful -- because I think I just heard from you that it wasn't, and I think all of us as oncologists would certainly agree that prolonging progression-free survival by less than one month in the AVADO trial does not constitute a clinically meaningful endpoint.

So I think the question at hand, really, is around the confidence that the E21 trial may in

fact not be an outlier. And I think none of us want to lose the possibility that there could be a benefit. However, there are some issues that have come up with regard to this clinical trial, and one of them is that it was unblinded. And we heard data about how blinded and unblinded trials, et cetera, don't necessarily result in biased outcomes.

So what I would like to understand and have Genentech address is the following. In the E21 trial, the median duration of paclitaxel treatment was 5.1 months, and the median time of progression was called at 5.9 months. The median time of treatment for the combined paclitaxel and Avastin was 7.1 months, but progression wasn't called until 11.8 months.

So I see a very large difference between stopping the control arm and calling progressive disease versus stopping the treatment arm and calling progressive disease. And I'm just curious because this could represent investigator bias in terms of when scans were done, looked at,

et cetera.

DR. REIMANN: First let me address the timing of scans issue, and then I'll hand off to Dr. Horning. I think in your preamble you also said that all of us as oncologists would agree that the confirmatory studies don't express benefit, and there I think I would respectfully disagree because the 2.9-month prolongation in PFS in RIBBON 1 and capecitabine we think is meaningful, given the side effect profile and approval in Europe.

If we could bring up the slide on the timing of scans in E2100. As mentioned in my core presentation, the timing of scans was balanced between the control arm and the Avastin arm.

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

So we see here that at the first year assessment, 2.6 months and 2.7 months to the first scan; second assessment, 5.4/5.5; 8.2/8.2; 11.1/11.0; 13.6/13.8. So with that aspect, the scans were balanced.

DR. HORNING: Well, I think the only other

point to be made is that it's not clear that it's appropriate to extrapolate from chemotherapy time from completing treatment to time of progression, to a combination of chemotherapy plus a biologic agent that may have a very different mechanism of action as it relates to the pace and the underlying biology of disease progression. But I do believe that Dr. Reimann addressed your question about the potential bias in scans.

DR. WILSON: Well, actually, no. I think you simply gave me times that these scans were done at, on average. However, that doesn't get into the nitty-gritty of this. I guess my response to the interaction would be that such an interaction was not seen in the AVADO trial, where I would also have expected to see a longer duration of response in the combination arm relative to when the drug was stopped, and I don't think we necessarily saw that.

The second question I wanted to get at was the overall toxicity. We have seen much summary toxicity, and numbers of slides were shown that

indicated that CDER has overstated a number of the known toxicities and that some of these are seen on the control arms as well.

Again, because my focus is the E21 trial because, again, I think that is the trial that most of us would agree shows clinical benefit. With all due respect to Genentech, .8 months in most clinical oncologists' minds is not clinical benefit.

I'd like to turn to the toxicity that actually is reported in the E21 trial. And if you actually look at that, you can see that there is very clear signal of increased toxicity in the treatment arm. In fact, if we look at infection in terms of grade 3 and grade 4, it's 9.3 percent versus 2.9 percent for the control arm. If we look at hypertension, it's 14.5 percent versus zero percent. I would contend that hypertension is not a benign finding; although it may be controlled, it requires the patient to come in for multiple visits, increases anxiety, et cetera.

Cardiovascular ischemia was 1.9 percent in

the treatment arm versus zero percent in the control arm. Hemorrhage was .5 percent versus zero percent in the control arm. And gastrointestinal perforation was .5 percent versus zero percent.

These are the actual data from the actual New England Journal study of the trial that I think we all agree is the main trial that putatively shows that this is an effective drug.

Perhaps you could comment on that in light of your summary data, which at least it was very unclear to me how to look at that data because it seemed like there was a lot of statements that these sorts of toxicities were seen on both arms equally. At least, that's the kind of general sense I got.

DR. HORNING: A number of issues that you've brought up. You yourself mentioned that the time on treatment was longer for the patients receiving paclitaxel plus Avastin versus paclitaxel alone. And I think that as we're looking across the toxicities, we need to think about those that might be related to the underlying chemotherapy, the

combination, or perhaps Avastin alone.

With regard to the summary that was presented this morning, there's no doubt that hypertension occurs with Avastin and doesn't occur with chemotherapy. And we've presented the available data from an expert panel with regard to its management. We've presented data from the CO8 study regarding its reversibility. And we certainly heard from patients yesterday about how troublesome hypertension is to them in their daily lives with management, which I think is probably the best testimonial of all.

We also described that the incidences in the pooled safety data, which I believe is important because it reflects the totality of the data. And when you think about E2100 and when it was conducted, it was very early on in the use of Avastin. And just as with any other medications, physicians become more refined in their clinical judgment as time goes on.

But nonetheless, there are increases, as we mentioned, in toxicities such as bleeding,

congestive heart failure, and arterial thromboembolism that are in the range of a 1.2 to 1.6 percent increase, somewhat more so in the E2100 trial. And the other adverse events are occurring with a lesser incidence, less than 1 percent, and they do occur in the pooled analysis on both the chemotherapy and the chemotherapy plus Avastin arms.

But I have to say that with regard to hands-on clinical experience, probably the person who's best able to describe this for us, for the ODAC panel, for the entire audience, is someone who does this on a day in and day out basis, and that's treat patients with metastatic breast cancer with paclitaxel plus Avastin.

So I'd like to ask Dr. O'Shaughnessy if she could comment.

DR. O'SHAUGHNESSY: Thank you. Obviously, these toxicities are very, very important, no question about it. Hypertension is definitely there. We've learned to recognize it early, get patients on therapies that are very, very well-

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. WILSON: And then my final question --

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

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

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

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

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

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

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

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

DR. MIDTHUN: Yes, Dr. Balis?

DR. BALIS: Thank you.

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

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

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

DR. BALIS: SO the term was used --

DR. HORNING: I'll just also add that these studies were designed with breast cancer investigators, and the feeling at that time was that a treatment effect with hazard ratios in the .7 to .75 range would be clinically relevant in terms of treatment benefit for patients with metastatic breast cancer.

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

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

into clinical benefit that we all believe in?

First-line metastatic is very difficult to show survival advantages, as we heard from Dr. Reimann, because of the duration that most patients live after first line. So survival is difficult.

We would like to have better quality of life measurement tools for symptom reduction and also prevention of symptoms because these are the things that we are tasked with doing for our patients. If we can't necessarily improve survival, or even if we can, preventing symptoms, reducing symptoms, our tools just don't seem to be where they need to be although, frankly, we need greater emphasis on that. No question about it.

So from a clinician, we want agents that definitely perturb the natural history because, as you well know, we're in this transition period from breast cancer trials that have been done with heterogeneous populations, and there's a lot of work going on at the subpopulations that lead to additional hypotheses. So we clinicians are

figuring it out, if you will.

But I just don't think our measurement tools, truthfully, for first-line metastatic breast cancer with regard to clinical benefit, are as well-established as we would like..

DR. BARRON: Can I just add one thing, too? Because I've made some of these comments. And if we could put the slide back up that you had.

I think it's particularly important to address your question. There's no question that you can have a statistically significant effect that's not clinically meaningful. However, it's also possible that you have a statistically significant effect that is clinically meaningful. And the reason we are focused on hazard ratios here is that what you heard -- and Dr. Schenkein's quote supports this.

When E2100 was first unblinded and described to the world, this hazard ratio of .48 is unprecedented. It is extremely robust. We then observed in AVADO a hazard ratio of .62. It is less, but it's only somewhat less. And the point

that we are trying to make is that .62 is a very significant hazard reduction. The studies were planned to have a hazard of .7 to .75 to represent clinical benefit. This far exceeds that.

So all we're concluding, and what we said, is we're not trying to convert E2100 to full approval. We're just stating that we don't think AVADO and RIBBON 1 invalidate the findings of E2100. And this hazard ratio of .62 is exactly why we state we don't think it invalidates the findings of E2100.

DR. BALIS: So I think at the end there we talked about getting down to that last question as to what we do in terms of proceeding forward with the current accelerated approval while you potentially study the drug. The way that I took what was being said from that discussion was that if we're unsure, then we shouldn't withdraw the approval. We should conduct a study to make sure that we are sure.

So my question to you, as having looked at this data better anybody, are you sure or are you

unsure as to whether this drug provides a clinical benefit that outweighs the risk of the drug?

DR. HORNING: Well, as provided on my assessment slide of clinical benefit-risk, we are saying that Avastin plus paclitaxel in first-line metastatic breast cancer provides a favorable clinical benefit-risk. And we say that on the basis of the E2100 results. It's a well-conducted study, robust results; that AVADO and RIBBON 1 do not invalidate these results. And we have a safety profile with no new findings.

So the E2100 results have not changed, and the safety profile has not changed. And we feel that the favorable clinical benefit-risk ratio, the favorable clinical benefit maintains for paclitaxel plus Avastin.

MR. LABSON: I would just add from the regulatory perspective that we're not saying accelerated approval should be maintained just if one is unsure, but because the data show that there's a reasonable likelihood of benefit. And it's really based on that as the standard that's in

the law.

DR. MIDTHUN: Dr. Sekeres next, and then Ms. Portis.

DR. SEKERES: Thank you so much. I was hoping to focus on two areas.

Would it be possible to put up slide 97 from the company?

I wanted to talk a little bit about overall survival because I think when we're talking about the effects of Avastin combinations, there are a couple of different focuses we've had during this meeting. One has been on what is the minimal acceptable effect to get approval from the FDA, and we've talked about median progression-free survival and hazard ratio. And then there's the effect that's going to be a benefit to patients that we can measure.

At the last ODAC when we met about this issue, almost a year ago, we talked about progression-free survival and how, if that were paired with patient-reported outcomes that were also positive, that may be a beneficial effect to

patients. In the absence of that, the gold standard for effect is overall survival, and that a progression-free survival without patient-reported outcome or quality of life improvement and without overall survival may just by a Pyrrhic victory.

So I was hoping to gain some insight into this slide. Was the point of showing this to say that it would be impossible to do an overall survival study in first-line metastatic breast cancer?

DR. REIMANN: No, that's not the point of the slide. And I just want to address your whole question because you talked about patient-reported outcomes and survival and PFS.

I think, first, we believe that a large magnitude of PFS benefit is clinical benefit in this setting. And we've heard that from FDA, that a large magnitude of PFS benefit is clinical benefit. We realize that there are some other perspectives out there, but that's the guidance we have from FDA.

The point of this slide is to say that in

the front-line setting, most studies performed by Genentech or performed by any other sponsor that typically have sample sizes of 500 to 800 patients are not optimally powered for survival. They do have a certain amount of power, and I'm not in any way suggesting we go to lowest common denominator studies of 2- or 300 patients. That's not the intent here.

What I'm saying is that there could be a real survival benefit, and you're not going to be able to detect it because of the dilution effect and because of the variability. And I think a four-month prolongation in median overall survival would be very important. It's on the order of what was seen with Herceptin in first-line metastatic breast cancer, but we see that in order to detect that magnitude of benefit, we would need studies on the order of 1500 to 2300 patients.

It's doable. It's just they're very big studies. And when we consider that PFS of a large magnitude has benefit on itself, we have to question where we're expending our patient

resources.

DR. SEKERES: So again, I think we're mixing a little bit about a regulatory threshold with what's a direct benefit to women. To say to a woman, congratulations, you haven't progressed with your breast cancer, in the absence of having any quality of life improvement, still remains a Pyrrhic victory to me. And conducting a study of 2,000 women powered on overall survival when, as you pointed out, there are 45,000 women diagnosed with this in the U.S. each year and many-fold more than that internationally, doesn't seem impossible. To me it seems like the right thing to do.

I also wanted to move on.

Dr. Horning, you asked us if there's one slide we should remember, it should be this one. And I actually remembered it, slide 26 from the presentation.

So when you talk about fewer total deaths, could you just clarify for me, are those deaths on study?

DR. REIMANN: That's deaths at any time. We

do survival sweeps, but not on study. It's any time.

DR. SEKERES: So you continue to record deaths after a patient has gone off study and gone on to other therapies?

DR. REIMANN: Yes. So the death events come from the overall survival analysis, where you assess all deaths, whether on study -- technically speaking, the patients are still on study because they still have survival follow-up.

DR. SEKERES: So on the E2100 study, there are still 25 to 30 percent of women who are still alive?

DR. REIMANN: The definitive analysis of overall survival on the E2100 was 481 deaths. And so your percentage is approximately correct.

DR. MIDTHUN: Dr. Freedman?

DR. FREEDMAN: Thank you.

Dr. O'Shaughnessy mentioned the fact that triple negative is highly symptomatic in most patients. I think that's correct. And also that improving or decreasing patient symptoms with the

least amount of toxicity is a major objective. And yet we didn't see any of this in the studies.

I just wondered -- my first question is what you feel about that, the results without that representing clinical benefit.

DR. O'SHAUGHNESSY: I think one of the important approaches is to look at these patients who we know clinically have a lot of symptoms. Like the triple negative is, arguably, the patients with HER2-negative disease that collectively have the highest burden. It's just the tempo of their disease and the sites of metastases.

When you see nice benefits in PFS in those patients and higher response rates, you can be pretty certain that that's translating into clinical benefit in those patients, just because the burden of disease is so great in those patients. So that to me makes it that easy.

The aggressive ER-positives, though, we don't want to forget them, very, very virulent disease, with a natural history almost as bad as triple negative disease. Heavily burdened. It's

the indolent ER-positives that live without symptoms for long periods of time.

DR. FREEDMAN: Were you disappointed not to see any symptom improvement in this subgroup of patients presented from this trial?

DR. HORNING: Let me just preface that by saying that certainly quality of life is extremely important for patients, and it's very important for the physicians who take care of them. And we do not have quality of life data that meet CDER's standards from our first-line metastatic breast cancer trials. Actually, meeting the standards is very difficult because we don't have validated instruments and because there are always issues of missing data based on patient death and progression.

If you actually look at the record for being able to determine quality of life to the place where it can be acceptable in the U.S. product labeling, the track record -- if we could show the slide -- for metastatic breast cancer is as it is, which is that in all of these agents that are

approved, quality of life was included in the studies.

But with regard to the limitations that we have with the instruments, with missing data, and the fact that in first-line metastatic breast cancer, many patients who actually enter the trials are not currently symptomatic, we're not able to do those. Nonetheless, quality of life is an extremely important measure, and we will be including quality of life measures in our planned confirmatory trial.

DR. FREEDMAN: My next question is related to the future trial, the proposed trial. And, obviously, the results of E2100 are the basis for this trial, for the parameters that you use there.

You got a response rate of 21 percent for weekly paclitaxel. And again, I ask Dr. O'Shaughnessy, is that what you would expect in a population of patients who had metastatic breast cancer who had limited, fairly limited, prior exposure to Taxol as an adjuvant, of course, only? Just wondering what -- and also if you consider

that the control arms of the subsequent studies had much higher responses. And I'm just wondering how relevant or significant the difference between the control arm and the study arm actually is.

DR. O'SHAUGHNESSY: I believe the data on E2100. I'm not surprised by the 21 percent on the weekly paclitaxel. These trials, as you know, have various patient populations. E2100 had 32 percent triple negative patients. Two-thirds had had adjuvant chemotherapy. I'm not surprised. Of course, there'll be variability around that point estimate, of course. But no, I'm not surprised by that.

DR. FREEDMAN: But generally speaking, you would expect a higher response rate with weekly paclitaxel.

DR. O'SHAUGHNESSY: Not necessarily.

DR. FREEDMAN: All right. Let's consider, then, that we had information about the treatment-free interval on these patients. And I asked the question yesterday, actually, and probably could bring it up again today, is do you have data, does

Genentech have data, on the difference in response rate in those patients who were less than 12 months with a treatment-free interval, in other words, indicating some degree of resistance to Taxol, potentially?

DR. O'SHAUGHNESSY: No.

DR. FREEDMAN: Thank you.

DR. MIDTHUN: I think, Ms. Portis, you had a question?

DR. PORTIS: Just following up on a couple things. I very much appreciate the testimony we received yesterday from patients, but I want to remind us all that we are not hearing from patients who discontinued treatment due to adverse effects, and we're not hearing from people who died due to Avastin. And I think the risks are still significant. And I know now we're talking a lot about E2100.

So my first question is, would you say that you then consider that E2100 was a success despite the fact that there is missing data, there's discrepancy of interpretations of the scans, there

is no quality of life data, and there is no improvement in overall survival? I hear people keep talking about no impairment of overall survival, but what matters to patients is improvement in overall survival. So that's my first question.

DR. HORNING: Let me begin, and then I'll ask perhaps Dr. Reimann to join in. I think that with regard to the comments about the toxicities of treatment for first-line metastatic breast cancer, they're well-taken. And as mentioned in my presentation, if we look across all of the metastatic breast cancer studies, the treatment-related mortality for standard dose Avastin plus chemotherapy versus chemotherapy is identical, 1.8 percent and 1.8 percent.

So, unfortunately, there are patients who have treatment-related deaths due to chemotherapy or chemotherapy plus Avastin. In this series, it was equal.

We also recognize that there are differences of opinion with regard to whether or not

progression-free survival of a sufficient magnitude provides direct clinical benefit. It's our view, and it was CDER's view as expressed yesterday and is CDER's view, I believe, that in first-line metastatic breast cancer, progression-free survival of sufficient magnitude without a statistically significant improvement in overall survival or quality of life data provides direct clinical benefit.

With regard to E2100 and some of the issues that Dr. Reimann addressed in his presentation today, I'll ask him to complete your question.

DR. REIMANN: I think your question was more about the magnitude of efficacy in E2100. And, yes, we do feel that the study was a big success, just like many other cooperative groups, that has led to labeling for the medication.

I think the aspects of it I think are important, the large benefit in progression-free survival, doubling an objective response rate. And really, every way we've looked at the data through sensitivity analyses, we see a similar magnitude

effect. And so we know this is a solid study, and we believe the study will be confirmed.

As far as overall survival, as I discussed in my presentation, I think it's specifically challenging in the first-line setting. That doesn't mean we shouldn't try it, but I think the long post-progression survival makes it difficult for this or any agent to demonstrate benefits. I think all of us like four months; we think it would be important.

Really, I think it's the impact of multiple medicines over multiple lines of therapy that will move survival forward. And we've seen that in the epidemiological data. You can't attribute that to any specific drug. It is epidemiological data. But I do really feel that over the last 20, 30 years, we have made progress.

DR. BARRON: Can I just add one more point that I think is important? It's absolutely true that there was no statistically significant improvement in overall survival in E2100, as you point out. But it is important to note that the

hazard ratio was, I think -- maybe we could pull it up -- .87, with a p value of .14.

You've heard the challenges in powering trials to show statistical significance. And I think it was one of the people who made a testimonial yesterday who said something that I think we need to remember, which is, the absence of evidence is not evidence of absence. These observations, had they been powered, may -- or may not; we can't know for sure -- demonstrate a survival advantage.

What we see at one year is a 7.4 percent absolute benefit in terms of overall survival, with confidence intervals that exclude zero. We can't ignore that data point. Maybe we can bring up the slide. You've seen it.

I don't mean to disagree with the statistical fact because it's absolutely correct that we have not seen a statistically significant improvement in overall survival. But I do think that the data is most consistent with benefit rather than no benefit. And we just need to take

into account and understand fully the comments that Dr. Reimann made about the challenges in interpreting underpowered assessments.

DR. PORTIS: The 1.8 that you mentioned, that's over what period of time?

Dr. Horning, you used that number, 1.8, of survival.

DR. HORNING: So we just talked about the safety assessments and when they were made. It's the same time period.

DR. PORTIS: Just a couple other things. So you continue to maintain that the risks are low, both adverse events and death and early death due to treatment with Avastin. And so my question is, are you saying that you're comfortable with a risk for patients in continuing to administer Avastin, especially if potentially this study that you're talking about wouldn't be completed until at least 2016? And are you comfortable with women continuing to bear those risks and the deaths that may come about with that much more time studying this drug? Because I think part of what I thought

we did in July, those last studies -- it sounds like we're not talking about that much right now -- were supposed to give us more data.

DR. HORNING: Absolutely. We're very comfortable with this because, once again, the deaths are not any different in the experience with our first-line metastatic breast cancer in terms of treatment-related mortality. And there are fewer deaths overall with E2100. So yes, we're comfortable.

The numbers are 52 percent deaths -- excuse me -- 70.5 percent deaths on E2100 versus 73.9 percent with paclitaxel alone. Yes, could you put the slide up? And clearly, Avastin does have serious side effects. We acknowledge that, and we think that those side effects are in line with other treatments for first-line metastatic breast cancer.

We also feel that the product guidelines serve to guide physicians in the management, and the fact that oncologists who are treating patients with breast cancer have a lot of experience with

Avastin because they're also treating patients with colorectal cancer and lung cancer. More than a million patients have been treated worldwide.

Perhaps I could ask Dr. O'Shaughnessy to also address your question again because she has such great experience in treating metastatic breast cancer.

DR. O'SHAUGHNESSY: Yes. I would really have to say to you that I'm very, very comfortable with the safety. We've heard very, I think, exhaustive data here about the death rates and the safety, and I am personally very, very comfortable with it.

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

DR. MIDTHUN: Dr. Logan?

DR. LOGAN: So I wanted to pursue the issue of the reliability of the magnitude of the PFS benefit that is claimed for the E2100 study. You previously showed that there are comparable analyses with the investigator progression versus the independent review assessment of progression.

My question is, how is the missing data handled in that analysis, particularly when patients had been identified as reaching investigator progression, which was unconfirmed by the Independent Review Committee, and then their subsequent missing scans? Were they censored at that point?

DR. REIMANN: Yes. So let me address it. Let me explain first the endpoint. There were cases, as with any independent review, where the investigator progression is not confirmed by the IRF. That's the reality of doing studies with an independent review, because patients are generally managed by the investigator's assessments, so once there's progression by investigator, you don't get additional scans.

Actually, this is an aspect we're building into the confirmatory study, so we will be continuing to collect tremor assessments even after the investigator progression until their second progression.

In E2100, we performed a sensitivity analysis where, if the investigator progression was not confirmed, we used the last available scan data plus one day as the progression day. And the hazard ratio for that is .46, and the absolute benefit went from 5 months to 9.2 months, which is a 4.2-month difference.

DR. LOGAN: I'm a little concerned about -- there may be some modest differences in the investigator progression not being confirmed by the independent committee between the control group and the Avastin group, from 15 percent versus 9 percent. That's modest, but there may be some sensitivity analysis that should be considered there.

So have you done additional sensitivity analysis? The FDA indicated that the range of

possible effects, in terms of the hazard ratios for progression-free survival that the sponsor had done ranged between .48 and .78. I wonder if you could confirm that.

DR. REIMANN: Yes. As FDA said yesterday, there are a variety of sensitivity analyses and they differ considerably.

If I could have the slide that was just there a moment ago.

I think you have to distinguish between sensitivity analyses that treat both treatment arms fairly and sensitivity analyses that treat one treatment arm different from the other.

If we could have the first table of results, where we treat the two treatment arms equally. It was just there a moment ago.

In that analysis of using a number of different analyses that treated the two treatment arms equally, we see no difference in the hazard ratios, and we don't see any difference in the medians. In analysis where we --

Yes, this is the slide, please. No. Let's

use this one.

So first we'll start with analysis that treat the two arms equally. So that would be the first two slides on the -- the two lines on the slides. We see clinical progressions. This means we are basing the decision based on radiographic progression, and the next one is no censoring for non-protocol therapy.

In these two analyses -- and we have a number of others that treat the two treatment arms equally -- there is no difference in hazard ratios. You see they're all very similar, around high .47 or low, .5. And the difference in absolute benefit is not shown on this slide, but it's about 5 months.

The other question you asked was, was there some sort of worst case analysis for progressions not confirmed by IRF? That's the bottom row of this table. In this case, we now don't treat the treatment arms equally. And in the control arm, the paclitaxel arm, you see the results are the same, and then the results come in for the Avastin

arm. In this case, you have a hazard ratio of .6, a confidence interval from .49 to .74, and it was very highly statistically significant.

If we go to an even more extreme analysis, which is patients not confirmed by the IRF or came off of study for any reason, then the hazard ratio is .78. Now, we do appreciate that that's a very extreme analysis and that point estimate doesn't really reflect truth, but it does show that even in that extreme analysis, there's still a treatment effect.

DR. LOGAN: So I understand, of course, the issue with the missing data is you don't know whether you should be treating them in with the extreme case or whether you should be treating them equally. And that certainly casts some questions, I think, about the reliability of the magnitude of the benefit.

DR. REIMANN: I think what's striking to me is when we look at all these issues that were raised, the frequency with which those issues are occurring in the control arm and the Avastin arm

were equal in almost every case. So from that perspective, there was no evidence of bias.

DR. MIDTHUN: I'd like to ask a few questions. We've had a lot of discussion about progression-free survival. I'd like to ask you, what do you think the magnitude of effect for progression-free survival should be to translate into a clinical benefit for Avastin?

I think, also in that, just consider the comment you made earlier, for example, that you accept that the EMEA was through the indication for using Avastin together with docetaxel.

DR. HORNING: I think that looking at, if you will, the hazard ratios and median PFS, that hazard ratios that are below a level of .7 and progression-free survivals that are in the range of the Ribbon 1 capecitabine results, which was 2.9 or about 3 months and above, have traditionally fit the bill, if you will, for approvals in first-line metastatic breast cancer.

With regard to our plan for the confirmatory study, as you heard from Dr. Reimann, listening to

what we heard from CDER and from the ODAC, we, in fact, are raising the bar.

DR. MIDTHUN: Thank you.

One other question I have, I believe that you had mentioned in some of the materials you submitted that if the accelerated approval were continued, that you would certainly contemplate label changes, and perhaps a REMs or some other items. And I just wondered if that was, indeed, the case.

DR. BARRON: Yes, it is.

DR. MIDTHUN: I'd like you to submit that to the docket, if you would, please, what your proposal would be, by July 28th.

One other question I had was I noticed that you indicated that there was approval in many, many countries for Avastin. And it seemed that there was a little bit of blackness over there on the right-hand side. And I just wondered, is it also approved in Japan?

DR. HELTERBRAND: It is under review right now in Japan.

DR. MIDTHUN: Okay. Thank you.

One other question I had was this. What I've heard is that there was agreement at the time of the accelerated approval that AVADO and Ribbon 1 could serve as the confirmatory studies. But I wondered, at the time those were actually initiated, which pre-dated the accelerated approval by quite some time, in what context they were submitted to the agency.

DR. HORNING: The regulatory history, I believe, is that the E2100 results had been submitted. And there was a request from CDER as to whether any other data would be available. And at that time, the AVADO study was actually complete. And we, as you've heard, shared the top-line data from AVADO at that point in time, at the time that the accelerated approval was granted.

With regard to the Ribbon 1 trial, that was submitted to CDER in 2005. There was advice from CDER about independently powering the capecitabine cohort. And then, as you've also heard, the acceptance of Ribbon 1, together with AVADO, as

potentially confirmatory studies.

DR. MIDTHUN: One other question, I think you also had in your submission to the docket, and I just wanted to make sure I understood this correctly, that if the accelerated approval were not withdrawn, while you conducted this additional trial, that you would continue the cessation of affirmative marketing for this indication. And I wanted to ensure that my understanding was correct in that regard.

DR. REIMANN: We'd certainly be willing to talk to CDER about that, as if we could come to some sort of a middle ground solution that worked to keep the drug as an option for patients.

DR. MIDTHUN: Any questions, Dr. Wilson?

DR. WILSON: I just very briefly wanted to go back to the overall survival because we've heard several times about an increased percent of patients being alive at one year.

On the CDER slide -- could we have slide 58 up? I just wanted to show this. Actually, I want number 58 -- 60. I'm sorry, number 60.

So this is the prespecified overall subgroup analysis. And I think that one has to be very careful about at what points one indicates an improvement in survival, because here you can actually see that the treatment arm is actually performing inferior.

Then the final slide would be slide number 125. And, again, we've seen this multiple times. But, again, you can see that, depending on where you look at this, it can favor the placebo or the treatment arm. So I just think one has to be very cautious about giving data at one year, because it doesn't give the full picture. It is possible that this actually may worsen outcome in some folks. Thank you.

DR. REIMANN: I think there was a question there, so I just want to make sure I address your question, because there were a number of things that flashed up.

There was the survival results for the Ribbon 1 taxane cohort, or maybe it was the docetaxel subcohort. And I think we have to be

very cautious at looking at very small subgroups, especially here. There was a 2 to 1 randomization in quite a small control arm. And I think in CDER's own internal review document, their conclusion was that this was an unreliable finding and that you shouldn't have too much emphasis on that. That was actually within their review document.

As far as the pooled overall survival as curves, as I showed earlier, the maturity for the AVADO and Ribbon 1 studies on the right-hand side of the curve isn't there. For example, that three years; there's 4 patients at risk in those studies. I do believe that the results in E2100 are meaningful in the early period. And in 3 out of 4 studies, we saw a favorable overall survival at one year.

DR. MIDTHUN: Dr. Sekeres?

DR. SEKERES: Sure. Thank you. I just wanted to comment on something that Dr. Barron said. You were referring yesterday to one of the many brave women who got up and talked about her

experience, and referred us back to the lack of evidence is not evidence of lack, and then referred to the survival curve from the E2100 study.

Could we see that survival curve?

So in the survival curve, your point was, even though it wasn't a statistically significant difference, there's a chance that the arm containing Avastin could provide a survival advantage, and thus the reference to the quote from yesterday.

Could we now see, from CDER's presentation yesterday, slide 41?

So in this curve, again, a non-statistically significant difference, but this time the patients who were on the placebo arm seemed to have a better survival advantage. You could just as easily make the argument here that treatment with Avastin actually shortens survival.

So I think it's important that we make the point that lack of evidence is lack of evidence. There's no survival advantage with Avastin.

DR. REIMANN: Just to respond to your

question in two ways, I think, from the purpose of an efficacy endpoint, we're not making the claim of improved overall survival. It's really in the context of overall clinical benefit-risk that we think this should be discussed.

But since the AVADO data has come up a number of times, I did want to share the most recent survival data from the AVADO study, beginning with the standard dose arm.

Yes. Data; hazard ratio from the standard dose arm in AVADO has a hazard ratio of .97.

Yes. If you could, show this please.

DR. CARTWRIGHT: Excuse me. We just wanted to note that the light is red, and also that CDER has not been made aware of this data.

DR. MIDTHUN: I think we will have to call this to a close. Thank you very much. And we will now break for 15 minutes, and that will give an opportunity for us to regroup before the next session. So in 15 minutes, which will be 12:30, we'll resume.

(Whereupon, a recess was taken.)

DR. MIDTHUN: We will now convene to the last portion before lunch. I think, first, Ms. Cartwright would like to make a clarification, and then we will go onto the 15-minute clarification session. Ms. Cartwright?

MS. CARTWRIGHT: Thank you. I just wanted to note for the record that CDER believes that the information Dr. Reimann was about to present was submitted to CDER in 2010. Thank you.

Clarifying Questions of

Genentech Witnesses by Genentech

DR. MIDTHUN: Thank you. So now, we will go onto the clarifying questions, and there will be 15 minutes for that opportunity.

MR. SCHMIDT: We appreciate that clarification as well. Just a few clarifying questions.

Dr. Reimann, I'd like to ask you the first question. You were asked by Dr. Logan about sensitivity analyses for E2100. And I'd like to ask you what you think are the most appropriate sensitivity analyses to use to characterize the

robustness of the magnitude of effect in E2100.

DR. REIMANN: Thank you. If we could bring this slide up. I think there are two questions that we look at when we're looking at sensitivity analysis. One is around the magnitude of effect, and one is around whether there is an effect. And I think when looking at magnitude of effect, it's best to look at analyses that treat the two treatment arms fairly. And that's what I'm showing in this slide here. And I'll walk through each of the rows of the table.

In each of these analyses, the first two rows of the analyses you mentioned in your question, we have the primary PFS analysis by the independent reviewer hazard ratio of .48; then we have the investigator PFS hazard ratio of .42 and absolute benefit in medians of 5.6 months.

The next one is an analysis where we do not censor for non-protocol therapy. So this non-censoring for non-protocol therapy was part of the study analysis plan and agreed with the FDA. It's also a standard practice in the United States and

has been included for the product labeling for Tykerb and Ixempra. So this is a standard sensitivity analysis. We do not censor for non-protocol therapy.

What we see here is a hazard ratio of .57 and an absolute difference in medians of 5.1 months. The next row I think really comes to your question, which was investigator progressions that were not confirmed by the independent review.

Here, you see the hazard ratio is .46, very similar to the primary result, and you see the medians in both treatment arms come shorter, because now we're imputing events one day after the very last tumor assessment in both arms. So that's kind of a very conservative thing to do, but it's doing that in both treatment arms.

The reason you see that the number, .46, is slightly stronger than the .48 of the primary result is that there was slightly more censoring of that reason in the control arm, which you noted in your question.

So what that would tend to do is censoring

on the control arm would tend to bring up the PFS curve in the tail, which I think you see a little bit after eight months in the couple of markers; you see progression-free survival coming up on the control arm.

The last row of the table is progression-free survival using the radiographic data only, so that's not using the clinical exam. There we see because you're only using some of the data, the medians move out in both arms.

But in all of these analyses that treat the two equal treatment arms fairly, we see a very similar hazard ratio to the primary result and a very similar absolute benefit. Then the other analysis that I showed you earlier really gets to the question about was there an effect under extreme assumptions.

If we could bring up the next slide?

So it's very important to explain what this analysis is doing and what it's not doing, because it's treating the two treatment arms very differently. You see in the control arm,

paclitaxel, the median PFS is 5.8 months in both analyses. So if a patient comes off study for non-protocol therapy or any other reason, they remain censored in this analysis, in the control arm.

In the Avastin arm, the moment they come off study for any reason, one day after they've come off study, they're immediately assumed to have an event. So this is very extreme, and, of course, it's unrealistic, because we saw in my main presentation, a lot of these issues were balanced almost identically by treatment arm.

But I think what this functions is, as an extreme analysis of whether there is a treatment effect. And even under this extreme analysis, we see a statistically significant effect.

MR. SCHMIDT: Dr. Horning, many of the questions focused on E2100 and the benefits in E2100. Why is it that you are confident that E21 represents real and meaningful clinical benefit?

DR. HORNING: We're confident that E2100 provides direct clinical benefit. This clinical benefit is in line with what we heard from CDER

yesterday, that PFS of a substantial magnitude defines direct clinical benefit for patients, even without a statistically significant improvement in overall survival or quality of life.

E2100 was a well-designed, well-conducted U.S. study. It was sponsored by the National Cancer Institute in this country and conducted by a leading cooperative group. On the safety side, we have fewer total deaths, fewer MBC deaths, and the same number of non-breast cancer deaths with E2100.

The common risks, hypertension and proteinuria, are manageable. There are product guidelines in our label that allow physicians to use this safely. Avastin has been widely used, and the serious adverse events are in low incidence. We feel on the safety side that Avastin is in line with other agents used in this indication, first-line MBC, and most of those agents also have black-box warnings.

On the efficacy side, we have a treatment effect in progression-free survival, a hazard ratio of 0.48, that represents more than a 50 percent

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

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

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

MR. SCHMIDT: Final question to Dr. Barron.

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

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

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

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

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

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

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

A F T E R N O O N S E S S I O N

(1:50 p.m.)

Advice and Recommendations from

Advisory Committee Members

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

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

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

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

issue. And after that, I will ask them to state how they voted and why. We will then repeat that process for the remaining issues. All of the members of the committee, except for the member whose role is to represent the views of industry, may vote.

As I noted in my opening statement, the vote of the advisory committee represents the committee's recommendation of the agency and will not, of course, decide the issues. Instead, Commissioner Hamburg will consider the advisory committee recommendations, along with the rest of the record, as she makes the final decision.

So if we could now please put the issues up, I will go through them.

First, as a reminder, in each question, the indication that is at issue is the one that has been the subject of this hearing; the use of Avastin, in combination with paclitaxel for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer.

Question 1. Do the AVADO and Ribbon 1 trials fail to verify the clinical benefit of Avastin for the breast cancer indication for which it was approved?

A yes vote means you find that the AVADO and Ribbon 1 trials failed to verify the clinical benefit of Avastin for the breast cancer indication at issue in this hearing. CDER asks for a yes vote. Genentech asks for a no vote.

Question 2(a). Does the available evidence on Avastin demonstrate that the drug has not been shown to be effective for the breast cancer indication for which it was approved?

A yes vote means you find that the available evidence demonstrates that Avastin has not been shown to be effective for the treatment of the breast cancer indication at issue in this hearing. CDER asks for a yes vote. Genentech asks for a no vote.

Question 2(b). Does the available evidence on Avastin demonstrate that the drug has not been shown to be safe for the breast cancer indication

for which it was approved and that Avastin has not been shown to present a clinical benefit that justified the risks associated with use of the product for this indication?

A yes vote means you find that the available evidence demonstrates that Avastin has not been shown to provide a clinical benefit that justifies the risks associated with its use for the breast cancer indication at issue in this hearing. CDER asks for a yes vote. Genentech asks for a no vote.

Question 3. If the Commissioner agrees with the grounds for withdrawal, set out in Issue 1, Issue 2(a), or Issue 2(b), should FDA nevertheless continue the approval of the breast cancer indication while the sponsor designs and conducts additional studies intended to verify the drug's clinical benefit?

The Commissioner will reach this issue if she concludes that the grounds for withdrawal or approval set out in one or more of the previous issues has been met.

On this question, a yes vote means you find

that available evidence nevertheless justifies the continued approval of Avastin for the indication at issue in this hearing during the time that will be necessary to design and conduct additional studies to verify the drug's clinical benefit.

A no vote means you think that the available evidence does not justify that continued approval, so that any further investigation of this drug for this use would be conducted under an investigational new drug application. Genentech asks for a yes vote. CDER asks for a no vote. I apologize for the typo there.

So now, those are the issues. And so what I would now like to do is go back to Question 1, and we will now discuss this issue. And after we've discussed and questions that you have, have been answered, we will then move to vote. But right now, it's open for discussion.

Dr. Curt?

DR. CURT: Thank you, Dr. Midthun.

Accelerated approval is not the ultimate goal for any sponsor; it's full or regular

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

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

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

DR. MIDTHUN: CDER panel?

DR. PAZDUR: What we could say is the

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

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

DR. MIDTHUN: Does that answer your question?

DR. CURT: Yes. Thank you.

DR. MIDTHUN: Yes. Dr. Wilson?

DR. WILSON: I think that what ODAC was asked to look at, at our last meeting, was the totality of the data, because at the end of the day, I believe what we're here to adjudicate is whether or not we feel that the original study has been confirmed.

My reading of the AVADO and Ribbon studies,

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

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

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

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

DR. MIDTHUN: Other comments? Dr. Logan?

DR. LOGAN: Well, certainly, there's a number of ways of measuring clinical benefit. I just want to address each of those in turn. First of all, survival is the clearest determination of clinical benefit, and this has been skirted around the issue by the company in a number of ways.

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

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

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

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

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

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

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

DR. MIDTHUN: Dr. Balis?

DR. BALIS: I think that this question could have been worded in two ways. The other way it

could have been worded is do these two trials invalidate the results of the first study?

I think the answer to that primarily gets down to the hypothesis presented as to whether this was a combination-specific effect. That is, that it was an effect that was seen with paclitaxel; it's not going to occur with other drugs.

Clearly, it's difficult to make that decision with the amount of data presented here. And I think that question relates potentially more to the last question we're going to address than maybe it does to this one, as to whether we continue to believe the results of the first study, and therefore think that, at least in one setting, there's potentially some benefit, or do we take the data as a whole here and say that, since we couldn't confirm that in the additional studies, then there must have been something wrong with the first one.

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

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

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

DR. MIDTHUN: Thank you.

Dr. Freedman?

DR. FREEDMAN: Now, I think a lot of this revolves around what efficacy means, and what does it mean to the physicians, and what does it mean to the patients. It cannot be an abstract or statistical concept by itself. The statistics certainly help to support or refute. But in this case, we've got a number of trials which were put forward, which were put forward in order to verify

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

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

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

the toxicity information is quite known.

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

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

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

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

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

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

DR. MIDTHUN: Dr. Sekeres?

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

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

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

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

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

statistical perspective, and I understand how progression-free survival can vary slightly, depending on what exactly is happening to the curves and whether they're pinching in at exactly the median or not. It won't vary significantly.

But I'd actually like to ask Dr. O'Shaughnessy a question, if that would be okay.

No one in this room would doubt that you're a fantastic breast cancer doctor. How would you explain to a patient a hazard ratio of .6 for progression-free survival when you're consenting her for chemotherapy?

DR. O'SHAUGHNESSY: The way I understand progression-free survival is I really have grown up always looking at the entire curve. And what that means to me and to my patient is that at any time along that curve, the average reduction in her risk of progressing will be 40 percent, for example.

I don't discuss medians with patients. I mean, I really don't. I just say, the data show -- obviously, I'm making a recommendation to

her based on her individual disease, of course, but my opinion is that you've got the kind of disease that would likely benefit. But for every step along that curve, no matter where you end up being -- because I don't know where she's going to end up being -- that she's going to have whatever that relative reduction in risk of progression is.

So I'm a total curve person.

DR. SEKERES: So I'm trying to think this through practically because I see patients just like you do and have these sort of conversations about the relative benefit of a therapy.

So if I were a patient hearing that, and I heard a 40 percent reduction at any point in that curve, I would think, gee, well, that sounds like it's 40 percent less likely that my breast cancer would come back.

DR. O'SHAUGHNESSY: No, no. In terms of the likelihood of progression, length of progression-free survival, so keeping the disease under control. It's a disease-control issue. How long will it be before I have to face a bad scan?

DR. SEKERES: So how long would it be? That sounds like a time of progression-free survival, which gets to a median.

DR. O'SHAUGHNESSY: No, no; at every point along the curve, though, because we don't know whether she's going to be a median, or a quick progressor, or a late progressor, but the average reduction in her risk of progression is going to be 40 percent at any time along that curve.

So I don't know where she's going to fall, but it's so meaningful to patients to have a scan that's okay, so she doesn't have to go onto something else. And that's important. And that's something that isn't in our classical clinical benefit list, but that's important.

But the main reason I recommend it to a patient is I think that for her particular disease, that that progression-free survival is going to be meaningful to her in the context of her risk for symptoms or other -- and organ failure.

DR. SEKERES: Again, I agree with you. I would have explained progression-free survival the

same way. I think my patients, at least in my experience, need something else to hang onto. Hearing they have a 40 percent less chance at each time they get a scan isn't going to satisfy somebody. They're not going to walk away from that interaction thinking, okay, so I have how long before my breast cancer comes back.

In terms of meaningful to patients, at face value, that seems like that would be true, yet the quality of life studies that have been conducted adjunct to the therapeutic aspects of the trials haven't validated that at all.

So I'm done with my thinking about this. Thank you.

DR. MIDTHUN: Ms. Portis?

DR. COMPAGNI-PORTIS: I know that this is a very emotional issue, and I concur with what Dr. Balis said, that any amount of time is meaningful for patients. And yet, what we have to do today is respond to the research that's been presented to us.

I think, after the E2100 studies were

presented, there was reason for many to be hopeful, despite the shortcomings in that research that we discussed at that time. And I think we all wanted Avastin to succeed. And the reality is, these studies that we're talking about here in Question 1 did not confirm that. These studies didn't bear out this hope.

Certainly, .8 months of progression-free survival doesn't translate into a better quality of life or more overall survival, even if that survival is short, which is meaningful to patients. I think that these studies absolutely didn't bear out that hope.

DR. MIDTHUN: Dr. Wilson?

DR. WILSON: I wanted to go back to a statement Dr. Balis made, which I thought was an interesting one. And that is, do these studies not support, invalidate the results of E2100 or simply not support it?

I think that's a real key issue here because it really gets at the fundamental basis of how the accelerated approval system works.

Accelerated approval, as you all know, is a mechanism to bring drugs forward that look to have reasonable likelihood of helping, but for whom we don't have adequate medical or statistical certainty of clinical benefit. And the only way that we're going to be able to do that in a reasonable fashion is to be mindful of the studies that follow. And if those studies confirm, then the drug becomes full approved. If those studies do not confirm, then statistically we have multiple studies. The original one, which was only conditional, has not been shown to be confirmed, and, hence, I don't believe it's a matter of proving or disproving the original study. It is simply, as has been said here multiple times, the totality of the data.

If, in fact, we always start to second-guess without compelling reasons the follow-on studies and say, well, maybe the original one was right and the following ones are wrong, we basically may as well give up the accelerated approval, because as was said, we're going to get multiple bites at the

apple, and I don't think that's in the patient's best interest.

DR. MIDTHUN: Are there any other points for discussion before we move on to vote?

[No response.]

DR. MIDTHUN: If not, then I will ask you to vote. Again, a yes vote means that you find that the AVADO and Ribbon 1 trials failed to verify the clinical benefit of Avastin for the breast cancer indication at issue in this hearing. CDER asks for a yes vote. Genentech asks for a no vote, and I'll ask you to vote simultaneously. Thank you.

[Votes taken.]

DR. MIDTHUN: Now, I'll ask each of you to state your name and explain how you voted and why you voted that way.

Dr. Wilson, would you like to start?

DR. WILSON: Yes. My name is Wyndham Wilson. I voted yes because there were two agreed-to or there were two confirmatory trials that were mandated ongoing, whatever the regulatory language is, to confirm the preliminary results

from the E2100.

I believe, based on the results of those trials, in the absence of a survival benefit or improvement of quality of life, that delaying progression on a CT scan, absent anything else that we can point to, for just a month or two, given the toxicity of this agent, not to mention the fact that quality of life does involve the number of times you come into the hospital, et cetera, which is going to be much greater in the patients who get proteinuria, hypertension, et cetera, I did not feel that these two studies confirmed clinical benefit.

DR. MIDTHUN: Dr. Freedman?

DR. FREEDMAN: I basically have the same reasons. I felt that they did not verify the magnitude and did not describe any better the clinical benefits that are expected of this Avastin with paclitaxel.

DR. MIDTHUN: Ms. Portis?

DR. COMPAGNI-PORTIS: Yes. I'm Natalie Compagni-Portis, and I voted yes. I feel that

these studies did not confirm E2100 and did not show significant clinical benefit. And they failed to show an increase in overall survival or an increase of quality of life, and that the risk of serious adverse events and risks of deaths were significant.

DR. LOGAN: Brent Logan. I voted yes. The subsequent studies failed to confirm the magnitude of benefit that was seen in the original study, and there was no additional information of a benefit in overall survival or quality of life.

DR. MIDTHUN: For the record, that was Dr. Logan speaking.

Dr. Sekeres?

DR. SEKERES: This is Mikkael Sekeres. I also voted yes. Unfortunately, the follow-up trials, which were supposed to have been confirmatory, did not confirm the magnitude of progression-free survival, and in my mind, didn't validate that as a clinical endpoint by demonstrating any improvement in overall survival or quality of life.

DR. MIDTHUN: Dr. Balis?

DR. BALIS: Frank Balis. I agree with the people here in the panel that the clinical significance of the statistical -- the valid change wasn't enough to validate or verify the outcome of the first study.

DR. MIDTHUN: Dr. Curt, I know that you were not able to vote, but would you like to express an opinion?

DR. CURT: No. I don't think that would be appropriate.

DR. MIDTHUN: Thank you.

For the record, the voting for Issue 1 was six yes votes, zero no votes, zero abstentions.

We'll now move onto Issue 2.

Question 2(a). Does the available evidence on Avastin demonstrate that the drug has not been shown to be effective for the breast cancer indication for which it was approved? This is now open to discussion.

Dr. Balis?

DR. BALIS: We talked a little bit about

quality of life, since I think we're going to have difficulty with overall survival as a potential endpoint. One of the points that was made as a secondary endpoint was that the drug produced more objective responses than the chemotherapy alone.

From Dr. O'Shaughnessy's talk, I gather that most of these patients who are treated with the drug are symptomatic at the time they get it. And the question I have for her is, is response a surrogate for relief of symptoms in these patients?

DR. O'SHAUGHNESSY: Yes. Response rate can be helpful for two groups of patients, one, those who are already symptomatic; there's no question. The higher the response rate, the higher the percentage of patients who will get clinical benefit, relief of symptoms.

The other group are people who if they do not get a response, that within a relatively short period of time, they will have significant symptoms, or threatening end organ functions. A response for those patients as well, I believe, translates into clinical benefit.

So I think those are the two places, so that doesn't mean everybody, but it means those particular patients with usually symptomatic, more rapidly advancing disease.

DR. MIDTHUN: Dr. Sekeres?

DR. SEKERES: Can I ask a follow-up question, Dr. O'Shaughnessy? So did response correlate with an improvement in the FACT-B scores in those patients?

DR. O'SHAUGHNESSY: I'm going to have to turn to Genentech here to ask them about that.

DR. REIMANN: As you know, response can happen at different time points on the study, and the FACT-B instrument was collected also at different time points of the study. So we don't have a correlation between changes in FACT-B score. We did look, but we didn't see a correlation, but it is a bit challenging, based on the timing of the FACT-B and the timing of the tumor assessments.

DR. SEKERES: Though, presumably, people who were responding at one time point would be responding to when the next FACT-B would be

administered to those patients?

DR. REIMANN: We don't have a correlation of FACT-B changes and objective response rate in AVADO.

DR. SEKERES: So there is no correlation between a validated instrument measuring quality of life and response to Avastin?

DR. REIMANN: It is a valid instrument in assessing quality of life. I think the question is, is it sensitive in this patient population? In a front-line setting, in a typical front-line population, probably fewer than 20 percent of patients are symptomatic. And that's the studies that are done by any sponsors. They have a mixture of ECOG zero and 1 patients. So I think you'd really want to focus on symptomatic patients, and that's a smaller group.

DR. SEKERES: So I think probably, the best instrument out there for measuring quality of life, in the U.S. at least, is the FACT for a number of different cancers, including breast cancer. And we don't have a clear correlation between improvement

in a woman's well-being, how she reports it herself and response to a drug.

I was once taught that the plural of anecdote is not data. So we each have one story of somebody who felt better while responding, but if the facts don't support that, then that's not something that we can rely on.

DR. MIDTHUN: Other comments? Dr. Wilson?

DR. WILSON: I think this is a very slippery slope. Response is an arbitrary number determined by the RECIST, and it's got a threshold. We all oncologically know well that patients can have significant improvement in symptoms without hitting a response endpoint. And so I just want to echo what Dr. Sekeres said, and that is that, yes, if you have a PR or more and you're symptomatic, then the chances are you will have amelioration of your symptoms. However, you can have amelioration of bone pain, et cetera, without a bona fide PR. And so I think that you can't use the response numbers as a surrogate for that.

Then, of course, that's confounded by the

fact that only a minority number of folks, I understand, even had a truly symptomatic disease. So I think we're back to ground zero in terms of, we have no evidence that the treatment arm improved quality of life.

DR. MIDTHUN: Any other comments, discussion? If not, then I think we're ready to vote on Question 2(a), does the available evidence on Avastin demonstrate that the drug has not been shown to be effective for the breast cancer indication for which it was approved? CDER asks for a yes vote. Genentech asks for a no vote. We'll now vote simultaneously.

[Votes taken.]

DR. MIDTHUN: For the record, the results of voting to Issue 2(a) are six yes votes, zero no votes, zero abstentions. I'll ask each of you to state your name, your vote, and why you voted that way.

Dr. Wilson, would you like to start?

DR. WILSON: Wyndham Wilson, this really is a variation on the first question. I suppose one

could have looked at it as somewhat different. But this really gets out what Dr. Balis said, which is did the subsequent studies invalidate the original study.

I think that's obviously at the heart of what we are discussing here. However, the way the accelerated approval system is set up -- and I think it's a very good one -- is that the subsequent studies need to validate the original study, and in my view, the subsequent studies did not. And, hence, the original accelerated approval, in my view, was not confirmed, and, hence, I voted yes.

DR. MIDTHUN: Dr. Freedman?

DR. FREEDMAN: Ralph Freedman, I voted yes on a similar basis, that the totality of the data do not show a clinical benefit in the absence of anything else that we can get our hands around.

I think the issue, again, is to look at the changing risk-benefit ratio, which changes as a result of doubts that are now raised. And they alter the threshold for acceptance of toxicity in

relation to benefit, at this point.

DR. MIDTHUN: Ms. Portis?

DR. COMPAGNI-PORTIS: Yes. This is Natalie Compagni-Portis. I voted yes for the same reasons. The research evidence does not demonstrate a clinical benefit. And even though we have anecdotal information, we don't show any improvement in quality of life or in overall survival.

DR. MIDTHUN: Dr. Logan?

DR. LOGAN: Brent Logan, I voted yes for many of the same reasons as in the prior question. The totality of the data suggests no survival benefit, a very modest improvement in progression-free survival, which has questionable clinical relevance, and no evidence of a benefit in quality of life.

DR. MIDTHUN: Dr. Sekeres?

DR. SEKERES: I'm Mikkael Sekeres. I voted yes as well. And I define efficacy in this setting as progression-free survival of significant magnitude coupled with a quality of life advantage

or an overall survival advantage, and Avastin didn't achieve either of those definitions for efficacy.

DR. MIDTHUN: Dr. Balis?

DR. BALIS: Frank Balis, I think, in looking at this question, it obviously is asking you about, again, the totality, what the outcome was, not just in one study, but in all of the studies. And effectiveness, I agree, it needs to be something more than a fairly short increase in progression-free survival. So for that reason, I voted yes also.

DR. MIDTHUN: We will go on now to Question 2(b).

Question 2(b). Does the available evidence on Avastin demonstrate that the drug has not been shown to be safe for the breast cancer indication for which it was approved and that Avastin has not been shown to present a clinical benefit that justifies the risk associated with use of the product for this indication?

CDER asks for a yes vote. Genentech asks

for a no vote. So we'll now open this up to discussion.

Dr. Freedman?

DR. FREEDMAN: I had a question that I wanted to ask Genentech, if I may, and that relates to the burden for these patients. It's something that's very hard to measure. And I'm clearly not talking about financial. What I'm talking about is the physical burden to subjects.

I wanted to know whether Genentech collected any information in E2100, or any of the others for that matter, about the frequency of hospitalizations that these patients had to undergo in the different arms of the studies, and if they've got information on the median duration of hospitalizations. I'm specifically referring to hospitalizations relating to SAEs.

DR. HORNING: The data were collected in the AVADO study, and there was no difference in hospitalizations.

DR. FREEDMAN: Do you have the information on the median duration of hospitalizations?

DR. HORNING: I don't have the information on the median duration of hospitalization at this time.

DR. MIDTHUN: Can I ask just a follow-up clarification? So were those data collected only in the AVADO study, the hospitalization data?

DR. HORNING: Yes.

DR. MIDTHUN: Thank you.

Dr. Wilson?

DR. WILSON: You may not have this, but with the increased incidence of hypertension, proteinuria, these would require more doctor visits to control blood pressure, to monitor, et cetera.

Was data collected on the two arms with regard to visits related to these various side effects?

DR. REIMANN: I don't believe we collected specific information on doctor visits, but of course, on clinical trials, patients are being seen quite regularly.

DR. WILSON: I'm sorry. Could you say that again? I didn't understand it.

DR. REIMANN: We didn't collect that specific information, but, of course, based on the frequency of chemotherapy, patients are coming in typically every two or three weeks.

DR. WILSON: Well, that might not explain regulation of high blood pressure, et cetera.

DR. HORNING: The answer is that we do not have specific data with regard to that, but perhaps, because we have a very experienced clinician, she could comment.

DR. O'SHAUGHNESSY: The patients don't have to make any extra trips to the office for hypertension or proteinuria monitoring. When you first pick up the blood pressure, you actually ask them to verify it. You ask them to get the home blood pressure monitor. You ask them to write it down, take it at different times of the day, bring it to you, which they do at their next visit.

Then it's pretty routine to get a urinalysis pretty much at the beginning of every cycle, so they're not coming in extra for that. So the blood pressure monitoring is done probably fairly

frequently because they're coming in to see the doc every -- once a month on this particular regimen, but no extra trips.

DR. MIDTHUN: Ms. Portis?

DR. COMPAGNI-PORTIS: We have heard repeatedly that the risks involved are usual, and that they're manageable, and even that they're similar to other drugs that are given for metastatic breast cancer, but it seems to me that the adverse effects of Avastin are significant, and the studies do show this; that the risks even include death without any demonstrated benefit.

Again, I know we've heard from those who say that the symptoms are tolerable, but as Dr. Sekeres pointed out, those anecdotes are not evidence. And so I think that the risks are considerable, and that we shouldn't minimize those risks; that they are very important and that we're not hearing from patients who have really suffered because of the drug.

DR. MIDTHUN: Any other? Dr. Wilson?

DR. WILSON: I guess from a philosophical

perspective, when I went through medical school, it was always do no harm. If a drug had no side effects but I could not determine any real meaningful clinical benefit, in my view, that drug should not be given to somebody.

This is not the case here. In this case, we have a totality of data to confirmatory trials, that while different people may look at them differently, I think reasonable people would agree that a month or so prolongation in progression free is not really a meaningfully beneficial endpoint. It's not really beneficial. And, yet, we all have heard that the side effects of the Avastin in these trials are similar to those that have been described in the package insert and in the black box warning, which while different from chemotherapy can be very, very serious and lead to acute death. So that's the way I look at this.

DR. MIDTHUN: If there is no more discussion, I think we're ready to vote. We'll vote simultaneously.

[Votes taken.]

DR. MIDTHUN: For the record, the voting results on issue 2(b) are six yes votes, zero no votes, zero abstentions. And I'll ask each panelist to indicate how they voted and why they voted that way, and this time, I'll start with Dr. Balis.

DR. BALIS: This is Frank Balis, and I voted yes. And I think it was quite striking, the disparity of the way these data were interpreted, the toxicity data. I think, in large part, obviously, it depends on the perspective that one has, but it's reflected I think in the way that the data, which should be relatively factual, was interpreted by the two sides that they presented here, as to whether this was tolerable or a scourge to humanity, in terms of the degree of toxicity that it had. And I'm sure it probably falls somewhere in between.

But I think what it gets down to here is that if we don't think it's effective, then we can't tolerate any toxicity from it. And there clearly is at least some, even from the best

perspective in terms of how it's presented. So for that reason, I voted yes.

DR. MIDTHUN: Dr. Sekeres?

DR. SEKERES: I am Mikkael Sekeres, and I also voted yes. For therapies for cancer, we are willing to accept a high rate of toxicity because the diseases we are treating are so awful. But that is predicated on therapy being effective.

We voted in the previous question on whether or not this therapy was effective for metastatic breast cancer, and we all agreed it was not effective. Given that, we cannot tolerate a 13 percent higher rate of serious toxicities.

DR. MIDTHUN: Dr. Logan?

DR. LOGAN: Brent Logan, I voted yes. Avastin resulted in a significant increase in grade 3 to 5 toxicities. These toxicities certainly have an adverse impact on patient quality of life. And the modest magnitude of benefit in progression-free survival that we have seen in the combined data is not substantial enough to justify this additional toxicity.

DR. MIDTHUN: Ms. Portis?

DR. COMPAGNI-PORTIS: Natalie Compagni-Portis, and I voted yes. The evidence that was presented to us demonstrates that there is a high risk to patients with little or no demonstrated clinical benefit. And I think we can only ask patients to take on this risk when there is significant benefit to them.

DR. MIDTHUN: Dr. Freedman?

DR. FREEDMAN: Ralph Freedman, I voted yes. I think we accept the fact that the toxicity information attached to the label indications has little change between the studies. However, what has now changed is the risk-benefit evaluation. And this is based on the fact that you have at least additive toxicities now that are being considered in relation to a clinical benefit, in quotes, “that is less well defined and less clear.” And it’s certainly not better described by the postmarketing studies that are being submitted.

As I’ve said, these uncertainties about the effectiveness alters now the risk-benefit ratio to

a point at which one can less tolerate the effects that have been described, the toxicity effects.

DR. MIDTHUN: Dr. Wilson?

DR. WILSON: Wyndham Wilson, in the absence of clinical benefit, I do not believe any toxicity is acceptable, and I voted yes.

DR. MIDTHUN: We'll now go onto the last issue. Question 3. If the Commissioner agrees with the grounds for withdrawal set out in Issue 1, Issue 2(a), or Issue 2(b), should FDA nevertheless continue the approval of the breast cancer indication while the sponsor designs and conducts additional studies intended to verify the drug's clinical benefit?

Genentech asks for a yes vote. CDER asks for a no vote. This is now open for discussion.

Dr. Wilson?

DR. WILSON: May I ask Genentech, as well as --

DR. MIDTHUN: Yes.

DR. WILSON: -- perhaps CDER, a question?

One of the reasons in the postmarketing

trials that are done following accelerated approval, that the clinical trials are not done in the exact same setting, is because it is very difficult to get patients to agree to be randomized to a therapy that has had at least accelerated approval, making the conduct of those trials very, very difficult.

I guess I have heard from Genentech the length of time that they think that they could do a randomized study with biomarkers, with paclitaxel. However, I really haven't heard a really good assessment of how this is going to be impacted by the indication still being approved. It seems to me that it will be extremely difficult to accrue to such a trial in the United States and Europe. And, hence, will this not be required to be done outside of the West; and, number two, will it not make it significantly longer before we have any answers, and therefore expose patients to even longer periods of risk if, in fact, the confirmatory trial turns out to be negative?

If CDER and Genentech could just give us

some sense of this because I don't think the timeline they presented -- I think the timeline they presented was more in line with what you would have expected for the original study.

DR. MIDTHUN: Does Genentech want to go first?

DR. HORNING: The timeline that was presented is based upon our preliminary feasibility. It is not based upon the accrual to the original E2100 study. As you heard earlier today, the feasibility at this point is preliminary, and we anticipate that we'll have final feasibility in July.

With regard to accrual, we also stated earlier today that we anticipate that the majority of patients will be accrued outside the United States. For those within the United States, we have discussed, among ourselves and advisors, about the feasibility of accrual if the indication is withdrawn or the indication is left such that a confirmatory trial is ongoing. And we heard from breast cancer experts that there are pros and cons

to each of those as it relates to feasibility.

We do feel that there are individuals in the United States, physicians and patients, who are at relative equipoise on this question and would be willing to participate in a trial, and be, perhaps, more interested in their participation because a biomarker hypothesis is included.

With regard to outside the United States, and specifically in Europe, there are places where Avastin is approved, but it's not necessarily accessible. The United Kingdom would be an example of that. There are other places in Western Europe as well.

So, overall, the plan is to finalize our feasibility. The feasibility that you heard about earlier today, with the timelines, is based upon a preliminary feasibility, based upon estimates from a CRO that we have worked with extensively. We'll complete the feasibility in July, and the anticipation is that this will be a global trial with participation from the United States, from Western Europe, and elsewhere.

DR. WILSON: May I ask CDER to comment on this? Because, again, the stance with the accelerated approval has not been to do this, because it is not considered to be feasible, so are we being realistic here?

DR. JENKINS: I can comment, and then if Dr. Pazdur wants to add. The general practice in oncology has been to look to confirm clinical benefit in either a different disease setting or in a different phase of the disease. I think that goes to the point of why CDER considered AVADO and Ribbon 1 as potential confirmatory trials, because the general pattern is not to repeat the accelerated approval study as the confirmatory study because of concerns about how will patients enroll in a study where they are being asked to forego an FDA-approved treatment option. I brought that up earlier. Dr. Pazdur mentioned to me that, in some cases, trials had already been enrolled at the time of the accelerated approval.

In the HIV setting, the pattern that's developed over time is that, basically, the same

trial that serves as the accelerated approval trial is the one that confirms benefit, because we look at an interim analysis at 24 weeks. The trial is ongoing while FDA is reviewing the data and the final decision is made on the 48-week data from that trial.

I'll ask Dr. Pazdur if he wants to add anything about any history of other approaches.

DR. PAZDUR: My only comment is I feel this is somewhat of a paradoxical situation. On one hand, we're saying, the FDA is saying, this drug is safe and effective in the proposed indication; and then on the other hand, we're saying, let's test that same indication to see if it's safe and effective. It's a paradox.

DR. WILSON: So, in FDA's experience of having follow-on studies, have you ever had a situation where you went back and said, well, the new ones weren't working because you did it in a different setting? I mean, this is a very unique circumstance.

DR. PAZDUR: I can't think of one off the

top of my head.

DR. MIDTHUN: Yes, Ms. Portis?

DR. COMPAGNI-PORTIS: Just so I understand. So what safeguards -- if this were to happen, what safeguards would be put in place to protect patients in the interim so there could be a period of time during which patients are continuing to use this drug? And how would we protect those patients? How would we collect data about the impact on these patients?

It just seems that we could have many years of women using this drug without proof of effectiveness or without monitoring the dangers. I don't know. I guess that question is for both the sponsor and for FDA.

DR. MIDTHUN: Genentech, would you like to respond first?

DR. HORNING: As we have said earlier, we're open to working with CDER regarding a potential path forward to keep this option open for patients.

DR. JENKINS: If I understand your question, you're asking if it stays as an approved indication

while the confirmatory trial is going on, how will we monitor what's happening to patients who may continue to use it under the approved indication?

I think that would have to continue under the same mechanisms we use now, as far as any reports that come in for spontaneous adverse events. I'm not aware of any systematic way of collecting data from that practice of medicine, use of the drug.

DR. MIDTHUN: Yes, Dr. Curt?

DR. CURT: I think this is the most important of the three questions which the committee has to consider. If the indication is withdrawn, and the sponsor indeed is able to confirm the results of E2100 with a preferred chemotherapy partner that can maintain dose intensity, then for that interim, patients will not be able to access, at least in the U.S., a treatment which prolongs PFS significantly. If, on the other hand, the indication is maintained and the sponsor is unable to confirm E2100, then patients will be exposed to a treatment which has

an overall poor risk-benefit profile.

So in some ways, the sponsor's middle ground makes some sense, which is to maintain the drug for use in specific subsets of patients who are likely to gain the most benefit and have the least harm.

The one thing that I haven't heard in this meeting was who those patients are, although I did hear from Dr. O'Shaughnessy that patients with symptomatic or a more aggressive disease might be appropriate candidates for open-label treatment.

Does the sponsor have any data to indicate that patients -- such as the ones that Dr. O'Shaughnessy describes, more aggressive, more symptomatic disease -- do better on the combination than they do on monotherapy with the drug alone?

Are there any patients subsets where you can answer that question of who's most likely to benefit, or, just as important, who's least likely to have toxicity?

DR. HORNING: Well, let me try to rephrase the question in a different way and see if this resonates. I think the issues that you heard from

Dr. O'Shaughnessy relate to the heterogeneity of metastatic breast cancer, and that there are some patients who are more symptomatic than others, there are some patients who have higher tumor burdens, and there are some patients who have fewer options, simply by virtue of the fact that they have triple negative disease and they have no hormonal agent options throughout the course of their disease.

So if we look at it that way, the patients that have shorter disease-free intervals, visceral sites of disease, three or more metastatic sites, or triple negative, what we see is that in E2100, that the hazard ratio continues as it is in the overall study. It's actually slightly lower in the triple negative patients.

But if you look, overall, at the effect of Avastin plus chemotherapy, we see an effect in essentially all subsets, but that includes those subsets like triple negative patients. And the patients that are not necessarily called out in our studies but would fit into the more heavily tumor-

burdened patients, as not necessarily having more response, but they have a response that is similar, they simply have more at stake, if you will, with regard to the status of their disease.

DR. CURT: I suppose the issue with that, with regard to the agency, is that this is post hoc unplanned subset analysis, and I wonder how CDER would respond to that sort of middle-ground approach.

DR. JENKINS: Thank you. Let me just point out that, generally, when we are talking about the type of labeling that you describe, we like to base it on data suggesting that data from the clinical trials demonstrate that a subgroup has a favorable benefit-risk profile. Dr. Keegan will review some analyses that we have in a back-up slide.

DR. KEEGAN: If you could put up back-up slide 59.

To start with, there were, as was mentioned, no data collected on symptoms, patient symptoms, at baseline. And the majority of the patients had an ECOG performance status of zero or 1, but we don't

know which of any of those symptoms might have been related to their cancer. So we have no data on whether or not symptomatic patients would benefit or to what degree they would benefit because they simply were not studied.

We did do exploratory analyses, looking within each trial and within each independently powered cohort, segregating the triple negative patients from those who were simply HER2-negative, but ER- or PR-positive. And so the triple negatives are designated by the little three dashes at the end of the cohort.

As you can see, at least based on survival and the progression-free survival data, subgroup analyses look similar. There are not, for the most part, differences between the treatment effects in patients who are HER2-negative, ER-, PR-positive, and in those who are triple negative. So we don't have any sense that they respond differently than the other.

DR. CURT: There is no claim here for overall survival. So the data for PFS looks the

same. Is that right?

DR. KEEGAN: Yes. I think that should be one slide before 58. And as I said, I just wanted to mention this for the record, that using the same exploratory subgroup analysis, there doesn't seem to be any difference in terms of treatment effects in the ER-, PR-, HER2-negative subgroup, than for those who are triple negative.

DR. MIDTHUN: Dr. Freedman?

DR. FREEDMAN: I think Dr. Curt put the dilemma for us very well. It's a question of whether you allow the approval to continue and then potentially do harm to patients versus stopping it. At this point, it's very difficult, in the absence of clear information, that indicates that a subset of patients are benefitting. Even intuitively, one might think, well, because patients have bulky disease and symptoms, they are the ones that are most likely to benefit. Maybe they could do worse, because they would have the disease plus the serious adverse events to deal with, and they would be additive in the case of two drugs.

From my reading of the literature also, it doesn't seem to be that there is clarity amongst oncologists about whether one or two agents are appropriate for this disease.

So there's just so many questions here. And I think when you're looking at things in a broad sense and you have to protect, the agency has to look at protecting a larger number of patients, sometimes they have to make a decision that doesn't favor individual patients, but it's on the basis of the whole. And often, you've got to do that when you've got factors that don't help you make the decision clearly.

DR. MIDTHUN: Dr. Sekeres?

DR. SEKERES: We have tried to slice this pie in a lot of different ways to try to find some kind of benefit for this drug in combination with chemotherapy for a desperate breast cancer population. And no matter which way we look at it, as what were supposed to be confirmatory studies in progression-free survival, looking at toxicity, looking at overall survival, looking for data about

subgroups, all we're left with are crumbs. There's nothing we can hang our hat on in these studies that would make me feel comfortable continuing to expose a lot of patients to risk without a clear benefit.

DR. MIDTHUN: Dr. Logan?

DR. LOGAN: I think it's important to remember that the accelerated approval process should not signal a change in the drug approval standard. It's just a mechanism to allow faster access to promising drugs. And part of that is, as the FDA has argued, they need to be able to withdraw accelerated approvals.

I think it's important that the label should reflect a current understanding of the benefit-risk profile, to provide accurate, up-to-date information to patients. If the current understanding of that benefit-risk profile is not favorable, as we have been discussing here today, then I think the label should reflect that.

DR. O'SHAUGHNESSY: Dr. Midthun, may I just respond to the question about the triple negatives?

I would just like to make a comment for the record, if I might, that the E2100 data showed a point estimate of .4 on progression-free survival, which is a 60 percent reduction in the risk of progression in this very high, unmet medical need population that has very few other options. Thank you.

DR. MIDTHUN: Yes, Dr. Balis?

DR. BALIS: Can we ask whether the conduct of the follow-up study is contingent on the outcome of this question? Meaning, would it be done no matter what the answer is?

DR. BARRON: As we stated before, I think we believe that the data from E2100 was robust and believe that patients will be best served by confirming the findings in a subsequent study. And our current thinking is that we would be, based on the data we have today, moving forward either way.

DR. MIDTHUN: Dr. Wilson?

DR. WILSON: I think Dr. Logan said it very well. He said that we have a standard and that we shouldn't be changing that standard unless we have

a very good reason. I think that -- as I said at the ODAC when we first looked at this last year, I said that I felt that Genentech had done an outstanding job in performing two excellent trials in a very timely fashion. By virtue of the accelerated approval process, those two trials do not confirm the original findings, and, hence, the withdrawal is indicated.

Having said that, I think to not do that, you need to have compelling evidence that the confirmatory trials or the original trial -- there is something different about them that is above and beyond anything we've seen before to I think change the regulatory standard.

We heard from Dr. Pazdur that all other trials, to his knowledge, that we've done -- they've done confirmatory trials in other settings, which is the standard -- that this has not come up before. So the question is, is there something compelling about the E2100 trial? And what has been put forward is a hypothesis that it is the drug, paclitaxel.

Well, the confirmatory trials used a very closely related analog, docetaxel. The Ribbon trial had a taxane arm, which was a combination of multiple different taxanes, I presume. And so I think that the confirmatory trials got about as close to the drug classes that you could possibly get. And I think it is not a scientifically rigorous and viable contention that there is just something magical about paclitaxel that isn't reflected in these other trials.

So, for me, you need a compelling reason to deny these other trials and to continue the indication, and I don't see a scientific one that is compelling, at least for me.

DR. MIDTHUN: Any other questions?

[No response.]

DR. MIDTHUN: If not, we will move to vote on Question 3.

[Votes taken.]

DR. MIDTHUN: For the record, there are zero yes votes, six no votes, and zero abstentions. And I will now ask each of you to state how you voted,

your name, and why you voted the way you did. And I'll start again with Dr. Balis.

DR. BALIS: Frank Balis. I voted no on this. I think it's contradictory, as we talked about, to conduct a study to show efficacy at the same time that you leave the drug approved for that indication. Granted, there was a lot of emotional testimony put forward here to keep the drug available. I think the evidence is, at this point -- the burden of evidence, as we talked about -- is there's not enough data to support this continuation of the approval. And, hopefully, the follow-up study will demonstrate to the contrary.

DR. SEKERES: I'm Mikkael Sekeres. I also voted no. It gave me pause to continue to make available a drug for an indication when that drug hasn't demonstrated the type of efficacy that women with breast cancer deserve and expose them to serious toxicities.

DR. LOGAN: Brent Logan. I voted no. As they indicated earlier, I think the label should reflect the current understanding of the benefit-

risk profile. And as we've discussed today, our current understanding, given the totality of the data, is that that benefit-risk profile is not favorable right now. s

DR. COMPAGNI-PORTIS: Natalie Compagni-Portis. I also voted no. There was some hope that perhaps there was a subset of patients that responded favorably, and it seems that that's not the case.

I also was concerned that the likelihood of this study being actually enrolled in a timely way would be compromised, which means that women would continue to be subjected to an unproven treatment with known serious risks, the risk of death, and no guarantee of increased survival or an improved quality of life.

DR. MIDTHUN: Dr. Freedman?

DR. FREEDMAN: Ralph Freedman. I voted no. I have to say that I struggled with this and struggled with this until just before the meeting. I don't know that people would believe me, but that's true. And, eventually, I felt that the lack

of clarity on the risk-benefit assessment, the fact that the label indications as exist really no longer adequately represent the current understanding in the light of the subsequent studies, and also the lack of feasibility -- the lack of uncertainty about whether it's feasible to conduct studies, because I feel that probably there's no longer equipoise for this particular issue. And the likelihood that the study will be done and meet its accrual objectives is certainly in doubt.

DR. WILSON: Wyndham Wilson. I voted no. I feel the confirmatory trials were extremely well done, used the same class agents, and did not show any reason, any clinically meaningful improvement in progression-free survival or in overall survival.

I would encourage the company, if they are in fact convinced that there is a clinical benefit here, to do this follow-up trial as quickly as possible. I would say to, also, patients out there with breast cancer that I think these have been

extremely important trials, and that I hope that they look at all of the evidence and look to see that, in very large, randomized studies using other very potent taxanes, there was no evidence that this drug was of help to them and not come away feeling as though an important drug that is going to make them feel better or make them live longer is being taken from them.

[Audience comments off mic - inaudible.]

DR. MIDTHUN: I thank you for your comments. I would now like to --

[Audience comments continued – inaudible.]

Closing Statement by Presiding Officer

DR. MIDTHUN: I would now like to move to make closing statements.

Thank you for your participation and your attention during this proceeding. This administrative hearing, provided for under our regulations, is a means to prepare a record that will form the basis for the final decision by Commissioner Hamburg. The hearing has also provided an opportunity for the public to observe

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

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

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

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

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

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

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

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

recognize the importance of resolving these issues expeditiously.

Adjournment

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

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