primary analysis methods for the endpoints were not described.

In October 2002, a second letter was issued to NCI regarding E2100. FDA reiterated that the study identified by Genentech as to support Avastin approval. NCI did not request a meeting to discuss adequacy of the trial design and analysis plan. FDA asked NCI for additional clarification regarding the statistical analysis plan. And the FDA stated that it was crucial that the primary endpoint and statistical plan be adequate if the study is to serve as basis for drug approval. In subsequent protocol amendments, NCI revised a primary endpoint from time to treatment failure to progression-free survival, and identified secondary endpoints as TTP, survival response rate, and duration of response.

In May 2004, E2100 completed patient accrual. In October 2004, Genentech

submitted a statistical analysis plan addressing FDA's letters to NCI, and requested a meeting to discuss the adequacy of E2100 to support Avastin label expansion.

At this meeting, FDA noted that the E2100 may not be adequate to support licensure due to, one, the non-blinded nature of the study; and, two, the lack of pre-specified, detailed, and objective radiological and clinical parameters for the termination of disease progression. During this meeting FDA noted that Genentech must provide overall survival data for regular approval of the proposed indication.

In reviewing the results of E2100, FDA will consider data from AVF2119g, the negative Phase III trial. Genentech asked if PFS would be an adequate endpoint for full approval. The FDA replied it depends on the overall robustness and magnitude of PFS and results of the survival data at the time of PFS analysis.

In April 2005, ECOG DMC conducted the first interim analysis. The study was found to have met its primary endpoint of PFS. PFS was reported to be 6.1 versus 10.9 months, in favor of the bevacizumab-paclitaxel arm, with a hazard ratio of.49 and log rank P value less than.001. Results of unplanned survival analysis was also reported with a hazard ratio of 0.67 and log rank test p = 0.01. The trial was stopped based on these findings.

Genentech made the results public on April 14, 2005. And the results were presented at the ASCO meeting in May 2005.

In September 2005, a pre-supplemental BLA meeting was held. At that meeting the FDA agreed that E2100 would form the basis for a supplemental BLA. FDA stated that PFS would support accelerated approval and final overall survival would be necessary for regular approval.

In May 2006, Genentech submitted the sBLA for labeling expansion of Avastin. After review of the submission, FDA determined that the information and data submitted were inadequate for a final approval action. The FDA issued a complete review letter on September 8, 2006.

The key issues of the completed review letters are, first, the data set was incomplete without data cutoff date for efficacy and safety. As per Genentech, data collection and clean-up was still ongoing.

And here I have to explain why the FDA need a data cutoff date and clean data set in order to be able to evaluate with confidence the primary endpoint of PFS and the entire data set. This table shows the number of PFS events reported by ECOG used to determine the primary endpoint of PFS in four different occasions.

At the time of the first interim analysis by ECOG, April '05, the data cutoff

date was February 9, '05. The number of PFS events used were 206.

Is that better? Okay. At the time that the data was presented at our school in May '05, when further data clean-up occurred with the same data cutoff, the number of PFS events was 355. When Genentech submitted the supplemental BLA in May '06, Genentech chose the data cutoff of April 14, '05, the date that the ECOG DMC results was disseminated to the public. The number of PFS events to determine the primary endpoint were 395. And finally, for the current submission, after data clean-up, with the same cutoff date of February 9, '05, the number of PFS events reported by ECOG is now 445. Please note that this fluctuating number of events happens with every single piece of information in the data set, either efficacy or safety information.

I'll continue now with the key issues of the FDA CR letter to Genentech.

FDA reiterated the need for independent radiology review of progression of events in at least a subset of patients, given the subjective nature of the PFS endpoint and the open-label design of E2100. Furthermore, the submission was incomplete in regards to documentation of eligibility, baseline tumor description, study violations, drug exposure, and treatment delays/discontinuation due to toxicity. In summary, the data submitted did not allow a full evaluation of efficacy and safety.

Between November 2006 and March 2007, several meetings were held. Agreement was reached regarding the data cutoff dates for efficacy and safety. Genentech was to submit a cleaned data set.

Genentech proposed, and the FDA agreed, to conduct an independent blinded review of all patients enrolled in the E2100 study to verify efficacy results. The primary regulatory endpoint would be PFS

adjudicated by independent review facility, and Genentech would submit updated survival data.

In August this year, the supplemental BLA was resubmitted for labeling expansion of Avastin. This submission is the subject of this ODAC.

I will now move on to FDA findings of this application.

(Interruption)

DR. PAI-SCHERF: Hello? I will now move on to the FDA findings of this application. E2100 was supported by NCI and conducted by ECOG. The study design is shown in this table: Patients with recurrent or metastatic adenocarcinoma of the breast, with no prior chemotherapy for recurrent or metastatic disease, the tumor must be HER2-negative.

Patients with HER2-positive tumor must have failed or are ineligible for treatment with Herceptin.

Prior to randomization, patients were stratified by disease-free interval, number of metastatic sites, prior adjuvant chemotherapy, and ER status. Eligible patients were randomized to Arm A, paclitaxel with bevacizumab or paclitaxel alone, at the doses and schedules shown in this slide.

Treatment was to continue until disease progression or an acceptable toxicity. Crossover was not allowed. Tumor assessment was to be performed every cycle or every 12 weeks. The protocol, two more imaging procedures, did not specify it beyond X-rays and scans. Patients were to be followed every three months if less than two years, and every six months if two to five years from randomization.

The efficacy endpoints of the study are listed on this slide. The primary regulatory endpoint is PFS adjudicated by a blinded independent radiographic facility. Secondary endpoints are survival, response

and duration, and quality of life.

Patients and disease characteristics are shown on this slide. I think I skipped one slide.

From December 2001 to May 2004, 720 patients were accrued, 368 in the PAC bevacizumab arm, and 355 in the PAC arm. Two hundred and fifty-eight centers from ECOG and other cooperative groups participated in the study.

Patients and disease characteristics are summarized in this study. In general, the two treatment groups were well-balanced except for measurable disease at baseline. These slides show you only the overall population enrolled. They were mostly females, as expected. The median age was 55, range 27 to 85. Fifty-five percent of the patients were pre-menopausal -- post-menopausal. And the majority of the patients had metastatic disease.

Fifty-four percent of the patients

had less than three involved sites and the most common sites of involvement were bone, liver, and lung with percentages shown here. Sixty-one percent of the patients were ER-negative. And as I said, there was an imbalance in terms of measurable disease at baseline: 23 percent in the PAC arm versus 32 percent in the PAC-bevacizumab arm.

(Interruption)

DR. HUSSAIN: I'm told it's going to take about 10 minutes to fix this, so why don't we take a break? And please come back promptly at 10:30.

(Recess)

DR. HUSSAIN: Okay, ladies and gentlemen, we're going to start again. Can you please have your seats? And considering all the interruptions and the fact that several members of the committee sitting at the periphery were not able to hear clearly the presentation, and members of the audience were not, I have allowed the FDA to restart

from the beginning. We've asked Dr. Pai to speak slightly faster. Thank you.

DR. PAI-SCHERF: Okay, I don't need to repeat this slide or this slide. Regulatory background. Given the importance of the information on these slides, I --

DR. HUSSAIN: Can you all hear in the back?

SPEAKER: No.

DR. HUSSAIN: No.

DR. PAI-SCHERF: Testing? Is that better? Okay. As I said, bevacizumab is approved by FDA for first-line and second-line metastatic colorectal cancer in combination with 5-FU-based chemotherapy.

It is also approved for first-line unresectable or metastatic nonsquamous, non-small cell lung cancer in combination with carboplatin and paclitaxel.

Approval for these indications were based on the results of randomized control studies showing a statistically significant

improvement in overall survival for Avastin in combination with chemotherapy when compared with chemotherapy alone.

The following slides will address the regulatory background of this current application.

First is for Study AVF2119. On July 2000, Genentech and FDA met to discuss the study design of AVF2119, a Phase III trial of capecitabine with or without bevacizumab for second- and third-line therapy of patients with metastatic breast cancer. The study was designed and was to be conducted by Genentech and it was intended to support licensure of Avastin. The study was opened for accrual from November 2000 through March 2002.

And in March 2002, after accrual was completed, Genentech met with FDA to discuss a BLA filing based on this trial. In September 2002, FDA was informed that the study had failed to meet its primary endpoint

of progression-free survival.

In October 2001, while accrual for Genentech's Study AVF2119g was ongoing, the National Cancer Institute submitted E2100. The study was not identified by NCI as intended to support drug approval.

And I here explained what does the FDA mean for "trial intended to support drug approval."

For studies intended to support drug approval it is strongly recommended that the drug company meet with the FDA to discuss the overall development plan, the trial design, and the statistical analysis plan prior to initiating the study.

Agreement regarding the trial endpoint, data analysis, and data collection should be reached prior to study initiation. When this does not happen, problems that could have been avoided or solved earlier persist and cause major issues when the final study results are submitted to the FDA.

Study E2100 opened for accrual on December 2001. In May 2002, Genentech identified E2100 as an additional study to support drug approval.

FDA provided comments to NCI and noted that a statistical analysis plan was extremely deficient. The key issues were that the analysis planned did not identify primary and important secondary efficacy endpoints. The primary analysis methods for the efficacy endpoints were not described in the analysis plan.

In October 2002, FDA issued a second letter regarding E2100. FDA reiterated that the study was identified by Genentech to support Avastin approval. FDA was very concerned that NCI did not request a meeting to discuss adequacy of the trial design and analysis plan and asked for additional clarification regarding the statistical analysis plan. FDA stated that it was crucial that the primary endpoint and

the statistical analysis plan be adequate if the study was to serve as basis for drug approval.

In May 2004, E2100 completed patient accrual. In October that year, Genentech submitted a statistical analysis plan addressing FDA's letters to NCI and requested a meeting to discuss the adequacy of E2100 to support Avastin label expansion.

FDA noted that the study may not be adequate to support licensure due to the non-blinded nature of the study and the lack of pre-specified, detailed, and objective radiological and clinical parameters for the termination of disease progression. In that meeting FDA also noted that Genentech must provide overall survival data for regular approval of the proposed indication and that in reviewing the results of E2100, FDA will consider data from AVF2119g, the negative Phase III study.

Genentech asked if PFS would be an

adequate endpoint for full approval. FDA replied it depends on the overall robustness and magnitude of PFS and results of survival data at the time of PFS analysis.

In April 2005, ECOG DMC conducted the first interim efficacy analysis. Improved PFS, 6.1 versus 10.9 months, in favor of the bevacizumab- paclitaxel arm was reported, with a hazard ratio of 0.49 and log rank P value less than.001. An unplanned survival analysis result was also reported with a hazard ratio of 0.67, log rank test p = 0.01.

The trial was stopped based on these findings. Genentech made the results public on April 14, 2005. And the results were presented at the ASCO meeting in May 2005.

In September 2005, a pre-supplemental BLA meeting was held. FDA agreed that E2100 could form the basis of a supplemental BLA. And FDA stated that PFS

would support accelerated approval, but final overall survival was necessary for regular approval.

In May 2006, Genentech submitted the supplemental BLA for labeling expansion of Avastin.

After review of the submission, FDA determined that the information and data submitted were inadequate for a final approval action. The FDA issued a complete review letter on September 8, 2006.

The key issues of the CR letter are, first, the data set was incomplete without a data cutoff date for efficacy and safety. Per Genentech, data collection and clean-up was still ongoing.

And here I repeat and explain why the FDA need a data cutoff date and clean data set in order to be able to evaluate with confidence the primary endpoint of PFS and the entire data set. This table shows the number of PFS events reported by ECOG used to

determine the primary endpoint of PFS in four different occasions.

First, at the time of the interim analysis by ECOG on April '04, using the data cutoff date was February 9, '05, the number of PFS events per ECOG was 260. A month later, when the data was presented at ASCO, in May '05, with the same data cutoff, the events were 355.

When Genentech submitted the supplemental BLA in May '06, the data cutoff of April 14 was chosen That was the date that the data from ECOG became public. The number of PFS events were 395.

And finally, for the current submission, after data clean-up and with the same cutoff date of February 9, 2005, the number of PFS events reported by ECOG is now 445. We note that this fluctuation in number of events happens with every single variable in the safety and efficacy data set. It's a moving target.

In continuing the key issues of the FDA CR letter, the FDA reiterated the need for independent radiology review of progression of events in at least a subset of patients, given the subjective nature of PFS endpoint and open-label design of E2100. Furthermore, the submission was incomplete in regards to documentation of eligibility, baseline tumor description, study violations, drug exposure, treatment delays/discontinuation due to toxicity. In summary, the data submitted did not allow a full evaluation of efficacy and safety.

For November 2006 through March '07, agreement was reached regarding the data cutoff dates for efficacy and safety. Genentech would submit a cleaned data set. And Genentech proposed, and the FDA agreed, to conduct an independent blinded review of all patients enrolled in the E2100 study to verify efficacy results. The primary regulatory endpoint was to be PFS adjudicated

by independent review facility, and Genentech would submit updated survival data.

In August this year, Genentech resubmitted the supplemental BLA for labeling expansion of Avastin. And this submission is the subject of this ODAC meeting.

I will now move on to E2100 study. Since Genentech has already gone over the trial design, I will not repeat it. Of the study planned it is important to stress that crossover was not allowed.

The efficacy endpoints of PFS adjudicated by a blinded independent review, and secondary endpoints are survival, response duration, and quality of life.

The days of enrollment and the number of patients and participation sites are shown in this slide.

The patients and disease characteristics also have been outlined by the sponsor and previously presented, so I will not repeat here. There was an imbalance

in the number of non- measurable disease at baseline, as I mentioned.

Prior to cancer therapy, and that's where we stopped, 61 percent of the patients in the trial had received prior hormonal therapy either in the adjuvant or metastatic setting. Sixty-six percent had received adjuvant chemotherapy and 20 percent had received prior taxane and half of the patients had received prior anthracycline.

Key protocol violations are shown in this slide. Of significance, 6 percent of the patients were treated beyond progression with a frequency higher in the bevacizumab arm: 4 in the PAC arm and 7 percent in the paclitaxel/bevacizumab arm. Stratification errors could not be fully verified due to lack of documentation by ECOG. Seven percent of the patients had stratification errors for ER status and prior adjuvant chemotherapy.

Initiation of non-protocol anti-cancer therapy prior to documented PD

occurred in 16 percent of the cases and were comparable in both arms. Reasons for initiating the non-protocol anti- cancer therapy was not captured in the study. And for the definition of PFS, these patients were censored at the time of the last tumor assessment prior to initiation of the non-protocol therapy.

The efficacy results. Before I turn the podium to Dr. Lu, who will present the efficacy results, I would like to explain the FDA's approach in reviewing the PFS as the primary efficacy endpoint. You have heard from Dr. Pazdur and Dr. Cortazar the difficulties in assessing this endpoint.

First, this application rests solely on evidence of an improvement on PFS in a single study.

A 5.5 months improvement in PFS is claimed by Genentech.

In considering Genentech's claim, the FDA needs to verify the robustness. That

is, is there an effect? And if there is an effect, the magnitude. That is, is the 5.5-month improvement in PFS reliable?

To evaluate the robustness of the effect on PFS, the FDA, and as you heard Genentech, conducted numbers of sensitivity analysis. And we also analyzed the objective responses of the study.

How to evaluation magnitude of effect? The optimal way to measure the magnitude of the treatment and effect is to have a reliable way of identifying when it occurs and to be able to detect it instantaneously as one does with death in analysis of overall survival. Because disease progression is assessed intermittently, in each 100 every 3 months, and not continuously, there's always a degree of uncertainty in measuring these endpoints. Is it 5.5 months, 4.4, 6.5? This uncertainty can be even greater if the assessment of progression does not occur at the

protocol-specified assessment time point or if the assessment of progression cannot be verified, as in the case of missing data.

To assess the magnitude of effect we evaluate the reliability of detecting progressive disease based on radiographic studies. Specifically, what we did, we asked whether two individuals reviewing the same set of X-ray films could arrive at the same conclusion regarding where, whether if there was disease progression occurred or not.

In Dr. Lu's presentation you will see that we look into the discrepancies between the two radiologists in the independent review facility and also between the independent radiologist in the review facility and the ECOG investigators. By looking at the same set of X-rays, did they arrive at the same conclusion regarding whether (off mike) progression occurred or not? Did they agree on the date of progression?

And the purpose of this exercise is to verify whether the 5.5 months claimed by Genentech, we can be confident of this number. So now, Dr. Lu will present FDA's efficacy findings.

MS. LU: Good morning. In this presentation I will first present a summary of issues regarding efficacy results that FDA concerned important for assessment of clinical benefit. Then I will present the results for PFS, both the primary IRF-based results and those based on investigator assessment. Next I will discusses the issues that affect our confidence in PFS measurements, including the lack of agreement between IRF radiologists in scan reading and also the level of discordance between IRF and ECOG readings, which evaluates for possible bias.

Finally, I will present the results of sensitivity analyses for PFS, assessing the robustness of the treatment effect. In

addition, I will present the final results for overall survival and objective response rates and durability.

In evaluating the E2100 results, FDA has considered the following issues and their impact on demonstration of efficacy. The first issue relates to FDA's confidence in the presence and magnitude of the effect on PFS. Factors negatively impacting FDA's confidence in the treatment effect on PFS include the amount of missing data, the number of patients lost to follow-up, and the ability of IRF and ECOG investigators to consistently identify disease progression events. In addition, FDA considered the lack of an effect on overall survival as important to the demonstration of clinical benefit of Avastin in this study.

First, I will present the results in PFS. This table shows the primary results of PFS based on IRF assessment with a data cutoff date of February 9, 2005. This

analysis shows a statistically significant effect on PFS, favoring the bevacizumab-containing arm.

In the paclitaxel arm, a total of 184 patients progressed or died on study, which accounts for 52 percent of patients in this arm. In the bevacizumab-containing arm, a total of 173 patients progressed or died on study, which accounts for 47 percent of the patients in this arm. The median time to progression was 5.8 months for the paclitaxel arm and 11.3 months for the paclitaxel plus bevacizumab arm. The hazard ratio was.48 with P value less than.0001. The P value is based on the stratified log rank test.

This slide provides a breakdown of the types of progression events identified by the IRF. In the paclitaxel arm, among the 184 patients with a PFS event, 79 percent of the events were based on radiographic evidence of disease progression; 11 percent were based on non-radiographic, clinically

detected disease progression; and 10 percent of the events were on-study death. Please note that on- study deaths were defined as death occurring within 84 days of the last dose of protocol-specified therapy.

In the paclitaxel plus bevacizumab arm, among the 173 patients with PFS events, 76 percent of the PFS events were radiographically detected disease progression, 15 percent were clinically detected disease progression, and 9 percent were on- study deaths.

These are the Kaplan-Meier curves for IRF- determined progression-free survival, which shows separation between the two treatment arms. In this table we provide a comparison of the results for PFS based on IRF-determined PFS events and ECOG investigator-determined PFS events, both with the data cutoff date of February 9, 2005. The results in white are for IRF-determined PFS events and those in yellow are for

ECOG-determined PFS events.

The ECOG investigators identified more PFS events than the IRF did. The results are similar for median PFS based on IRF-determined events and ECOG-determined events, and the P values are also similar. However, the hazard ratio shows a greater effect based on ECOG-determined PFS,.42 as compared to.48 for IRF-determined PFS.

Next, I will discuss the issues that led to FDA concerns regarding confidence in PFS results.

The first issue is the failure to obtain radiographic information in all study patients for tumor status determination by the IRF. Scans were retrospectively collected by Genentech and forwarded to the independent reviewer -- the review facility for determination of disease progression events and for objective tumor response assessment.

Genentech was unable to collect

scans for percent of the study population. In addition, there is incomplete information in some patients with the informative censoring due to lack of follow-up. There are a total of 247 patients, which accounts for 30 percent of the study population who were not followed until an IRF-determined PFS event or the end of the study.

In order to explain the next issue I will first briefly summarize the IRF review process. The IRF results for PFS were determined by the following procedures.

There were two radiologists who read all available scans for each clinical trial subject in order to determine the presence and date for radiographic disease progression. These readings were performed independently and without knowledge of the treatment which the patient received. If the results of the two readings were discordant, a third radiologist performed an additional reading to arrive at final adjudicated

interpretation of their radiology results. In addition, a medical oncologist reviewed clinical records and other information to make a determination of disease based on clinical or non-radiologic criteria. In order to assess the reliability of radiologically based tumor-related endpoints, FDA evaluated the consistency between the two radiologists that are working independently, but reveal the same information regarding the presence of disease progression and the date of progression.

There were a total of 649 patients for whom radiologic scans were provided to the IRF. Among these 649 patients there were 328 patients, approximately 51 percent, where the two radiologists did not agree on the status of disease progression or of tumor response or in whom they identified a different data for disease progression or onset of response. The scans for these patients were also reviewed by a third

radiologist to reach a final IRF determination. The discordance rates between the two radiologists were similar between the two treatment arms.

FDA then conducted an assessment of the lack of consistency with regard to the two IRF radiologists for disease progression events. Among the 649 patients with scans available for IRF review, there were 222 patients, which account for 34.2 percent of the study population, where the two radiologists reached different conclusions regarding disease progression status or date of disease progression.

The level of disagreement on disease status or date of disease progression was higher among patients with a final IRF determination of disease progression. Among the 278 patients with a final IRF determination of disease progression, the two radiologists did not agree on the disease progression status or data progression in

47.1 percent of these patients. Among the 371 patients that did not have radiographic progression by the final IRF assessment, the two radiologists did not agree on disease progression status in 24.5 percent of these patients.

FDA 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. However, the level of discordance suggests a lack of reliability, particularly for patients with disease progression events.

Now we turn to an evaluation of the reliability of the measurements, of disease progression events, by evaluating the lack of consistency or discordant rate between IRF-determined PFS events and ECOG investigator-determined PFS events. This table presents the results of this evaluation for the

overall study population.

There were 174 patients for which the IRF and ECOG investigators did not agree on disease progression status. Across the entire study population 6 percent of the patients were determined to have disease progression by the IRF, but not to have disease progression by ECOG investigators. And an additional 18 percent were determined not to have disease progression by the IRF, but as having disease progression by ECOG investigators.

There was also discordance in the date of disease progression for patients where the IRF and ECOG investigators agreed that the disease progression had occurred. The overall discordance rate for the date of disease progression date is 27 percent. In total, the discordance rate is 51 percent for disease progression status or data progression.

In the next two slides we provide

the results of analysis conducted primarily to evaluate for the presence of bias, unintentionally or as well as intentional. In this assessment we are evaluating the rate of disagreement and the direction of the disagreements between the IRF and ECOG investigators.

In looking at the direction of the disagreements, we consider whether the investigators consistently or generally favor the experimental arm over the control arm. In the table we provide this discordance rate between the IRF and ECOG investigators for disease progression status as a function of the treatment arm.

In the first column, 3.4 percent of patients in the paclitaxel arm and 8.4 percent patients in the paclitaxel plus bevacizumab arm were determined to have disease progression by the IRF, but no evidence of disease progression by ECOG investigators. The discordance rate are

highly different for the two study arms, with the difference favoring the paclitaxel plus -- I'm sorry, the discordance date are slightly different for the two study arms, which the difference favoring the paclitaxel plus bevacizumab arm over the paclitaxel arm, an ECOG investigator-determined assessment of PFS.

In this slide we now highlight the discordant rates where the IRF did not find evidence of disease progression and ECOG investigators did. There are 20.3 percent of patients in the paclitaxel arm and 16 percent of patients in the paclitaxel plus bevacizumab arm, who are determined as having no evidence of disease progression by the IRF, but as having progressed by ECOG investigators. Again, there are slight differences in the discordance rates between the two study arms, which, by ECOG assessment, favor the bevacizumab-containing arm.

A number of sensitivity analyses were conducted based primarily on IRF-determined PFS status and date. These analyses were conducted to evaluate the robustness of the PFS findings and to assess whether protocol violations or either aspects of study conduct substantially impact the study results. The FDA agreed-upon primary PFS analysis is provided in the first row for comparison. The next row displays the results of an additional analysis in which the use of non-protocol-specified anti-cancer therapy, referred as NPT, and early study discontinuations were also treated as PFS events. The estimated median PFS is 4.2 months for the paclitaxel arm, 8.1 month for the paclitaxel plus bevacizumab arm. In the bottom row are the results for analysis in which time to PFS was not censored by the use of non-protocol anti-cancer therapy. In this analysis, the estimated mean PFS is 6.1 month in paclitaxel arm and 11.2 months in

paclitaxel plus bevacizumab arm.

In this table the first row summarizes the results of the worst-case scenario. In this analysis the use of non-protocol anti-cancer therapy and early discontinuations were treated as PFS events only for patients in the paclitaxel plus bevacizumab arm, and were censored for PFS on these days for patients in the paclitaxel arm. The hazard ratio for this worst-case analysis is.78, with estimated median PFS of 5.8 months in paclitaxel arm and 8.1 months in paclitaxel plus bevacizumab arm.

The middle row summarizes the results of analysis in which the earliest recorded date of a PFS event by either ECOG investigators or the IRF, was used to determine PFS. The final row summarizes the results of analysis in which the PFS events by ECOG or the IRF, the use of non-protocol-specified anti-cancer therapy, and early study discontinuation were all

considered PFS events. In all of these analyses the treatment effect persists, which support the conclusion that the addition of bevacizumab does prolong PFS in this setting.

This table shows the results of the final analysis of overall survival with a data cutoff date of October 21, 2006. This cutoff date coincides with the timing of the protocol-specific final analysis, which was to be conducted after 481 deaths occurred.

In the paclitaxel arm a total of 238 patients died, which accounts for 67 percent of the patients in that arm. In the paclitaxel plus bevacizumab arm, a total of 243 patients died, which accounts for 66 percent of the patients in that arm.

There's no evidence of an effect on overall survival with an estimated median time to death of 24.8 months for the paclitaxel arm and 26.5 months for the paclitaxel plus bevacizumab arm. The hazard radio is.87 with P value.14. This slide

shows the Kaplan-Meier curves for overall survival.

This table shows the results for IRF- determined objective response rates by study arm with a study cutoff date of February 9, 2005. In the paclitaxel arm a total of 54 patients, which accounts 22 percent, were determined by the IRF to have an objective tumor response. In the paclitaxel plus bevacizumab arm, a total of 112 patients, which accounts for 49 percent were determined by the IRF to have an objective tumor response.

The IRF determined that tumor responses or partial responses. The difference in response rates between the two study arms is 27 percent, with a P value of less than.0001. The P value is by stratified (off mike) test. Among patients who achieved an IRF-determined objective tumor response, the median duration of response was 9.7 months in the paclitaxel arm and 9.4 months

for the paclitaxel plus bevacizumab arm.

The FDA's evaluation of the study data analysis supports the conclusion that bevacizumab treatment delays time to progression or early death.

However, the magnitude of the treatment effect is less certain. Our confidence in the estimated 5.5- month improvement in progression-free survival is limited by the following factors.

Genentech was unable to obtain scans for percent of patients. There is a large percent of patients, which is 34 percent, who were not followed until an IRF-determined PFS event or until the end of study. The lack of reliability in the determination of radiologic disease progression and the date of progression between independent radiologists and between independent radiologists and the study investigators. In addition, E2100 failed to show an effect on overall survival. Thank

you.

DR. PAI-SCHERF: We'll now move on to the safety analysis of E2100. Estimated drug exposure is shown in this slide. Because E2100 did not capture the height, weight, or BSS/BSA of the patients, assumptions were made retrospectively by Genentech to estimate cumulative dose and dose intensity.

The dose administered was estimated as the highest dose of drug given from first cycle divided by 10, and BSA was estimated as the highest paclitaxel dose from the first cycle divided by 90.

As you can see in this table, patients in the PAC/bevacizumab arm received longer treatment, 9 months compared to 5 months with the PAC alone, and more cycles, 10 cycles versus 6 cycles in the PAC alone. This is reflected in a higher total cumulative dose of paclitaxel. However, dose intensity was lower in the

paclitaxel/bevacizumab arm due to dose deletions and reductions.

Those modifications, omission, dose delays, and dose reductions occurred overall at a much higher incidence in the paclitaxel/bevacizumab arm than the paclitaxel alone arm as you can see in this table. Because E2100 did not capture the reasons for dose modification, the toxicities leading to these changes are not known to us.

Regarding treatment discontinuation due to toxicity, a total of 142 patients discontinued therapy due to serious adverse events: 70 in the PAC arm and 72 in the PAC/bevacizumab arm. Again, specific events leading to treatment discontinuation was not collected in the E2100 study. Retrospectively, Genentech, looking at -- by temporal association of treatment discontinuation and toxicity reports, appears that most common causes leading to paclitaxel discontinuation was neuropathy and allergic

reaction. For the paclitaxel/bevacizumab arm the leading causes of drug discontinuation were neuropathy, thrombosis, proteinuria, hypertension, arterial thromboembolic event, fatigue, left ventricular dysfunction. But again, this is retrospectively collected and based on temporal association of the date of discontinuation and the case report forms.

The following two slides summary the ECOG safety data collection. Adverse events were collected once every 3 cycles, every 12 weeks. During the protocol therapy the investigators were to fill out the E2100 toxicity form at the end of every three cycles. Date of onset and resolutions of the AEs were not collected. Only Grade 3 through 5 non-hematologic toxicities and Grade 4 to 5 hematologic toxicities were collected.

The NCI/AdEERS collected serious events from only the paclitaxel/bevacizumab arm, but not from the control arm. Overall, when compared to the case report forms filled

out by the investigators, the AdEERS reporting system had a slightly higher number of serious events and of higher grade. Because the control arm data was not collected, we will not present that information here. Laboratory data was also not collected in this study.

Because Grade 1 to 2 toxicity and because of the ECOG safety data collection, a comprehensive description and evaluation of all adverse events related to bevacizumab plus paclitaxel therapy cannot be made.

This slide shows the Grade 3 and 4 toxicities that were collected. And as you can see, the incidence of serious toxicity was significantly higher in the paclitaxel/bevacizumab arm: 71 percent versus 51 percent. There were more deaths, more Grade 3 and 4 toxicities.

Serious adverse events known to occur with bevacizumab is shown in this slide. With the exception of venous

thromboembolic events all the rest occurred at a much higher frequency in the bevacizumab-containing arm: Hypertension, proteinuria, arterial thromboembolic events with cerebrovascular ischemia, cardia ischemia, bleeding/hemorrhage, congestive heart failure, GI perforation and fistula, and neutropenia and infection. The most frequent events in this table were hypertension, 15 percent compared to 1.4 percent in the control arm, and neutropenia and infection 17 percent in the paclitaxel/bevacizumab arm compared to 8 percent in the paclitaxel arm.

Other additional treatment emergent Grade and 4 AEs are shown in this slide. Sensory neuropathy, vomiting, diarrhea, dehydration, fatigue, and pain, Grade 3 and 4, all occurred at a much higher frequency in the paclitaxel/bevacizumab arm.

All deaths occurring on study are reported in this slide. More than 70 percent

of the patients are reported to have died at the time of the data submission: 70 percent in the paclitaxel/bevacizumab and 74 percent in the paclitaxel arm. The causes of death, according to Genentech, are shown here. The majority of the patients died: 69 percent in the PAC arm and 67 in the paclitaxel/bevacizumab arm died due to breast cancer. Death was attributed to protocol treatment in only one patient in the paclitaxel arm. No patients died due to protocol treatment in the paclitaxel/bevacizumab arm in Genentech's submission in August this year.

We were very puzzled with the lack of survival benefit in the bevacizumab/paclitaxel arm despite the reported improvement in PFS. And knowing the toxicity profile of bevacizumab we were concerned about possible toxic deaths. This slide shows the Applicant and FDA's attribution of the cause of death on study

within 30 days of end of study of treatment. Seven patients in the paclitaxel arm and 12 patients in the paclitaxel/bevacizumab arm died either on study or within 30 days of the end of the study. None of the deaths were attributed to protocol treatment according to the Applicant. After careful review of the case report forms and case narratives, the FDA disagreed with the Applicant's death attribution in 13 out of 19 cases. Of importance, the FDA identified five deaths as definite or probably related to protocol treatment in the paclitaxel and bevacizumab arm.

As I said, this analysis was based on Genentech's submission of August this year. During our review process, we were in continuous communication with Genentech and we are pleased that they have reviewed may of these cases and changed the attribution.

The following slides are short summaries of the patients who, in our view,

the patients died of toxic death associated to the protocol treatment.

And as you can see here, many of these are well- known to be associated to bevacizumab.

I will end my safety presentation session of E2100 by showing the Kaplan-Meier survival curve of E2100. Survival data is important for proof of direct efficacy as well as a demonstration of toxicity safety. Because bevacizumab is known to have substantial toxicity it is not always possible to know whether the cause of death is due to drug toxicity or tumor progression or both. Survival is the end net effect of deaths from both tumor and drug toxicity.

Despite the observed and reported improvement in PFS, no statistically significant improvement in survival was observed with bevacizumab and paclitaxel. Whether this lack of survival benefit is due to the increased toxic effect of bevacizumab

in combination with paclitaxel in breast cancer patients we do not know.

I'll now move on to summary results for the AVF2119. This study enrolled 462 patients with progressive metastatic breast cancer previously treated with anthracycline and a taxane. Prior to randomization patients were stratified by ECOG performance status and number of prior chemotherapy for metastatic breast cancer. Patients were randomized to capecitabine alone or capecitabine plus bevacizumab at the doses and schedules shown here.

The primary endpoint of the study was PFS adjudicated by an independent review. Please note that the efficacy results shown here were extracted directly from the clinical study report submitted by Genentech in August this year. As you can see, the study failed to meet its primary endpoint of PFS. The median PFS was 4.1 versus 4.8 months for the capecitabine and bevacizumab

arm with a hazard ratio of 0.98 and log rank P value of 0.857.

The study also failed to meet its primary endpoint -- the secondary endpoint of overall survival. Addition to bevacizumab to capecitabine did not show a survival benefit when compared to capecitabine alone. The median survival was 14.5 months for the capecitabine-alone arm and 15.1 months in the capecitabine and bevacizumab arm.

There was a statistically significant increase in response rate in this trial: 19.8 percent in the capecitabine and bevacizumab arm compared to only 9.1 percent in the capecitabine arm. In terms of duration of response, the capecitabine arm responders, the duration of response was 7.5 months compared to a shorter duration of response of 4.9 months in the bevacizumab-containing arm.

The diverse events in the study are shown here. The incidence of Grade 3 and 4

toxicity was 15 percent higher in the capecitabine/bevacizumab arm compared with capecitabine arm: 72 percent versus 57 percent. Common AEs in both arms were asthenia, pain, diarrhea, nausea, vomiting, hand- foot syndrome, events contributed to capecitabine. Common AEs in the capecitabine and bevacizumab arm were headache, hypertension, epistaxis, and proteinuria.

For the Grade 3 and 4 AEs known to occur with bevacizumab, hypertension, thromboembolism, congestive heart failure, proteinuria, and bleeding, are reported in this slide with a higher incidence in the bevacizumab-containing arm. Hypertension was the most common side effect related to the bevacizumab.

Of note, there were no reports of cerebrovascular ischemia, myocardial infarction, or gastrointestinal perforation in the AVF2119 study. There was one death attributed to protocol treatment due to

chemotherapy neutropenia and sepsis.

I'll now summarize the FDA findings of this application. In the E2100 study there was an estimated 5.5 months improvement in PFS by independent review. This PFS improvement is similar to the ECOG investigators' findings. There was no survival advantage and there was a 27 percent increase in objective response rate in the bevacizumab/paclitaxel arm compared to paclitaxel alone.

To get back regarding the robustness of effect and magnitude of effect in conclusion, the robustness of effect, yes, the FDA believes that the result is robust based on the sensitivity analysis conducted for PFS and also supported by the increased objective response rate in the bevacizumab/paclitaxel arm. Yes, there is an effect.

How about the magnitude of effect? Not so. Factors affecting our confidence in

the magnitude of PFS has been outlined by Dr. Lu: Missing scans, 34 percent of patients not followed until an IRF-PFS event or end of study, the lack of reliability in determination of radiologic disease progression and the date of progression between two independent radiologists and between the study investigators and the independent radiologists.

In terms of the E2100 safety there was incomplete assessment of toxicity profile due to the data collection. Grade 1-2 toxicity was not collected. Laboratory information was not available. However, there was clearly a 20.2 increased in Grade 3 and 5 toxicity and 1.7 treatment-related death in the bevacizumab plus paclitaxel arm.

AVF2119 did not increase PFS, no survival advantage. Again, there was an increase in objective response albeit of short duration. And a 14.4 percent increase in Grade 3 and 4 toxicity was reported for

the bevacizumab-containing regimen compared to capecitabine-alone arm.

Thank you and this ends my presentation. We'll have two questions for ODAC this afternoon.

DR. HUSSAIN: Thank you, Dr. Lee. Ms. Vesely's going to read the statement for the beginning of the public hearing.

MS. VESELY: Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making to ensure such transparency at the open public hearing session of the Advisory Committee meeting. FDA believes that it is important to understand the context of an individual's presentation. For this reason FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and, if known, its

direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of our statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is

listened to carefully and treated with dignity, courtesy, and respect.

There is one speaker registered for the open public hearing, Mr. Robert Erwin, president, Marti Nelson Cancer Foundation.

MR. ERWIN: Thank you for the opportunity to talk with you. Can you hear me? Okay, how's this? This better? Okay.

I have no financial interest or ties with Genentech. The Marti Nelson Cancer Foundation is an all-volunteer organization. It has received no funding from the biotech or pharmaceutical industry over the last two years. However, I'm also on the board of directors of C3, the Colorectal Cancer Coalition, and that organization is funded by Genentech and other pharmaceutical and biotech companies.

I'd like to briefly address two things, one of which is not really the primary subject of this ODAC meeting, but indirectly it is. And it has to do with the

complete response letter issued by Genentech -- I'm sorry, by --

DR. HUSSAIN: Can you please speak louder? Can you speak louder?

MR. ERWIN: Okay, is this better? I'll stay a little bit closer.

I want to briefly address one issue that's not technically a matter for ODAC consideration and that's the FDA's issuance of the complete response letter a little over a year ago. To me, that raises some questions that are worth further consideration and it has to do with the relationships among the National Cancer Institute, the cooperative groups, companies such as Genentech, and the FDA. And I suppose a simple way of asking the question is has the year-plus delay made any difference? Has it provided benefit in the overall process?

And although the complete response letter has never been made public, the

briefing documents provide at least insights into what may have been in it. And I would say that the year delay has been valuable if the following was achieved, and that is reconfirmation and reestablishment of the FDA's high bar for new drug approval. And by "high bar" I'm referring essentially to three components: The quality of data used in the review -- quality, reliability, believability of the data; also the performance required for a product to be approved; and the safety required for a product to be approved in the context of the oncology indication. And I hope that the last year and a quarter has provided a basis for a lot of both private and public debate about what may have gone wrong that led to the necessity of the complete response letter being issued.

It raises some additional questions. You know, should the National Cancer Institute essentially be a CRO for industry? You know, I would argue no, it

should not. However, the NCI and industry should cooperate in the advancement of the field of oncology, and I think in general it does. The cooperative group system has been responsible for major advances in oncology over the years and I think it's extremely important that its integrity be maintained. And that partly requires open, constructive, and, to a very large extent, non-confidential disclosure and discussion of all of the things relevant to decisions about treating patients, information relevant to the patient and to the physician making the treatment decision.

Obviously it's important to know how influential money coming from industry into NCI or into the cooperative groups is in determining the priorities of clinical trials and in determining clinical trial design. This particular study raises, I think, important questions. You know, why did apparently NCI ignore input from the FDA in

May of 2002 regarding the clinical trial design? Did -- or if it did, why did Genentech ignore FDA's request for an independent radiology review back in September of 2005? It's obviously been done now and the results of the analysis are extremely interesting.

So in one sense, we don't know any more than we did before. The questions are still there.

I think they're extremely important questions. And I would like to see as much cooperation as possible among all of the parties interested in advancement of the field of oncology, but cooperation with disclosure, cooperation with transparency.

The other thing that I'd like to just very briefly comment on, going back to my concern that FDA maintain its high standards, FDA really is the organization that represents consumers, taxpayers, all of us in determining what does and doesn't work

and how it does and doesn't work in the context of oncology. And keeping those standards high is incredibly important. This application should not be approved if approving it requires lowering the bar for approval.

That's not to say that I'm saying it shouldn't be approved. I'm focusing on the standards of approval. And of critical importance today is this whole issue around progression-free survival. What does it mean and what does it not mean?

In 1999, when the last ODAC session considered this, and back then it was focused on time to tumor progression, I was opposed to the use of time to tumor progression as a primary basis for approving a new drug in oncology. I've moderated my view quite a bit with progression-free survival.

From the perspective of an individual patient who experiences an extension of progression- free survival

there's no question that that's meaningful, personally and clinically. The real question is can you statistically capture that in a large body of data across a large number of people? So it, again, comes down to the reliability and believability of the data.

A person taking a drug, hoping to obtain an extension in progression-free survival, particularly in this case, faces the possibility of early death, and that should never be taken lightly.

The death of one individual is a tragic event. However, in the context of this large study, there are individuals who probably receive substantial benefits, probably even an extension of survival. And those people cannot be taken lightly either because that as an individual event is incredibly important.

So in evaluating this application and looking at the importance of progression-free survival, I think it's

pretty clear that it is clinically meaningful, progression-free survival. The question is how do you deal with this data and this endpoint when you have problems with concordance in the independent review? Which to me raises as much questions about the state of the art in radiology as an approach to assessing objectively tumor progression as it does the competence of the clinical trialists or the integrity of the people running the study. You know, the technology is a problem.

But the other thing that I think is extremely interesting about this data is that there is so much positive information here combined with so much negative information in terms of toxicity and some deaths that it raises a lot of questions that I really wish could have been answered at the very beginning. The five of the six deaths that FDA attributed to protocol therapy were in people over the age of 65, and the one

remaining death was a person who was 64. You know, what would happen, and I know that it's not valid to retrospectively dredge data, but what would happen if the trial had been designed only for patients below the age of 65? Would we be looking at a very different outcome?

Teasing out this sort of data and asking questions going forward in determining how these drugs work and for whom and for whom they don't work I think is incredibly important. And it's something that I hope this group will take seriously as you go into the next stage of your deliberations.

Thank you very much.

DR. HUSSAIN: Thank you, Mr. Erwin. On behalf of the committee I want to thank you for the very thoughtful comments. And certainly these are the critical issues you've captured that is going to be part of the discussion for this committee.

This ends the public hearing

session and no more comments will be taken. I'm going to suggest we break for lunch and plan on being here at about 20 to 1:00. Thank you.

(Whereupon, at 11:40 a.m., a luncheon recess was taken.)

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

(1:40 p.m.)

DR. HUSSAIN: Okay, good afternoon. We're going to start the afternoon session. I'd like to invite -- before we begin, I'm sorry, before we begin the questions from the committee, I'd like to invite Ms. Carolina Hinestrosa to make a statement. Ms. Hinestrosa is from the National Breast Cancer Coalition. Is she here? We'll give her a couple of minutes.

(Recess)

DR. HUSSAIN: So for the purpose of the questions to the FDA or to the sponsor, I'm going to request that the committee members raise their hand, catch my eye or Nicole's eye. We'll put on a list and I promise we'll get to you. And then please only speak when you are acknowledged or your name is mentioned.

So I'm going to open up the floor now for members of the committee to ask the

FDA or the sponsor. Dr. D'Agostino?

MR. D'AGOSTINO: Thank you. I understand, I think, the issue with the PFS as an endpoint as being extremely important, but, nonetheless, not complete. What I'm confused about, and I'd like maybe the sponsor respond to it, they did an interim analysis and in the interim analysis, if I understand the data that was presented, they obtained significance based on the traditional.05 level on both the progression-free survival and also on survival, and that probably motivated them to think they had a winner here. Later on, their data, either more data coming in or cleaning and what have you, it changed that around. The survival presumably when that was happening was a much shorter period than the overall survival that we have ultimately presented.

And what I'd like is some discussion, if possible, that makes sense in

terms of what was happening to these subjects that sort of changed the survival. Were they put on different treatments and so forth? And I understand that we're looking at how the survival came regardless of the, you know, things that were happening to them. But could the sponsor say something about what was actually happening that lost the significance in the survival and that later on led to this sort of equivocal result with the survival, which now puts us in our dilemma?

DR. BOWDEN: Yes, thank you. Is it on? Can you hear me back there? Chris Bowden, Genentech.

I'd like to ask Dr. Miller, the principal investigator of the study, to come to the podium to address the actions that came about from the time of the interim analysis going forward.

DR. MILLER: So first, let me tell you a little bit about the ECOG DMC and their

process. The primary endpoints of the trial and the only endpoint that the DMC considered at the interim analysis to determine if the results should be made public were the progression-free survival analysis.

Once that decision had been made we did an analysis of the other secondary endpoints based on the data available at the time, including overall survival. Though at that point, the overall survival data were extremely premature with a very small number of events. And, in fact, had overall survival had been the primary endpoint of that trial, even though the P value was.01, it would not have met the statistical criteria to say that we had met that endpoint and the results would not have been released.

We had long and, as you can imagine, sometimes contentious debates within ECOG at that first presentation as to whether we should show those early curves or not, realizing that they were very premature and

subject to change and to change in directions that we might not be able to predict.

We ultimately decided that it was best to show all of the data that we had at that interim time point to give people as much information to make decisions and to let them make their own decisions about the weight of such premature data.

I think it is most likely that the reason why we think we saw that P value of.01 at that early time point is that with such premature data, the early deaths are really highlighted and have a much bigger impact on that analysis. And there is a separation in the curves, particularly in that early time point. So I think that's what we're seeing that just didn't maintain significance with longer events. So the release from the DMC had nothing to do with those overall survival curves at that first time point.

To your other question, what do we know about treatments that patients might

have received after progression and the impact that might have had on overall survival, the reality is we don't know. We did not collect data on subsequent therapies that were received, so I can't speak to any potential imbalances and exposure to subsequent therapy or response or potential benefits to therapies after progression.

MR. D'AGOSTINO: So we have to take -- with all the changes that were made and all the updates and the number of events jumping all over the place, the final bottom line is we have a significant result of progression-free survival, but we do not have a significant result for survival?

DR. MILLER: That is indeed the bottom line. And if I could speak for just a minute to the question that you alluded to, but didn't ask, the different number of events and the different analyses. At the time the Data Monitoring Committee first reviewed the interim analysis, the ECOG

process has three defined levels of data review and cleanliness. The data that is reviewed by the Data Monitoring Committee has been fully submitted by the sites, fully reviewed by the coordinating office, and fully reviewed by the study chair, and is essentially complete for those patients. There are data that have been submitted and reviewed by the coordinating office, but not yet reviewed by the PI, and data that has been submitted to the coordinating office, but has not yet been fully reviewed. And each of those levels provide additional number of events that result in this differing number of events for what appears to be the same data cutoff.

What's important and was not mentioned is that in each of those populations the PFS result was essentially the same. It gave us even more confidence in the data that it was not going to change.

MR. D'AGOSTINO: And I don't want

to prolong my asking questions, but it seemed like there were so many potential flip-flops, where one said progression-free and one didn't, that you may end up at the same bottom line number, but, you know, you may very well be talking about a substantial number of different people. And again, you have the significance no matter what is done, but it is very disturbing to see all the disagreements.

DR. MILLER: Well, I think we will probably have a chance in a minute to look more at those sources of disagreements in detail, but we do that sort of analysis to see if there is a systematic bias that might be influencing our results. And, in fact, we saw no systematic bias at all.

DR. HUSSAIN: Dr. Mortimer?

DR. MORTIMER: I have two quick questions for the sponsor. One is I just wondered out of curiosity, in 2119 the frequency of radiologic reassessment was it

two months in 2119 as opposed to three months?

And the second question I had is there's a very high incidence or proportion of patients with negative estrogen receptors on this trial. And is there a signal here for triple-negative breast cancers doing better with Avastin than receptor- positive patients?

DR. BOWDEN: So with regards to the frequency of assessments on 2119, they were every 6 weeks for the first 24 weeks and then every 9 weeks going forward until PD.

With regards to estrogen receptor positivity that you saw in the FDA presentation, it's 65 percent actually. Sixty-five percent of patients are estrogen receptor-positive. However, in the subset analysis for PFS, the patients who were triple-negative did have a treatment effect with the combination.

DR. HUSSAIN: Dr. Buzdar?

DR. BUZDAR: I have a couple of comments and maybe questions which the sponsor could address.

One thing is that if you're looking at the time to progression as the primary endpoint, then up front in the protocol it should have been that every patient should have a measurable disease. Over here in the two arms, if you look at it, there is at least more than 20+ percent of patients have evaluable disease, but not measurable disease. All of us who treat breast cancer, those are the hardest ones to define, when they progress, when they're stable. That is a final endpoint, which is no question about it.

The other thing is that the difference between the evaluable patient, between the two arms, there is absolute difference of about 9 percent in patients who were in one arm versus the other, which would be partly responsible for some of the

interpretation and how these data are interpreted by the investigator or even by the independent reviewer because there is no clearly measurable disease.

The other point which I -- it was not brought up over here, but looking at the earlier presentation by Miller and the group, that there are also other -- some of the small differences between the two arms, like, say, less than three sites of disease or other potential prognostic factors. It might not be therapy, but it may be that subgroups by chance are substantially different, which translates in a different outcome in the time to progression. I wanted to see what your thoughts are on that.

DR. BOWDEN: Thank you for the question. With regards to measurable and non-measurable patients, they were assessed in the same manner as patients who had measurable disease by the IRF as well as by the ECOG investigators. The subset analyses

for progression-free survival demonstrate a treatment effect for the combination in both the measurable as well as the non-measurable subset.

And I'd just like Dr. Miller to come to the podium and address that important aspect of why non-measurable patients were included in this trial.

DR. MILLER: So, Aman, in some ways I have to disagree with you. If objective response rate is your primary endpoint you absolutely need measurable disease. But for progression-free survival I need the investigators to reliably able to tell me when the patient's disease has progressed such that they are in need of a change in their therapy. And I am confident that they are able to do that. I'm confident that you will be able to do that when you are back in your clinic. I doubt that any of us have ever looked a woman with only bone disease and said I'm sorry, Mrs. Jones, I can't treat

you because I can't evaluate your response.

It is admittedly more difficult and it does introduce the potential for bias into the results. That was not a stratification factor in this study and there is a slight imbalance in the measurable and non-measurable disease patients. There were not significant imbalances in any of the other prognostic factors that we evaluated, so I think it's highly unlikely that those differences account for the magnitude of the results that we see.

The ECOG statisticians did multivariate Cox model analysis to see if those potential imbalances in the factors that we could measure and perhaps others that we don't know about or don't yet know how to measure might influence the results, and they did not. It did not change the results and our conclusions at all.

So I'm actually quite proud of this study, including that significant subset of

patients who are otherwise excluded from clinical trials and the potential to get access to new therapies.

DR. BUZDAR: Yeah, I disagree. I think the thing is that it is very -- if they were evenly distributed there is 9 percent absolute difference between the one group with evaluable disease versus the other group, and I think that could bias.

The other point which also is of interest is that, yes, in this study and your capecitabine with Avastin study showed that, yes, the response rates are (off mike).

Yeah, the other point which I wanted to see and elaborate is that in both studies, this and the capecitabine study, response rates were substantially increased. And if you look at the responding patients, in both studies the time to progression of a responding patient is very similar.

Why do you think that in the capecitabine study you don't see any (off

mike) progression (off mike)? Okay, now I think it is back. So the thing which I am kind of confused is that if responses in both studies were substantially increased, but in both studies the time to progression for responding patient is -- or duration of response is very similar, how can we explain that dichotomy between the two trials?

DR. BOWDEN: Thanks for your question. For E2100 you pointed out that the duration of response is 9.4 versus 9.7 months. If we can look at the -- I'll project the slide 77. TU-77, please.

Anyway, the ration of response on E2100 for responding patients, 9.7 versus 9.4 months. Now, there's a doubling of the response rate for patients who are on the combination arm, so you're going to see twice as many patients having a response.

One of the things that we wanted to look at was to see what would happen to that median duration of response if we used a

different -- if we did not use the February 9, 2005, cut date and just let the patients go because some of these patients would have just been censored at that time. And it turns out when you look at that the duration of response is 10 versus 12 months.

There's another important aspect here as well. We looked at patients whose best response was stable disease. And in that analysis the treatment effect was maintained and the hazard ratio was.50 for paclitaxel and Avastin.

DR. HUSSAIN: I wanted to follow-up just briefly on his question. So coming from prostate cancer, where we live with bone disease, I will tell you that I agree that they ought to be included, but there's question that progression is not always easy to pick up. And so my question is how was progression defined in bone?

And the other question I had is as I noticed in your slide, the timing of

assessment was not irrespective of courses. It was indeed every so many cycles. And there were much more dose delays or cycle delays in the combo arm, which could cushion that progression-free survival. So could you please comment on those, too?

DR. BOWDEN: Thank you for your question. I'll ask Dr. Miller to comment, please.

DR. MILLER: So Dr. Hussain's absolutely correct that evaluating response in bone is difficult and there are patients who may have flare responses that can complicate that. We did not include a specific definition for progression in bone, per se. I have seen protocols that have tried to do that, but they have, in essence, tried to make something that is not measurable, measurable by looking at lytic lesions and MRIs of bone lesions and such, and we didn't think that was going to make this more useful. So our definition was the

same definition that's included in the RECIST criteria for patients with non-measurable disease, that they had to have unequivocal progression of either their --

SPEAKER: (off mike)

DR. HUSSAIN: Yes, my question is means what? What does "unequivocal progression?"

DR. MILLER: So it includes a clearly identified new lesion, which was the case for many patients. There is no question that worsening on bone scan of existing disease without new lesions is subjective, and I think that does account for some of the potential variation between the IRF and the independent review facility.

Our biggest concern was that that subjectivity in the assessment for that proportion of patients might have been different between the two different treatment arms. And we looked very carefully for that sort of systematic bias that would influence

our results and we could find no evidence of that.

We did define evaluations for all patients based on number of cycles. And there were some additional treatment delays, though most of those actually occurred much later in treatment. If treatment was delayed or there were low blood counts and such, those were considered missed treatments and were not made up, so that did not have a major impact in prolonging time from evaluation.

The ECOG statisticians did a couple of other analyses to see if there might be what's essentially an ascertainment bias. Because of those differences or perhaps as patients had been on therapy for a longer time, people might have gotten more lax about sticking to the schedule. They did that in a couple of ways.

We looked at for time on study a projected number of scans that a patient

would have had compared to the actual number of scans that the patient had had and they were identical.

We also looked at patients who had progression documented at what would have been a non-scheduled assessment. So if assessments were due every three months, we assumed a two-week window on either side for holidays, vacations, CT scan breaking down, and schedule issues, and assumed that if your progression was documented outside of that window it was a non-scheduled scan likely prompted by symptoms or physical exam findings. And that was about a third of the patients in both arms. They were within 1 percent of being identical in the proportion of patients. They then took it a final step and said, well, for those patients for whom progression was documented at a non-scheduled time point, let's eliminate that potential bias and move those progressions forward to the next scheduled assessment and see if that

impacts the progression- free survival difference and the significance of it.

And it didn't have any impact on our results. So we absolutely acknowledge that including those non-measurable patients, which we thought was very important, does bring with it for that group of patients some potential for more subjectivity and potentially more bias. And we looked very hard to try and find an impact of that on our results and we simply could not find a way that that alone accounts for our results or has any impact.

DR. HUSSAIN: If I may just follow up on that. So if I give you an example. So a lady has two lung lesions, they're two centimeters, and has seven bone lesions, and the lung lesions went away and now she has two more soft-looking bony lesions.

Would the investigators have counted her as a responder or a progressor?

DR. MILLER: So I can actually

speak to that because I had patients of my own who did that and I was frequently called about patients. I can tell you for the ECOG database those patients were considered to have progressed, though in the opinion of the investigators and in my opinion in the one patient where I was in that situation, I think those bone scans were flare reactions and were not progression. And that accounts for a small portion of those patients who continued progression beyond treatment. But for the data that you see, that patient that you described would have been considered to have disease progression.

DR. HUSSAIN: Dr. Link?

DR. LINK: I'll confess my unfamiliarity with breast cancer, but if you had shown a survival advantage we wouldn't be having these discussions. And one of the concerns looking at the trial results is that one of the reasons not to have a statistically significant improvement is that

the control group is a lot better than your experimental group. And it looks, at least if you look at from the presentation from Dr. Winer, that this control group performed spectacularly well and out -- you know, sort of an over-achieving group.

Now, we heard at the beginning of our presentation that salvage therapies don't affect overall survival. That was one of the conclusions of the FDA. So I'm not sure who should address this question, either the FDA or sponsors. But how do you explain this terrific performance in survival of the control group of this treatment compared to sort of other studies that have been done?

DR. BOWDEN: Thank you for your question. Could I ask Dr. Winer to comment on his view of the survival on the control arm, E2100?

DR. WINER: So in the end, this is why we do randomized trials because comparing across trials is, of course, problematic.

This group of patients did not include any patients with HER2-positive disease. Many of those older trials included patients with HER2-positive disease. In fact, one would presume that somewhere in the range of 20 to 30 percent of the patients in those older trials had HER2-positive disease and at that point in time would not have been treated with HER2-directed therapy. Those patients would have been expected to have a worse overall outcome. And two-thirds of these patients had ER-positive disease. And we know that even from the initiation of chemotherapy that patients with ER-positive and HER2-negative disease actually have a more favorable outcome.

DR. LINK: But you included HER2-positive patients who had already been treated with trastuzumab, so that would be even like the worse group, I would think.

DR. WINER: So, in fact, I can address that because, I mean, it was on

Kathy's slides and I'm also familiar with the data. Across the trial approximately 2 percent of the patients had HER2- positive disease. And the reason for that is that patients who had previously been treated in the metastatic setting were excluded, so the only patients who could have had HER2-positive disease with prior treatment would have been patients treated on a preoperative or pilot adjuvant trial.

DR. HUSSAIN: Dr. Lyman?

DR. LYMAN: Yes, two questions, one the sponsor may or may not respond to. But one of the concerning things to me in the presentations this morning was what appeared to be, at least from the FDA perspective, a breakdown in communication not only with the sponsor, but with the ECOG and the NCI. And having been, not currently, but a member of ECOG and done a lot of cooperative group studies this concerns me if this is true. I realize it came down to specific issues with

regard to the labeling parameters, but this is concerning and I would be interested in your perspective of the series of events and how this was perceived from the sponsor's standpoint.

The other issue, we haven't weighed in yet, at least the current membership of ODAC, on the legitimacy of progression-free survival for labeling approval for first-line metastatic disease. But if we do favorably, then the real issue comes down to the toxicity signals. And clearly the data shows a 20 percent increase in Grade 3 to 5 adverse events in the bevacizumab group, but it's confounded or complexified by the longer duration of response and observation. It seems to me this would be amenable to -- and you may have done -- I think there was some allusion to an analysis that wasn't presented to an adjustment for -- based on the rate of events per unit time or a time to event analysis that is the time to first Grade 3 to

5 adverse event. If this -- was this done? What did you find if that was done? Are we really dealing with a standalone increased toxicity due to the Avastin or is it simply that it controlled the disease longer so there was more chance to experience adverse events?

DR. BOWDEN: Thank you for your question. With regards to the CR letter and the communication back and forth between Genentech, FDA, and between the other groups involved is there were a number of communications as outlined in our presentation this morning. And at the time that -- we had the 2119 study ongoing and E2100 at the same time. And our decision to file E2100 initially was on the basis of the strength of the data, discussions with investigators. And in the subsequent discussions with FDA when it was outlined that things that were needed to be done in order to resubmit, including the IRF for all

722 patients, and the database cutoffs as outlined, we went ahead and did those things and resubmitted them and that's what you're seeing now. And we think that speaks to the strength of the Avastin/paclitaxel combination.

With regards to toxicity, we did do a time looking at whether duration of therapy has impacted on neuropathy. And, in fact, it certainly appears to be the case because when you balance for time on treatment, the frequency looks the same.

With regards to some of the other side effects, we did not do a time on treatment analysis.

I think one of the important things to point out in that delta, that difference of 20 percent, is several of those are Avastin-specific toxicities. The one that occurred with the most frequency is hypertension. The frequency of Grade 3 hypertension, which requires a medical

intervention, was 15.4 percent. So the vast majority was manageable as the same for proteinuria.

Now, those are the data and I'd just like Dr. Miller to comment on how that looks in terms of thinking about time to event analyses and thinking about the totality of the data in talking to a patient or thinking about this as a treatment.

DR. MILLER: So Chris is right. In this study the only time to event analysis we've done with toxicity is looking neuropathy. We have done in a previous study of Avastin monotherapy that allowed patients to continue treatment until progression and included a substantial number of patients and multiple disease sites treated for more than a year, looked at time to even analysis for hypertension and proteinuria. And there was a fairly smooth risk of those over time. We don't see an accelerated rate after any particular time on therapy. So some of this

toxicity is indeed just a function of our success, if you will. If you were on therapy for a longer period of time there is a greater potential for events that occur at fairly low frequency to occur in those patients.

I think what is lost in lumping all of the toxicities together is really looking at what those toxicities mean to women with metastatic disease who are living with this disease on a day-to-day basis.

When my patients tell me about toxicities that are troubling to them, they tell me about nausea, fatigue, diarrhea, hair loss, neuropathy, and myalgias. They never mention hypertension as something that limits them in their day-to-day lives. It's certainly an important toxicity that women and their physicians need to know about, it needs to be monitored. And in 15 to 16 percent of the patients they needed a medical intervention, usually taking an oral

anti-hypertensive to manage that and avoid it becoming more serious. But I think it's important in our minds to separate that 20 percent into those that are important and need management, but don't add to the day-to-day symptom burden of patients in the way that the more classical chemotherapy toxicities do.

DR. HUSSAIN: Dr. Curt?

DR. CURT: Thank you. I think it would be important for the committee to hear from the agency your philosophy around when progression-free survival and response rate appear to be adequate for approval as in the case of lapatinib and ixabepilone and when you'd like to see more of a survival advantage.

DR. PAZDUR: Well, it has to do with the risk-benefit situation. And obviously in a more refractory disease setting there is a different risk-benefit than in a first-line setting. But more

importantly, we've had numerous discussions with this committee and other committees in dealing with other endpoints. And one of the important areas that came out in those discussions is when we're dealing with more refractory disease patients, we're dealing usually a more symptomatic patient population. Hence a delay in progression in a symptomatic population probably has a little more clinical meaning than a delay -- simply a radiographic delay in asymptomatic patient populations.

So that's how we were able to really look at this whole issue of looking perhaps at PFS in a more refractory disease setting as a regulatory endpoint. And that's why we have a question in the first-line setting where we do have obviously a different risk-benefit situation than in a more refractory disease setting. There's fewer therapies that are available to those patients. And in addition to that, one is

taking a look probably at a more symptomatic patient population and that's how we view these as different situations here.

DR. HUSSAIN: Ms. Portis?

MS. PORTIS: A couple things. I am concerned about the incomplete and the missing data that's here. And I absolutely agree that we need meaningful treatments for metastatic disease. For me that does mean overall survival and an increase in quality of life.

And to piggyback on what Dr. Lyman was saying, there is a significant increase in the Grade 3 to 5 adverse events and yet the sponsors say that quality of life is not impacted. And I'm very concerned that the severe toxicity is really being minimized and that in the literature they say that these toxicities were expected or that they're being managed. But it's very concerning to me and I think that this is a really serious issue here, and that just because it's

expected, because it was in the packaging, doesn't mean that that's acceptable to patients or perhaps somebody can say it's manageable, but I don't know if that really feels manageable in the overall quality of life if you're also not getting any overall survival benefit.

DR. HUSSAIN: Thank you. Dr. Buzdar?

DR. BUZDAR: One question which I am still grappling in my mind is that we have capecitabine/Avastin study which is negative, which is a fairly large randomized trial. And at that time the logic was that because it was carried out in a heavily treated patient population, that's why the study did not translate into longer control of the disease or having any favorable impact on the survival. Subsequently, a straight Phase II study with capecitabine and Avastin was carried out in a less treated patient population and that Phase II study also was