UNITED STATES FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

OPEN SESSION

Gaithersburg, Maryland

Wednesday, December 5, 2007

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P R O C E E D I N G S

(8:00 a.m.)

DR. HUSSAIN: My name is Maha Hussain and I'd like to welcome you to this morning's session. Before we begin I'd like to read a statement.

For topics such as those being discussed at today's meetings there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that the individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take

place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

I'd like to first begin by introducing the committee, and I'll begin on my right with Dr. Curt.

DR. CURT: I'm Greg Curt, medical oncologist with AstraZeneca, U.S. Medical Science Lead for Emerging Products.

DR. BUZDAR: Aman Buzdar from M.D. Anderson Cancer Center.

MR. D'AGOSTINO: Ralph D'Agostino from Boston University, statistician.

MS. PORTIS: I'm Natalie Compagni Portis and I'm the patient representative today.

MS. MASON: I'm Ginny Mason. I'm with the Inflammatory Breast Cancer Research Foundation and the consumer rep.

DR. LYMAN: I'm Gary Lyman, medical oncologist and health services researcher for Duke University.

DR. MORTIMER: Joanne Mortimer, medical oncologist, City of Hope.

DR. HUSSAIN: Maha Hussain, medical oncology, University of Michigan.

MS. VESELY: Nicole Vesely, designated federal official, Oncologic Drugs Advisory Committee.

DR. ECKHARDT: Gail Eckhardt, medical oncologist, University of Colorado.

DR. LINK: Michael Link, pediatric oncologist from Stanford.

DR. CORTAZAR: Patricia Cortazar, medical oncologist, FDA.

MS. LU: Laura Lu, statistical reviewer, FDA.

DR. PAI-SCHERF: Lee Pai-Scherf,

medical officer, FDA.

DR. KEEGAN: Patricia Keegan, Division of Biological Oncology Products, FDA.

DR. PAZDUR: Richard Pazdur, office director, FDA.

DR. HUSSAIN: Thank you. Nicole Vesely, who is the designated federal official, will read the Conflict of Interest Statement.

MS. VESELY: The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committee's compliance with

federal ethics and conflict of interest laws covered, but not limited to, those found at 18 U.S.C. Section 208 and 712 of the federal Food, Drug, and Cosmetic Act is being provided to participants in today's meeting and to the public. FDA has determined that members and consultants of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion of today's meeting, members and consultants of this committee who are special government employees have been screened for potential conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of supplemental biologic application 125085/91 Avastin (bevacizumab) sponsored by Genentech, Inc., proposed indication, in combination with paclitaxel for the treatment of patients who have not received chemotherapy for their locally recurrent or metastatic, HER2-negative breast cancer. Based on the agenda for today's meeting and

all financial interests reported by the committee members and consultants, conflict of interest waivers have been granted in accordance with 18 U.S.C. Section 208(b)(3) to Drs. Joanne Mortimer, S. Gail Eckhardt, Maha Hussain, and Aman Buzdar; and waivers have been issued in accordance with Section 712 of the FD&C Act for Drs. Mortimer, Eckhardt, and Hussain.

Dr. Mortimer's waivers involve unrelated consulting with the sponsor for which she receives less than $10,001.

Dr. Eckhardt's waivers cover unrelated consulting with a sponsor for which she receives less than $10,001.

Dr. Hussain's waivers entail her employer's interest in a competing firm's study. She receives salary support. Her institute received more than $300,000 in funding. Her spouse also owns stock in the sponsor firm and six competing firms.

Dr. Buzdar's waiver also involves

his employer's interest in a competing firm's study for which he received no personal remuneration. His institute received more than $300,000.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waivers document, which are posted on FDA's web site at www.fda.gov/ohrms/dockets/default.htm. Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Office, Room 6-30 of the Parklawn Building. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Gregory Curt is serving as the industry representative acting on behalf of all regulated industry. Dr. Curt is an employee of AstraZeneca.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue. Thank you.

DR. HUSSAIN: Thank you, Ms. Vesely. I'd like to invite Dr. Pazdur to begin which his opening remarks.

DR. PAZDUR: Thank you, Dr. Hussain. And I think a lot of people will be joining us late considering the snow out. When I was traveling here (off mike). Okay, you can hear me now. All I was saying is that it's bad weather and we're going to anticipate probably some latecomers. The traffic was really backed up on the

expressways with multiple accidents, et cetera, so we probably will be getting people coming in late.

As far as opening comments I'd like to make the following statement. In June 1999, the ODAC discussed the use of time to progression, or TTP, as a primary registration endpoint for clinical trials in first-line metastatic breast cancer. At that time, the committee recommended that TTP was not an acceptable endpoint for regular approval in first-line cytotoxic therapy for breast cancer and that overall survival should remain the primary efficacy endpoint for registration trails. At today's ODAC we will be revisiting this discussion.

TTP is defined as the time from randomization until objective tumor progression. And the closely related endpoint, progression-free survival, or PFS, is defined as the time from randomization until objective tumor progression or death.

These endpoints have been used as registration endpoints and the ODAC committee suggested relying on these endpoints in selected clinical situations, such as diseases where survival benefit in clinical trials may be difficult. Past ODAC discussions have recommended that PFS is a better predictor of clinical benefit than TTP because the definition of PFS includes death. Unanticipated effects of drugs on survival would be included in this endpoint. Important considerations on the use of PFS as an endpoint should include the magnitude of effect on PFS, the treatment's toxicity profile, and the clinical benefits and toxicities of available therapy.

The use of PFS has certain advantages and disadvantages in comparison to using overall survival as a registration endpoint. Conceptually PFS has the desirable qualities of a surrogate endpoint because it reflects tumor growth, a phenomena likely to

be on the causal pathway for cancer-associated morbidity and death. In addition, an effect on PFS can be assessed prior to the demonstration of a survival benefit and is not subject to the potential confounding impact of subsequent therapies. Moreover, an effect on PFS occurs earlier than an effect on overall survival.

The use of PFS requires careful planning and attention to detail in assessing progression. Unlike the endpoint of overall survival, bias can be easily introduced in assessing PFS. In our guidance for industry clinical trial endpoints for the approval of cancer drugs and biologics, we have attempted to address problems associated with the use of PFS as a primary endpoint for registration trials.

It is important that the methodology for assessing, measuring, and analyzing PFS be detailed in the protocol and statistical analysis plan. When possible,

studies should be blinded. In oncology trials, where different toxicities or drug schedules preclude blinding, an independent endpoints review committee provides a mechanism to evaluate and minimize bias in this assessment of radiographic findings. Other difficulties with the assessment of PFS include problems associated with missing assessments or incomplete assessments either at baseline or at periodic evaluation.

In today's ODAC meeting Genentech has submitted an application for marketing Avastin in combination with paclitaxel for the treatment of patients who have not received chemotherapy for their locally recurrent or metastatic breast cancer.

This application is primarily supported by trial E2100 that enrolled 722 patients from December 2001 to May 2004. Two hundred and sixty-eight centers primarily representing United States cooperative groups enrolled the patients. The primary endpoint

of the trial was determined to be PFS adjudicated by a blinded independent radiographic facility. Secondary endpoints were overall survival, response rates and duration, and health-related quality of life.

The sponsor claims an estimated 5.5-month media improvement in PFS by an independent review. This finding is similar to that reported by the clinical investigators of the trial. This improvement in PFS was accompanied by an improvement in response rate. Importantly, a mature survival analysis does not demonstrate an improvement in overall survival. In addition, the addition of Avastin to paclitaxel resulted in over a 20 percent increase in Grade 3 to 5 toxicities and an increase in treatment-related death rate.

In addition to the primary trial, a second trial was submitted with this application. This trial was conducted in a different patient population: Breast cancer

patients previously treated with anthracyclines and taxanes. This trial randomized patients to either capecitabine alone or capecitabine plus Avastin. This trial showed neither an improvement in PFS nor overall survival associated with the addition of Avastin to capecitabine.

For regular approval the sponsor must show direct evidence of clinical benefit or an improvement in an established surrogate for clinical benefit. Clinical benefit has generally been defined as an improvement in survival or disease- related symptoms. In today's application an improvement in PFS is observed without an improvement in overall survival. Hence PFS cannot, in this application, be considered a surrogate for clinical benefit.

We will be asking the ODAC to discuss if PFS alone, without a demonstrated improvement in survival, should be considered direct clinical benefit in the initial

treatment of metastatic breast cancer.

Secondly, we will ask you to consider the risk versus benefit relationship associated with the improvement in PFS and the increased toxicities and toxic deaths associated with Avastin in this setting. The ODAC should consider the totality of the information associated with this drug in formulating their comments. This should include the lack of an effect on PFS in overall survival in the second- and third-line metastatic breast cancer setting.

Lastly, since an improvement in overall survival has been recommended by the ODAC in 1999 for the primary approval endpoint in first-line breast cancer, we have asked Dr. Patricia Cortazar to review our history of breast cancer approvals, both in the first-line setting as well as in more refractory breast cancer disease settings. Thank you.

DR. HUSSAIN: Dr. Cortazar?

DR. CORTAZAR: Thank you, Dr. Hussain. Good morning. Members of the advisory committee, colleagues, ladies and gentlemen, I am going to present a summary of the FDA approval of cytotoxic and biologic drugs for metastatic breast cancer. First, I will discuss all the drugs that FDA had approved for this (off mike) setting, then I will summarize the endpoints that have served as bases of approval.

Before I start I would like to acknowledge Dr. John Johnson, who made a major contribution to this presentation.

There have been cytotoxic drugs that have been approved for metastatic breast cancer and the following list -- methotrexate, cyclophosphamide, thiotepa, vinblastine, 5-fluorouracil, and doxorubicin -- were all approved more than 30 years ago. These drugs had a very broad and general base approval without regard to stage of disease. Therefore, I am not going to spend time

talking about these previous approvals since they were not approved under modern review standards.

These slides show the drugs that the FDA has approved for second- or third-line metastatic breast cancer. There was a gap of 20 years between the doxorubicin approval and the approval of paclitaxel. However, in the last 13 years, FDA has approved several additional drugs as monotherapy or in combination. The study (off mike) of these drugs have been somewhat similar. We have generally required comparative trials, especially because it would be very difficult to interpret efficacy in a single arm trial. I will discuss all the drugs from this list except Abraxane, which was approved under a different standard through a 505(b)(2) regulation.

Paclitaxel was approved in 1994 for the treatment of metastatic breast cancer after failure of an anthracycline. This

slide shows the study design that supported Taxol approval. It was a randomized control study in 471 patients with metastatic breast cancer who failed one or two chemotherapy regimens. Sixty-seven percent of these patients had received prior anthracyclines.

The treatment arms compared two doses of paclitaxel: 175 milligrams per meter-squared with 135 milligrams per meter-squared. Time to preparation was the basis for approval of paclitaxel's second-line treatment of metastatic breast cancer. And as you can see, it was significantly longer on the paclitaxel higher-dose arm.

Docetaxel was approved in 1996 for patients with metastatic breast cancer after failure of prior chemotherapy. Initially docetaxel received accelerated approval. The safety and efficacy were related in three Phase II studies conducted in a total of 134 patients who had anthracycline-resistant

metastatic breast cancer. An overall response rate of 41 percent was the basis of this approval. Median response duration was six months and median time to progression was four months. The post-marketing commitment of this accelerated approval was to submit the study results of the ongoing controlled clinical trials in advanced breast cancer.

Study TAX304 was the basis of docetaxel full approval. It was a randomized trial in 392 patients with a history of prior treatment with an anthracycline-containing regimen. Fifteen percent of the patient population received treatment as first-line. Patients were randomized to docetaxel or the combination of mitomycin plus vinblastine at the doses shown in the slide.

This table summarizes TAX304 study results. Full approval was based on a statistical significant survival advantage. P value was.01. There was also a statistical significant advantage in time to progression.

Herceptin was approved in 1998 for patients with metastatic breast cancer whose tumors over-expressed the HER2 protein who had received one or more chemotherapy regimens for their metastatic disease. This approval was also supported by the first-line metastatic breast cancer approval, which I will discuss with the first-line approvals.

Herceptin was studied as a single agent in a single arm clinical trial in 222 patients with HER2 or expressing metastatic breast cancer who had progress after one or two prior anthracycline and taxane chemotherapy regimens for their metastatic disease. The Herceptin dose is shown in this slide.

Herceptin full approval in second-line metastatic breast cancer was based on overall response rate of 14 percent with a 2 percent complete response rate. Median duration of response was 9 months and median survival was 12.8 months.

Capecitabine initially received accelerated approval in 1998 for the treatment of patients with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing regimen. This indication was approved based on a 25.6 response rate in a single arm trial in patients considered to have refractory breast cancer. No results were available from control trials that demonstrated a clinical benefit, such as improvement in disease-related symptoms, disease progression, or survival. The post-marketing commitment was to submit data on the randomized control trial in a similar patient population.

In 2001, capecitabine was approved in combination with docetaxel for the treatment of patients who had filed prior anthracycline- containing chemotherapy. The registration trial consisted of one randomized control study in 511 patients with

metastatic breast cancer who had failed an anthracycline-containing regimen. Thirty percent of the patients received treatment as first- line. Patients were randomized to receive capecitabine in combination with docetaxel or docetaxel monotherapy at the doses listed on the slide.

This table summarizes the study results. Full approval of capecitabine was based on a statistical significant survival advantage. There was a P value of.01. There was also a statistical significant advantage in time to progression.

This Kaplan-Meier curve depicts the same data I just showed you, a statistical significant overall survival of the capecitabine-docetaxel combination.

Lapatinib was approved in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors over-express HER2 and have received prior

therapy, including an anthracycline, a taxane, and trastuzumab. The study that supported the approval of lapatinib in combination with capecitabine was a randomized Phase III trial in 399 patients with locally advanced or metastatic breast cancer over- expressing HER2 by 3-plus or 2-plus by immunohistochemistry and confirmed by FSH. These patients had progressed after prior treatments that included anthracyclines, taxanes, and trastuzumab, so this was a very refractory population. Patients were randomized to receive either lapatinib plus capecitabine or to receive capecitabine alone at the doses shown on the slide.

This table summarizes the study results. The basis of full approval was an improvement in time to progression in patients treated with lapatinib in combination with capecitabine compared to capecitabine alone. The median time to

progression was 27.1 weeks versus 18.6 weeks, with a hazard ratio of.57 per independently reviewed assessments. As you can see, the magnitude of the treatment benefit was different when comparing the independent radiology review and the investigators.

The study was stopped early based on an interim analysis of time to progression and there were some missing data. Some data available to the investigators were not available to the IRC. This may account for the differences. The survival data were not mature at the time this (off mike) was submitted. This Kaplan-Meier curve shows the severity in time to progression of the lapatinib-capecitabine combination arm.

Ixabepilone was the most recent approval in a second third-line metastatic breast cancer setting. The submission was based on two studies that supported each other. It is approved in combination with capecitabine for the treatment of patients

resistant to treatment with an anthracycline and a taxane. The study that supported the approval of ixabepilone was a randomized trial of 752 patients with metastatic breast cancer who had tumor progression or resistance to taxanes and anthracyclines. Patients were treated with a combination of ixabepilone and capecitabine and compared to patients treated with capecitabine monotherapy at the doses listed on the slide.

The primary endpoint of the study was progression-free survival and it was defined as the time from randomization to radiologic progression as determined by an independent radiology review, clinical progression of measurable skin lesions, or death from any cause. Ixabepilone in combination with capecitabine received full approval based on a statistically significant improvement in progression-free survival compared to capecitabine monotherapy. The data on overall survival are not yet mature.

The results of the study are presented in this Kaplan-Meier figure. The progression-free survival difference was about six weeks.

Ixabepilone is also approved as monotherapy for the treatment of metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine. The monotherapy indication was supported by a single arm study in 126 women with metastatic breast cancer and had progress following two more chemotherapy regimens, including an anthracycline, a taxane, and capecitabine.

This table summarizes the study results. The objective response rate based on independent radiology review was 12.4 percent. The objective response rate based on investigator assessment was 18.3 percent. The median response duration was six months. Again, this indication was also supported by the ixabepilone plus capecitabine study.

Now I will move on to discuss the first- line metastatic breast cancer approvals. This slide shows the drugs that the FDA has approved for the initial treatment of metastatic breast cancer. As you can see, we have very few approvals in first- line metastatic breast cancer.

Herceptin was approved in 1998 in combination with paclitaxel for treatment of patients with metastatic breast cancer whose tumors over-expressed HER2 protein and who have not received chemotherapy for their metastatic disease.

The study that supported the approval of Herceptin in first-line metastatic breast cancer was a randomized control trial conducted in 469 women with metastatic breast cancer who had not received treatment with chemotherapy for their disease. Only patients with HER2 over-expressing tumors 2-plus and 3-plus positive by immunohistochemistry were

eligible.

Patients were randomized to receive chemotherapy alone or in combination with Herceptin.

Patients who received prior anthracycline in the adjuvant setting were treated with paclitaxel and for the other patients chemotherapy consisted of anthracycline plus cyclophosphamide. Herceptin was administered at the dose shown on the slide. I would like to point out that 65 percent of the patients in control arm cross over to Herceptin at the time of disease progression.

The basis of full approval of Herceptin was a superior time to progression supported by a statistically significant improvement in 12-month survival rates. And we made this decision because this overall survival data was not mature.

These figures show the Herceptin updated survival data. And as you can see,

it still shows the positive survival effects with a median survival of 12.8 months in patients treated with chemotherapy plus Herceptin compared to patients treated with chemotherapy alone. The magnitude of the survival effect was greater in the paclitaxel subgroup. This slide shows the improvement of time to progression for patients on the Herceptin arm, both overall and in the subgroups.

Gemcitabine was approved May 2004, in combination with paclitaxel, for the first-line treatment of patients with metastatic breast cancer.

A randomized Phase III study in 529 patients supported the approval of gemcitabine in combination with paclitaxel for treatment of breast cancer patients who had received prior adjuvant (off mike) anthracycline chemotherapy unless clinically contraindicated. Gemcitabine plus paclitaxel was compared with single agent paclitaxel at

the dosages shown in this slide.

The basis of full approval of gemcitabine was a positive time to progression supported by a strong trend toward improved survival for the group given gemcitabine based on an interim survival analysis. With about 30 percent patients still censored, the median overall survival on the gemcitabine-paclitaxel arm is 18.6 months and on the paclitaxel monotherapy it's 15.8 months. The hazard ratio is.823 with a stratified lower rank P value near the.05 level. This Kaplan-Meier curve shows the statistically significant improvement in time to document it. This is progression with the addition of gemcitabine to paclitaxel compared to paclitaxel monotherapy.

Now I would like to summarize the endpoints that have been used in metastatic breast cancer. An improvement in overall survival in a randomized control study is the gold standard endpoint in first-line

metastatic breast cancer. We have required a meaningful improvement on survival for safety and efficacy reasons.

Safety reasons because cytotoxic as well as biologic drugs are usually very toxic. Due to this toxicity, FDA has not considered tumor response or time to progression as adequate basis for approval. For this reason, requiring survival data in a randomized control trial is also considered a safety endpoint. Sometimes survival can be caused by the net effect of drug toxicity or progressive disease or both or, in some cases, it might not be clear which is the cause of death. Taking into account all these issues, survival data can assure that the new treatment is effective and has reasonable toxicity.

Another reason for requiring survival is that effective drugs prolong survival. As discussed in a previous ODAC meeting, doxorubicin-based regimens improved

median survival around six months when compared to regimens that do not contain doxorubicin. Herceptin in combination with chemotherapy has a five-month increase in median survival when compared to other chemotherapy regimens in patients who over-express HER2 new protein. Docetaxel monotherapy as well as capecitabine-docetaxel combination also has a three-month prolongation of survival. So as you can see, doxorubicin and Herceptin have been probably the most active agents in metastatic breast cancer treatment.

This slide shows the instances where survival has served as a basis for approval. In the first-line setting, Herceptin in combination with paclitaxel and gemcitabine in combination with paclitaxel. In the second-line setting, docetaxel monotherapy and capecitabine in combination with docetaxel. Because survival has been demonstrated in this setting, FDA wants

assurance that the survival effect gains are not lost when a new drug is introduced.

The most common criticism of survival as an endpoint is that secondary drug therapy after tumor progression may confound any survival effect of the tested drug. This issue was discussed previously at ODAC and according to previous discussions, this is not the case. In addition, there is no literature to support the statement.

A drug used after tumor progression should have the same effect in both arms and should not obscure the effect of the drug tested in the rare event that a drug might obscure the survival effect.

That can also be expected in clinical practice, so it does not matter if the patient gets the tested drug or not. In the event of crossover of the control arm after progression to the tested drug there is no evidence that (off mike) survival, and here are two examples.

In a randomized control study of Herceptin in first-line treatment of metastatic breast cancer a five-month median survival advantage was demonstrated in spite of a 65 percent crossover rate from the control arm to the Herceptin arm. In colorectal cancer Camptosar plus 5-FU/leucovorin was better than 5-FU/leucovorin in spite of a 40 percent crossover rate.

So these two examples showed that when the survival effect is robust we can still see an effect regardless of the crossover therapy. Therefore, the problem is not the survival endpoint. The problem is the lack of good drugs that can show survival benefit.

In this particular application the sponsor has established that there is no survival benefit from Avastin in second- or third-line metastatic breast cancer, so it does not apply this application. Dr. Lee Pai

and Dr. Lu will talk about this later.

The acceptability of time to progression as basis of approval in first-line metastatic breast cancer was discussed at the previous ODAC meeting in June 1999, and was considered not acceptable. The committee discussed the limitations of measuring time to progression and, in my opinion, those limitations or difficulties can also be applicable to progression-free survival.

This slide shows the instances where time to progression has served as the basis for approval.

The two approvals, paclitaxel and lapatinib, are in second- and third-line metastatic breast cancer.

Progression-free survival is not validated as a surrogate endpoint of survival in first-line treatment of metastatic breast cancer. Progression- free survival has only been used once as the basis of approval of

ixabepilone and that is second third- line metastatic breast cancer.

Progression-free survival is an endpoint that is very difficult to measure properly. First of all, progression-free survival should be assessed only in a randomized control trial with a blinded assessment by an independent radiology review. It is very important that registration trials are determined earlier so they can be properly designed.

This slide shows some of the problems with progression-free survival assessment. Missed or incomplete assessments at baseline are occasional problems. There are also occasional problems with patients without measurable disease. The most frequently problems are with missed assessments or incomplete assessments at follow-up.

There are also problems when there are infrequent assessments. There are

problem when there are uneven assessments in each arm, and this happens often when the two treatment arms have different treatment schedules.

Another important issue is when you find a high rate of discordance between reviewers. This can indicate the data is not reliable. Because of the subjectivity of the endpoint it might be necessary to have two trials to support each other.

We are seeking advice in today's ODAC. Is the use of progression-free survival in the first- line treatment of metastatic breast cancer appropriate, especially in a situation where there is no improvement in survival? We have serious concerns that NDA submissions based on progression- free survival in the first-line metastatic breast cancer setting will affect survival data.

First of all, studies probably will be stopped before accrual is complete or stop

following patients for survival.

Second, there is a risk that in future trials we will never know whether there is a real survival benefit to the new drugs.

If survival is not a needed endpoint, then companies would not collect or submit survival data.

This risk is too high in the first-line metastatic breast cancer setting. I would like to reemphasize that survival is an efficacy and safety endpoint, and this is particularly important for therapies that have a high toxicity profile.

In addition, losing survival effect in a disease setting where there is already a modest but a real survival is very problematic. Thank you.

DR. HUSSAIN: Thank you, Dr. Cortazar. We'll begin the sponsor presentation. Dr. David Schenkein will begin.

DR. SCHENKEIN: Good morning and thank you, Dr. Hussain, committee members, FDA representatives and guests. My name is Dr. David Schenkein with the Clinical Hematology & Oncology at Genentech. We'd like to thank the Food and Drug Administration for the opportunity to present to the Oncology Drugs Advisory Committee data in support of Avastin in combination with paclitaxel for the treatment of metastatic breast cancer. We'd also like to thank the members of the committee for their careful consideration of this topic and the patients who participated in the studies that support this BLA without whom this work would not have been possible.

In this overview we will cover the following topics: The indication statement, a brief Avastin overview, an executive summary of E2100, and a review of the agenda and speakers for today's presentation by Genentech. Our objective is to seek

regulatory approval of Genentech's supplemental BLA for Avastin in combination with paclitaxel for the treatment of patients who have not received chemotherapy for their locally recurrent or metastatic HER2-negative breast cancer.

Avastin, a monoclonal antibody, highly specific for the VEGF ligand, has validated the concept of antiangiogenesis in cancer therapy. It is estimated that more than 200,000 patients worldwide have received Avastin since its initial approval.

The clinical validation has come from numerous settings. Avastin is currently FDA- approved in both first- and second-line colorectal cancer in first-line non-small cell lung cancer based on randomized trials with both a progression- free survival and an overall survival advantage of clinically important magnitude.

Outside the United States, in addition colorectal cancer and lung cancer,

Avastin was also approved for use in metastatic breast cancer based on the E2100 study. E2100 also serves as the foundation of our FDA supplemental application in first-line metastatic breast cancer that we will present to you today.

Following the cloning of VEGF at Genentech, a broad development program for Avastin was initiated. Breast cancer has been a focus of this clinical development plan from its inception. As shown in this timeline, a single agent Phase I/II trial in patients with metastatic breast cancer, initiated in 1998, demonstrated activity for Avastin with a well- tolerated safety profile. This Phase I/II trial was followed by two Phase III trials in two different populations of breast cancer patients.

Study AVF2119, sponsored by Genentech, was designed for patients requiring second- or third- line chemotherapy for metastatic breast cancer, who had

progressed after receiving the most active chemotherapy agents available. It demonstrated a statistically significant improvement in response rate, a secondary endpoint, but did not improve progression-free survival.

In parallel to AVF2119, the E2100 study was designed, but for a very different patient population: Women who had not received prior chemotherapy for their metastatic disease. E2100 was sponsored by the National Cancer Institute and conducted by the Eastern Cooperative Oncology Group as part of the clinical research agreement, or CRADA, between Genentech and the NCI. The strongly positive results from E2100 have generated a number of studies in both the metastatic and adjuvant settings that will enroll upwards of 15,000 patients over the next several years. Let's walk through the regulatory milestones for E2100.

Study E2100 was a multi-center

randomized Phase III trial that enrolled patients almost exclusively in the United States. The enrollment period was from January 2002 to May of 2004. The trial was declared positive by the independent Data Monitoring Committee at its first interim analysis based on clearly meeting its primary endpoint 11 months after the last subject was enrolled on the trial.

Genentech discussed the results of this trial with the FDA in a pre-submission meeting and reached agreement on the package that was needed to support a BLA. E2100 was the primary basis for this sBLA. The BLA supplement was then submitted in May of 2006.

In September 2006, the FDA issued a complete response letter and stopped the review clock for this application. Following agreement between the FDA and Genentech on the approach to address the FDA requests, the application was resubmitted in August of 2007. The key agreements with the FDA to

support resubmission are shown on this slide. In response to the agency's request for additional information, Genentech sponsored an independent radiological review assessment of progression-free survival, which also became the primary endpoint to support a supplemental label in this indication.

Additionally, as per industry standard, a data cutoff date for efficacy based on the date of the ECOG interim analysis was applied to a final, clean database and final, mature survival data were submitted. The contents of the BLA are shown on this slide.

In agreement with the FDA and due to their later line of therapy, studies AVF0776 and AVF2119 were agreed to be relevant for assessing safety. And only safety data from these studies were included in the submission package.

In summary, Study E2100 was a strongly positive, multi-center, randomized

Phase III trial conducted by a preeminent oncology cooperative group. The data in this BLA submission demonstrate the combination of Avastin and paclitaxel improves outcome for patients with metastatic breast cancer based on compelling evidence from three endpoints: Progression-free survival, response rate, and overall survival.

The primary endpoint, progression-free survival, was appropriately measured. It demonstrated a large treatment effect and is robust based on consistency within all subsets and the retention of statistical significance in all sensitivity analyses. In addition, the overall response rate was improved and there was evidence for an improvement in survival with a clear separation of the survival curves for the first 30 months, although the hazard ratio was not statistically significant.

Avastin has a very favorable benefit-to- risk ratio. The increase in side

effects from the addition of Avastin to chemotherapy was manageable and was in the range of other agents used and approved for use in breast cancer and was similar to that seen with Avastin in other indications.

Finally, while today's discussion will focus on PFS as an endpoint for regulatory approval in metastatic breast cancer, it is important to note that both PFS and TTP have served as the primary endpoint for the full approval of most of the chemotherapy and hormonal agents currently and recently approved for use in metastatic breast cancer.

In summary, three key points. One, the data demonstrate a robust and clinically meaningful PFS treatment effect. In fact, it represents the longest PFS seen to date with any treatment in this setting. Two, a PFS of this magnitude represents clinical benefit for first-line treatment of metastatic breast cancer patients, especially with Avastin's

manageable and well-established safety profile. And three, Genentech has made a commitment to continue to evaluate Avastin's role in the treatment of breast cancer.

Today's speakers, as shown on this slide, will be emphasizing these and other key points throughout our discussion. Thank you for the opportunity to present to you today and we look forward to your thoughts and questions at the end of the presentation.

And now, I'd like to introduce Dr. Kathy Miller, associate professor of medicine at the University of Indiana and principal investigator for this study.

DR. MILLER: Thank you, David and Dr. Hussain. First let me acknowledge that I have no financial interest in Genentech. My institution does receive research support for ongoing studies that we are currently conducting, and I have been compensated only for my time in preparing to be with you today.

It's my pleasure to be here to discuss with you the results of the E2100 study. I was the study chair for this trial which was conducted by the Eastern Cooperative Oncology Group with the widespread support of all U.S. cooperative groups. E2100 was the first major trial to show the benefit of an antiangiogenic agent when added to initial chemotherapy for metastatic breast cancer and as such represents an important milestone for patients.

In my presentation I'll first review for you the treatment landscape available to patients with metastatic breast cancer at the time the E2100 study was conceived, the E2100 study design and the rationale behind that design, and the efficacy data.

Despite improvements in the treatment and survival of patients with early stage breast cancer, overt metastatic disease

remains largely incurable.

Our goals for any therapy in metastatic disease are best put simply: We hope to help patients live long and prosper. This includes relieving pain when it exists, improving or maintaining quality of life, controlling disease, and, when possible, extending survival.

While chemotherapy remains the mainstay of treatment for many patients, toxicity can be substantial and drug resistance remains common. I've compiled published results of many of the Phase III chemotherapy-based trials that were reported in the decade prior to the initiation of E2100, that is, from 1991 to 2001. The benefits of initial chemotherapy are quite modest with a median progression-free survival of less than 9 months and an overall survival of less than 20 months. Progress in the last six years using drugs and regimens that are arguably more effective has been

sobering. The median progression-free survival has remained stagnant at nine months or less. Despite this, four recent trials have reported a median overall survival of greater than 20 months, perhaps suggesting benefit from subsequent therapies administered after initial progression.

The E2100 study design was based on biological, clinical, and pragmatic considerations.

Numerous pre-clinical studies had shown that the vascular endothelial growth factor, the target of Avastin, was frequently over-expressed by breast tumors and correlated with adverse prognosis. Pre-clinical studies had also shown that the taxanes have distinct antiangiogenic activity with striking synergy when combined with Avastin. Maximizing that antiangiogenic activity, however, requires using lower doses of the taxanes, but more consistent continuous exposure as would be obtained with

a weekly schedule.

A Phase II trial had shown some activity of Avastin monotherapy in patients with heavily pretreated breast cancer. And at the conception of E2100, a Genentech-sponsored Phase III study of Avastin and capecitabine versus capecitabine alone in patients with refractory metastatic breast cancer was ongoing. Pathologic studies had suggested that proangiogenic factors become more redundant as breast cancers progress and thus the benefits of inhibiting VEGF were expected to have a much greater impact earlier in the course of the disease.

Finally, the use of an intravenous placebo was considered unacceptable to many patients and treating physicians, and was seen as a major barrier to accrual. Thus the E2100 study employed an open- label design.

E2100 randomized patients to paclitaxel alone, 90 milligrams per

meter-squared, on days 1, 8, and 15 of every 28-day cycle. Patients randomized to the combination also received Avastin, 10 milligrams per kilogram, on days 1 and 15. Patients continued therapy until disease progression or prohibitive toxicity. Patients randomized to the combination therapy who discontinued paclitaxel without progression, either due to cumulative toxicity or the patient and investigator's discretion, could continue Avastin monotherapy until progression or toxicity. Thus patients who were randomized to paclitaxel monotherapy could not receive Avastin at any time. Prior to randomization patients were stratified for known prognostic factors, including their disease-free interval, exposure to previous adjuvant chemotherapy, estrogen receptor status, and the number of metastatic sites.

The initial primary endpoint of E2100 was time to treatment failure.

However, after consultation and review by the FDA, the primary endpoint was amended to progression-free survival. Secondary endpoints included objective response rate, overall survival, quality of life, and safety.

Patients who were eligible for E2100 were expected to have few symptoms of their disease and to enjoy an overall good quality of life. Our goal was to maintain disease control and quality of life, sparing patients the symptoms of disease progression, toxicities of subsequent therapies, and psychological burden and uncertainty that accompanies progression for as long as possible.

In addition, we realize that patients frequently receive multiple effective therapies for the treatment of their metastatic disease and that could potentially obscure any survival benefit obtained in first-line setting. Thus a

progression- based endpoint was specifically chosen as the primary endpoint for E2100 as the endpoint most important to patients in the first-line setting and most reflective of the benefits of first-line therapy.

E2100 had an 85 percent power to detect a percent increase in progression-free survival assuming a one-sided Type 1 error of 2.5 percent. That would be a two-month improvement from an estimated six-month progression-free survival in patients treated with paclitaxel alone to eight months in patients treated with the combination. The sample size that was required to meet this primary endpoint, coupled with the median projected overall survival in the control arm, resulted in an 80 percent power to detect a 7-month improvement in overall survival and only a 15 to 25 percent power to detect a much more modest, but clinically meaningful, 2- to 3-month improvement.

Patients were eligible for E2100 if

they had locally recurrent or metastatic breast cancer and had not received chemotherapy for their metastatic disease. Patients with HER2-positive disease were excluded unless they had received previous therapy with Herceptin or Herceptin was considered to be contraindicated.

E2100 specifically did not require patients to have measurable disease. Patients without measurable disease, largely those patients with disease limited to bony sites, represent 20 to 25 percent of the patients receiving their initial chemotherapy for metastatic disease and yet they are routinely excluded from clinical trials. The ECOG investigators felt strongly that those patients and their treating physicians deserve to know the benefits and toxicities of treatment in their situation.

In addition, we allowed patients to have had taxane-containing adjuvant therapy as long as their disease-free interval was at

least 12 months.

And patients were excluded if they had significant proteinuria, uncontrolled hypertension, or CNS metastasis. Our patients were required to have a good performance status, either 0 or 1 on the ECOG scale.

As we wished to exclude patients with CNS metastasis, screening CNS imaging was required in all patients. Patients were evaluated with a history and physical examination and safety assessments at the beginning of each cycle of therapy. And tumor assessments based on physical examination and appropriate imaging was required every three cycles or more frequently if clinically indicated.

Treatment assessments were balanced in both arms and compliance with assessments were balanced in both arms. Health-related quality of life was assessed with a FACT-B subscale at baseline, at week 17 when

response to therapy might have been the predominant factor, and at week 33 when we thought that perhaps toxicities of chronic therapy may have become more apparent. Consistent with the primary endpoint, data on therapies administered after progression was not collected.

The E2100 study was a well-conducted and well-balanced, open-label, randomized Phase III trial. All 10 major U.S. cooperative groups participated in this study. Patients were enrolled between late December of 2001 and May of 2004 in 258 centers across North America, Peru, and South Africa, but less than 10 percent of the patients were enrolled outside of the U.S. and Canada.

Let's now turn our attention to the efficacy results. Seven hundred twenty-two patients were enrolled in the E2100 study. Baseline treatment characteristics are well balanced across all the two arms with the

exception of slightly more patients with measurable disease at baseline in the paclitaxel alone arm. The median age was 55 years.

And please note that 65 percent of our patients had received previous adjuvant chemotherapy with nearly 20 percent of patients received taxane-based chemotherapy.

The primary efficacy endpoint, progression-free survival, is based on an independent review of progression events. It is an intent to treat analysis of all randomized subjects, including events that occurred on or before February 9, 2005, consistent with the data cutoff for the original interim analysis. At the time of that data cutoff, events had occurred in approximately half of the patients that had enrolled. The hazard ratio is 0.483, demonstrating that the risk of progression was more than twice as likely in patients randomized to paclitaxel monotherapy. The

median progression- free survival increased from 5.8 to 11.3 months. This represents a highly statistically significant and clinically meaningful improvement.

The paclitaxel alone arm, shown for you here in yellow, performed exactly as we had expected, with a median progression-free survival of nearly six months. The paclitaxel and Avastin arm is shown in blue. The curves diverge early and remain separate throughout the period of follow-up.

The median progression-free survival of 11.3 months is the longest ever reported in this patient population.

We performed a number of pre-specified exploratory analysis to confirm the robustness, generalizability, and validity of the progression- free survival data. First the consistency of the treatment effect was explored across a number of subsets.

Next, PFS was explored using the

investigator-assessed progression data. The comparison of the primary analysis of progression- free survival based on the independent review assessments compared with those based on the investigator assessments allows us to evaluate the impact of any differences or discordance between those assessments for individual patients.

Finally, a series of sensitivity analyses were performed in order to further test the robustness of these data. Let's start with the subset analyses.

Here is a forest plot that displays the treatment effect across several clinical subsets. The vertical line is set at a hazard ratio of 1 and thus all values that fall to the left of this line suggest a benefit for the combination of Avastin and paclitaxel. The treatment effect in the entire population is shown in the top row labeled as "All Patients" for reference. Seventeen factors were explored. I've

displayed only a selected few for you here, but in all subsets, all 17 subsets, the hazard ratio clearly favored the addition of Avastin.

The second group of exploratory analyses examined the consistency or level of agreement in the PFS data between the independent review and the investigator assessments. Here I've displayed the Kaplan-Meier curves for progression-free survival determined by the independent review with both arms shown in yellow. When the progression-free survival was determined by the investigator, now shown in purple, the PFS result, including the medians and hazard ratios, are nearly identical. Both of these PFS analyses were conducted as an intent to treat analysis of all randomized patients with the February 2005 cutoff data applied and with the same PFS definition and censoring rules.

Finally, let's turn to the PFS

sensitivity analyses. A total of eight sensitivity analyses were conducted. Each examined the impact of varying a key assumption on the primary analysis. All eight demonstrated statistical significance for the addition of Avastin. Let's review just one as an example of the sort of sensitivity testing that was performed.

Here we see the primary analysis in the first row in yellow, again for your reference. This sensitivity analysis evaluates the impact of discordance between the independent review and investigator assessment of progression. Specifically, this analysis evaluated those patients whose investigator assessment of progression could not be confirmed by the independent review. This sensitivity analysis penalized patients in the Avastin arm by assuming that they had indeed progressed while patients who received the paclitaxel alone were merely censored. As you can see, the treatment benefit, as

reflected by the PFS hazard ratio of 0.6, is maintained. All eight sensitivity analyses, including two where the assumption of progression was applied only to one arm, retained the significance for Avastin, again speaking to the robustness of the E2100 data.

Finally, let's move our attention to the secondary efficacy endpoints, including objective response rate, overall survival, and quality of life. The objective response was assessed for patients with measurable disease at baseline using the resist criteria. These results are displayed as assessed by the independent review.

The response rate more than doubled in patients with the addition of Avastin from 22 to 50 percent. Patients with progressive disease as their best response was decreased by half from 26 to 12 percent. And only a small portion of patients were unevaluable.

The objective response rate based on the investigator data was 23 percent for

paclitaxel alone and 48 percent for patients receiving the combination. Very similar to the objective response data for patients with measurable disease using the IRF assessments.

Survival data are now mature, with 481 deaths as specified by both the E2100 protocol and the Genentech's statistical analysis plan. The hazard ratio is 0.869 with 95 percent confidence intervals from 0.722 to 1.046 and a P value by the log-rank test of just under 0.14. The median survivals are 24.8 months in patients randomized to paclitaxel alone and 26.5 months in patients randomized to paclitaxel and Avastin, an improvement of 1.7 months.

The Kaplan-Meier curves shown for you here separate early and that separation persists for nearly 30 months. Landmark analysis to determine the 12- and 24-month survivals were not specified, but the 12-month survival was 81.4 percent versus 74 percent, a marked improvement, with a P value

of 0.017. The 24-month survivals were 55 and 50.1 percent.

Baseline quality of life scores are not shown, but were similar across the two arms. As they expected -- excuse me, as we expected, they indicated a relatively asymptomatic patient population and thus an improvement in quality of life was not expected. Quality of life was evaluated with the trial outcome index, a summation of three of the five subscales of the FACT-B. In this analysis, patients with missing data who had progressed or died were given a score of zero. The change from baseline to week 17 and week 33 for the two treatment arms are shown for you here. The primary analysis of quality of life favors the Avastin arm. In this primary analysis, patients with missing data who had progressed or died were given a score of zero. And while this accepted method of analysis was pre-specified, it is imperative that we examine the impact of

missing data on these results.

Four sensitivity analyses were performed and in each of these four the quality of life for patients randomized to Avastin was never lower than the quality of life reported by patients randomized to paclitaxel alone. That is, the addition of Avastin does not impair quality of life.

In summary, the E2100 study was a strongly positive, multi-center, randomized Phase III trial conducted by a highly experienced U.S. cooperative group. The trial was declared positive by the ECOG Data Monitoring Committee at the first interim analysis based on the study clearly meeting its primary endpoint. At that time the data were released publicly, but patients who had not yet progressed continued treatment and follow-up according to the study protocol.

A blinded independent review has now validated the findings of the substantial and clinically meaningful improvement in

progression- free survival associated with the addition of Avastin to weekly paclitaxel. This review supports the general applicability of these results with the consistency of treatment effect in all patient subgroups. The strong consistency of these results and the concordance between the independent review and investigator data validates the rigor of the investigator assessments and the ECOG review process in this multi-institution study.

The robustness of the PFS result was further tested and verified by a variety of sensitivity analyses. Secondary endpoints, including objective response rate, improvement in one-year survival, and quality of life, support the primary endpoint and the significant improvement that this represents for patients.

I'd now like to introduce Dr. Barbara Klencke, associate group medical director at Genentech, who will review the

safety findings from this study.

DR. KLENCKE: Thank you, Dr. Miller. It is indeed a pleasure to be here with you today to discuss with you the safety findings from E2100. And I'll also spend some time reviewing the safety findings from AVF2119 as that study is also relevant to today's discussion.

Let's first look at the treatment summary for E2100. Displayed here you'll see the patients in the Avastin plus weekly paclitaxel arm receive significantly more therapy, receiving a median of 10 4-week cycles as compared with 6.

The reasons for treatment discontinuation are displayed here. As we see in the first row, only 1.4 percent of patients did not receive protocol therapy. Next, we see that treatment was ongoing at the time of the final safety analysis for more patients in the Avastin-containing arm: 11 percent as compared to 2 percent. Most

patients have discontinued therapy for progressive disease and there was no imbalance in the discontinuation rate for toxicity, death on study, or other reasons.

Specifically, approximately 20 percent of patients in both arms discontinued protocol therapy due to toxicity, side effects, or complications.

This slide displays the causes of death as reported by investigators. There were more deaths in patients who received paclitaxel alone. The vast majority of deaths in both treatment arms was due to metastatic disease. Based on this information alone there were no deaths due to protocol therapy in the Avastin-containing arm. However, we agree with the FDA that the treatment-related death rate is higher than the 0 percent as reported by investigators.

Genentech conducted a comprehensive review of the patients in the Avastin plus weekly paclitaxel arm. Based on this review,

1.7 percent of patients likely died due to protocol therapy. However, a similar review was not possible for patients who received paclitaxel alone. This was due to the unequal safety reporting requirements of the E2100 protocol. Specifically, the NCI required expedited reporting of serious adverse events only for the patients in Avastin-containing arm, making an additional review of the investigator-reported data nearly impossible for patients who received paclitaxel alone.

Let's now look at the specific types of adverse events reported in this study. The most Grade 3 and higher adverse events reported are displayed here. Events included on this slide are limited to those that occurred in more than 5 percent in patients in either arm. Paclitaxel, when given on a weekly schedule, as in E2100, is a relatively well-tolerated regimen with the exception of sensory neuropathy. This is the

most frequent adverse event for patients in either treatment arm and appears to be directly related to the paclitaxel exposure. Although the rate reported in the Avastin-treated patients is higher, the rate was similar across the treatment arms when adjusted for time on study.

As expected, the most frequent Avastin- related event was Grade 3 hypertension. Typically Grade 3 hypertension is easily managed with an oral anti-hypertensive medication. Other than the increases observed in neuropathy, hypertension, and fatigue, no other event occurred -- increased by more than 5 percent with the addition of Avastin to weekly paclitaxel. And this was despite their significantly longer duration of treatment.

More than 200,000 patients have received commercial Avastin worldwide and data have been analyzed and reported for nearly 10,000 patients enrolled in clinical

trials. This allows us to identify Avastin-related events across the database that occur relatively infrequently in any one individual trial. So now let's take a closer look at selected events in E2100.

As shown, the rates of all of these events were higher in the Avastin-containing arm as expected. This table also shows these events now by highest grade reported. Avastin Grade 4 and 5 events were relatively infrequent. However, fatal toxicity did occur from GI perforation and arterial thromboembolic events. The toxicity observed in E2100 is entirely consistent with that currently described in the U.S. Avastin package insert with the exception of hemorrhage and GI perforation, which are actually somewhat lower than in the improved indications.

To summarize the safety findings of E2100 we see that the combination of Avastin with weekly paclitaxel was relatively well

tolerated for the vast majority of patients even with their significantly longer duration of therapy. However, fatal toxicity did occur. Discontinuation of treatment for toxicity was balanced across the two arms. And the safety profile is consistent with what has been previously reported.

Before I conclude, I want to briefly describe the safety results from AVF2119 as this will provide additional context for the safety profile of Avastin for the treatment of women with metastatic breast cancer. This randomized Phase III trial, referred to as AVF2119, compared Avastin plus capecitabine to capecitabine alone. Prior anthracycline and taxane treatment were required. The vast majority of the patients enrolled had previously received at least one regimen for their treatment of metastatic disease. Fifteen percent had not, but had instead relapsed within 12 months of completing adjuvant chemotherapy which

incorporated both of these agents. HER2-positive patients were eligible, making up approximately 25 percent of this patient population. Compared to E2100, patients enrolled to AVF2119 comprised a very different patient population in that they were much more heavily pretreated and had poorer prognosis in terms of their expected outcome for metastatic disease.

The primary endpoint of the study was progression-free survival. A doubling of the objective response verified by independent review as observed. However, there was no improvement in the progression-free survival.

In recognizing that AVF2119 enrolled a very different patient population, the FDA agreed that only the safety results from 2119 would be included in the Avastin E2100 sBLA. So let's look at the safety results from this study.

This slide shows the patients in

the capecitabine plus Avastin arm of 2119 received significantly more therapy, receiving a median of six three-week cycles as compared to four. Despite this longer treatment duration there was again no increase in the rate of treatment discontinuation due to toxicity: 12 percent compared to 10 percent.

There was one treatment-related death in the Avastin arm and this was in a patient who died of sepsis.

I would again like to return to a discussion of the selected Avastin events. The rates for these events in E2100 are displayed first for reference. I have also added the rate of neuropathy to this table because of the increase observed in E2100.

In AVF2119, we see a somewhat higher rate of hypertension, but all of these events were Grade 3 and thus manageable. There was no increase observed in the rate of several of the events in AVF2119. Left

ventricular dysfunction was more frequent in both arms of that study, presumably related to prior anthracycline exposure in all patients. Finally, no neuropathy events were observed in the Avastin arm, consistent with the prior conclusion that the increase observed in E2100 was related to paclitaxel exposure.

In conclusion, the safety results of AVF2119 provide additional confidence regarding the acceptability of the safety profile of Avastin for the treatment of women with metastatic breast cancer. The side effect profile observed in both studies remains consistent with that currently described in the Avastin package insert. The favorable quality of life outcome observed in E2100 presented by Dr. Miller just a little while ago provides additional support for the conclusion that Avastin, when given in combination with paclitaxel, for the treatment of patients with metastatic breast

cancer does indeed have an acceptable toxicity profile.

I would now like to introduce Dr. Eric Winer, associate professor of medicine at Harvard and the director of the Breast Oncology Center at the Dana-Farber Cancer Institute.

DR. WINER: Thank you, Barb. Dr. Hussain, Dr. Pazdur, it's a pleasure to be here today both to talk about bevacizumab and paclitaxel and, if called upon, to participate in this discussion about progression-free survival as an endpoint. Before starting let me acknowledge that at Dana-Farber we have support from Genentech for clinical trials, both investigator-initiated trials and two company- sponsored trials. Prior to October of 2006, I received honoraria for participation in occasional advisory boards. I have not taken any honoraria from Genentech over the course of the past year. I own no

stock. I am on no speakers bureaus. I have not been compensated for the time I've put into preparing to be here today nor am I being compensated financially for my participation in the proceedings today.

So that said, my job is to try to put all of this in context and to talk about ECOG 2100 and bevacizumab and the treatment of metastatic breast cancer. We develop new treatments for patients with metastatic breast cancer with two goals in mind: To improve treatment outcomes for women living with the disease today and to identify promising new therapies that can be applied in the adjuvant setting tomorrow.

In terms of women living with the disease today, as outlined by Dr. Miller so eloquently, our goals are pretty straightforward: We try to maximize survival and to maintain or enhance quality of life. In terms of survival it's worth noting that for women with HER2-negative breast cancer

who are beginning first-line chemotherapy that the median survival is in the range of two years or somewhat less. And from the standpoint of quality of life, we do this largely by trying to maintain disease control with active treatment by minimizing symptoms from the disease through a combination of active treatment and supportive care and minimizing toxicity from therapy.

I want to spend a few minutes focusing on four of the agents that have been approved for metastatic breast cancer since 2001: Capecitabine, gemcitabine, lapatinib, and ixabepilone. Of course the last two drugs were approved over the course of the past year and the relevant clinical trials that led to those approvals are listed in the middle column.

One of these agents, gemcitabine, is approved in the first-line setting, the others in the second-line setting. And I do want to make a comment about this. I realize

that historically there has been this distinction between the first- and the second-line setting. Increasingly, this distinction, at least from the standpoint of study endpoints, appears to have less and less relevance and appears, at least to me and certainly to many of my colleagues, as somewhat arbitrary and there are two reasons for this.

One is that there is a great deal of variability in terms of adjuvant therapy that's administered. There can be a woman who is receiving first-line treatment in the metastatic setting who has had far more therapy and has far more refractory disease than a patient who may be receiving second-line therapy who received no adjuvant therapy.

Second, our understanding of breast cancer has evolved dramatically over the past 10 years. We understand breast cancer to be a family of diseases.

We appreciate the molecular heterogeneity. Increasingly in the future we will be focusing on different subtypes of breast cancer. Line of therapy may be less important and, in particular, having different approval criteria for patients in different settings in terms of line of therapy may make less sense than it ever has.

Shown here from those four studies are the efficacy results, both in terms of progression-free survival and overall survival. And what you can see is that in each of the four studies there was an improvement in progression-free survival that ranged, as you heard earlier, from approximately six weeks to just under five months. Two of the trials, the trials that involved capecitabine and gemcitabine, demonstrated an improvement in overall survival in the range of two to three months. Two of the trials -- specifically, one of the trials did not show an improvement in overall

survival and for one the data have yet to be reported.

Shown here on this slide are actually first-line studies focusing just on first-line studies using a taxane in at least one of the treatment arms. And as outlined by Dr. Miller earlier, what you can see is that improvement in outcome with the addition of bevacizumab to paclitaxel is more substantial and, in many cases, far more substantial than has been seen in any other randomized trial involving a taxane in the first- line setting conducted over the course of the past decade.

The question, of course, in this first- line setting is whether progression-free survival is a meaningful endpoint, and I do want to address this. Improvements in progression-free survival for many patients delay the onset of disease-related symptoms and the side effects from a new therapy. And while there are

indeed patients in the first- line setting who go on treatment without symptoms, symptoms become more and more common as breast cancer progresses. Moreover, improving progression- free survival avoids the psychological consequences associated with disease progression and changing therapy, and eliminates, at least for some amount of time, the uncertainty as to whether a new treatment will be effective or not.

Our patients who face metastatic breast cancer get used to changing therapies. They become veterans of what I often call surfing the waves of metastatic breast cancer. But the truth is these are always hard moments. Tomorrow I go back to clinic and I know already that I'm spending time with two patients whose breast cancer has progressed and who will need additional therapy, and those are hard conversations and I don't think we should minimize this. And so in answer to the question, yes, prolonging

progression-free survival can be highly meaningful both in the second- and third-line setting and, yes, in this first-line setting as well.

That said, for progression-free survival to equal benefit, for it to be meaningful, 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 here let's look at bevacizumab and paclitaxel at ECOG 2100 and see how it scores on this report card.

In terms of the magnitude of the benefit, as you've heard now multiple times, the improvement in outcome in terms of progression-free survival is substantial with a hazard ratio of.48 and an absolute improvement of 5-1/2 months. I think there's little doubt that this improvement in

progression-free survival has been established with confidence. There is a high and actually striking degree of agreement between the investigator assessment of response and time to progression and that of the independent review. And as you've heard, there have been a number of sensitivity analyses conducted. And in each of these, the improvement in progression-free survival was demonstrated.

In terms of overall survival, while there was not a statistically significant difference in overall survival, the hazard ratio for overall survival was.87 with an absolute difference of 1.7 months. The quality of life data, if anything, favored bevacizumab. And there was a doubling or response rate.

So I show this slide again, highlighting the four agents that have been approved over the course of the past six years. And by the way, I did not include

Abraxane on this list because of the different approval mechanism and the fact that it was approved based on response rate only. And now I add in the ECOG 2100 data showing an even more dramatic improvement in progression-free survival than seen in any of these other studies.

But there is, of course, one final criteria that has to be met and that relates to toxicity. And there is always in each and every patient decision a trade-off, a trade-off between treatment that may control the disease and side effects and risks associated with the treatment. And in terms of those side effects and risks, we have to focus both on the frequency and the severity.

What kinds of side effects and risks does a patient face if she chooses to go on paclitaxel and bevacizumab? Well, indeed, there is a 20 percent increase in Grade 3 to 5 toxicity that one trades off or one accepts in exchange for the longer time

to progression, the longer progression-free survival in women who are receiving the combination therapy. Asymptomatic Grade 3 hypertension and proteinuria were the most common adverse events. Generally speaking, these are adverse events that are easy to manage.

Neuropathy was more common on the arm in which bevacizumab was administered, which is thought to be a result of the greater total dose and greater number of doses of paclitaxel that were administered. There was a small increase in severe toxicity in arterial thrombotic events, congestive heart failure, GI perforation, and bleeding. Thankfully, these events were extremely rare in this study. And the bottom line is that the added day- to-day toxicity for most patients who received paclitaxel and bevacizumab in the trial, and I might add in clinical experience since the trial has been completed, is quite limited.

So to summarize, I believe that progression-free survival is a meaningful endpoint in this first-line setting since it has been accepted as a meaningful endpoint in the setting of endocrine therapy and in the setting of second- and third-line therapy for cytotoxic agents. It doesn't seem to be a high bar to cross to convince all of you that it should be a meaningful endpoint here as well.

The combination of bevacizumab and paclitaxel results in a substantial and I think unquestioned improvement in progression-free survival with modest additional toxicity for the majority of patients. And with that in mind, bevacizumab in combination with paclitaxel is a valuable treatment option with metastatic breast cancer. Since Dr. Miller's presentation in May of 2005, at a special session at ASCO, it is a treatment option that has been used by many patients with metastatic breast cancer.

It is by no means the only treatment, but it is a treatment that very much should be on the menu. It has been on the menu over the past two years, it continues to be, and it will be in the future.

And just to end, let me say that I wouldn't be here today if I didn't believe that this should be a treatment option that should be available to women with metastatic breast cancer. Thank you very much. Chris Bowden is going to speak next.

DR. BOWDEN: Thank you, Dr. Winer, and thank you, ladies and gentlemen for your attention.

In my concluding remarks let's consider the strength of the data in this application from three perspectives: Benefit, risk, and confidence.

From the perspective of benefit, the Avastin plus paclitaxel combination demonstrated a clinically meaningful effect on progression-free survival. The secondary

endpoints, objective response, survival, and quality of life, further support the clinical benefit of the combination.

From the perspective of risk, the safety profile of Avastin plus paclitaxel is comparable to what is currently described in the U.S. package insert and familiar to oncologists prescribing Avastin in other approved indications.

Finally, several additional aspects provide a high level of confidence in the results. First, E2100 was conducted by an independent U.S. Cooperative group and thus provides assurance that the results are applicable to U.S. practice. Second, there is a high level of consistency across subsets and agreement between the independent review and investigators. And finally, we have seen the robustness of the treatment effect to multiple sensitivity analyses.

The results you have seen today validate the strong scientific concept behind

the blockade of VEGF in the first-line treatment of metastatic breast cancer. These considerations support the full approval of Avastin in combination with paclitaxel for the treatment of patients who have not received chemotherapy for their locally recurrent or metastatic HER2-negative breast cancer.

Again, thank you for your attention and I look forward to facilitating questions shortly.

DR. HUSSAIN: Thank you. We will take a break right now and we will come back -- please come back just before 10:00, so we can start sharp at 10:00. Thank you.

(Recess)

DR. HUSSAIN: I'm going to ask the committee members to please have your seats. This session will involve two parts. The first part is the FDA presentation and the second part is the open public hearing. I'd like to invite Dr. Lee Pai-Scherf to begin

the FDA discussion.

DR. PAI-SCHERF: Good morning. My name is Lee Pai-Scherf and -- you cannot hear it? Hello?

Good morning. My name is Lee Pai-Scherf and I will present the FDA review of the bevacizumab application for breast cancer. My colleague Dr. Lu will be presenting the efficacy evaluation of the pivotal trial. The supplemental BLA we are discussing today is STN 125085, Amendment 91.

The proposed indication is for Avastin in combination with paclitaxel is indicated for the treatment of patients who have not received chemotherapy for their locally recurrent or metastatic breast cancer. This slide outlines the topics I will cover this morning: Regulatory background; clinical studies, E2100, AVF2119g; summary of FDA findings; and questions to ODAC.

First, regulatory background.

Bevacizumab is approved by FDA for first-line and second-line metastatic colorectal cancer in combination with 5-FU-based chemotherapy. Bevacizumab 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 trials 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, the regulatory background for Study AVF2119g. On July 2000, Genentech and FDA met to discuss the study design of AVF2119g, 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. This study opened for accrual from November 2000 through March 2002.

In March 2002, Genentech and FDA met to discuss a BLA filing based on this trial. On September 2002, the FDA was informed that AVF2119g failed to meet its primary endpoint of progression- free survival.

On October 2001, while accrual for Genentech's Study AVF2119g was ongoing, the National Cancer Institute submitted E2100, a randomized clinical trial for paclitaxel with or without bevacizumab for first-line therapy of metastatic breast cancer. The study was not identified by NCI as intended to support drug approval.

And here I would like to explain what does the FDA mean by "trial intended to support drug approval." For studies in which

the studies will be used 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 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.

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 statistical analysis planned did not clearly identify primary and important secondary efficacy endpoints. The