ORIGINAL

TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

58TH MEETING

Pages 1 thru 415

Bethesda, Maryland
September 2, 1998

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

sgg

AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

58TH MEETING

This transcript has not been edited or corrected, but appears as received from the commercial transcribing service; the Food and Drug Administration makes no representation as to its accuracy.

Tuesday, September 2, 1998

8:00 a.m.

Holiday Inn Bethesda
Versailles I, II, III
8120 Wisconsin Avenue
Bethesda, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

PARTICIPANTS

Janice Dutcher, M.D., Chairperson
Karen Templeton-Somers, Executive Secretary

MEMBERS

Kathy S. Albain, M.D.
David H. Johnson, M.D.
Kim A. Margolin, M.D.
Robert Ozols, M.D.
Richard L. Schilsky, M.D.
Richard Simon, D.Sc.
Derek Raghavan, M.D., Ph.D.

E. Carolyn Beaman, Consumer Representative
Deborah Cassel, Patient Representative
Sandra Zook-Fischler, Patient Representative

CONSULTANTS

George Sledge, M.D.
Carole Miller, M.D.
Julie M. Vose, M.D.
Steven E. Lipschultz, M.D.

GUEST EXPERTS

Susan Ashley
Trevor Powles, M.D.
Timothy O'Leary
James H. Doroshow, M.D.
James L. Weiss, M.D.

FDA

Rachel Behrman, M.D., M.P.H.
Julia Goldstein, M.D.
Susan Honig, M.D.
Susan Jerian, M.D.
Robert Justice, M.D.
Kathryn Stein, M.D.
Patricia Keegan
Jay Seigel, M.D.
John Johnson, Clinical Team Leader
Julie Beitz, Medical Team Leader

C O N T E N T S

A.M. SESSION
NDA Supplement 17-970/S-040 Nolvadex (tamoxifen)
Zeneca Pharmaceuticals

P.M. SESSION
Biologics License Application (BLA) 98-0369
Herceptin (trastuzumab)
Genentech, Inc.

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Introductions

DR. DUTCHER: Good morning. In case you are in the wrong room, this is the Oncologic Drugs Advisory Committee. We are going to start a three-day meeting. Two of our committee members were unable to make it here because they live in cities that are served only by Northwest Airlines, Drs. Krook and Santana. They send their regards.

As I am sure everyone in the room is aware, we have a tremendous amount of material to cover today, and our goal is to carefully evaluate the data that are presented by both the sponsor and FDA, and that is the goal of both the committee and the audience.

We do have a large number of members of the public who requested to speak and participate, which we welcome. We are going to ask that everyone, including members of the committee and members of the audience, to be as succinct with their comments as possible so that we can get through what should be a very interesting and pretty power-packed day full of information. So, we hope that everyone will work together so that we are not all here until midnight. Thank you all for your interest and for your willingness to participate.

We will go around the room and introduce the members of the committee. I am Janice Dutcher, from Albert

Einstein Cancer Center, in New York.

DR. JOHNSON: David Johnson, Vanderbilt University, Nashville.

DR. MARGOLIN: Kim Margolin, City of Hope, Duarte, California.

DR. ALBAIN: Kathy Albain, Loyola University of Chicago.

DR. SIMON: Richard Simon, National Cancer Institute.

DR. SCHILSKY: Richard Schilsky, University of Chicago.

DR. OZOLS: Bob Ozols, Fox Chase Cancer Center, Philadelphia.

DR. TEMPLETON-SOMERS: Karen Somers, Executive Secretary to the committee, FDA.

DR. SLEDGE: George Sledge, Indiana University.

DR. RAGHAVAN: Derek Raghavan, University of Southern California.

MS. BEAMAN: Carolyn Beaman, consumer rep, Sisters Breast Cancer Network.

DR. BEITZ: Julie Beitz, Medical Team Leader, FDA.

DR. HONIG: Susan Honig, Medical Reviewer, FDA.

DR. JUSTICE: Bob Justice, Acting Director, Division of Oncology Drug Products, FDA.

DR. TEMPLETON-SOMERS: We have also two guests for

the FDA, Dr. Trevor Powles, if you could stand up for us? Thank you. And, Dr. Susan Ashley, statistician for his group? Thank you.

DR. DUTCHER: All right. We are now going to read the conflict of interest statement.

Conflict of Interest Statement

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for a conflict of interest at this meeting, with the following exceptions:

Dr. James Krook is excluded from participating in today's discussions and vote concerning Nolvadex. In addition, Dr. Robert Ozols has been granted a waiver that permits him to participate in all matters concerning Nolvadex.

A copy of this waiver statement may be obtained by submitting a written request to the FDA's Freedom of Information Office, Room 12A-30 at the Parklawn Building.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous involvement with any firm whose products they may wish to comment upon. Thank you.

DR. DUTCHER: Thank you. I think you can see from the agenda that the open public hearing has been expanded due to the interest in the agents being discussed today. So, we will start with the open public hearing, which will occur before the presentation, and then following the two presentations we will have additional comments from the public.

We will begin with the people who have requested to speak. The first is Marilyn McGregor. We would appreciate it if all speakers would identify themselves as well as any sponsorship, either the sponsor or otherwise. We would appreciate it if those who speak could use the podium if possible.

Open Public Hearing

MS. MCGREGOR: My name is Marilyn McGregor, and I

am Administrative Director of the Cancer Support Community located in San Francisco. I have no financial interest in tamoxifen.

There is a great longing to believe that there is a preventative drug for breast cancer. Given the dismal and long-term unchanging mortality rate of breast cancer, there is a willingness to believe that this drug could be the answer to so many people's prayers. But as scientists and as an organization responsible for the public good, I urge this committee not to approve the application of tamoxifen as a breast cancer prevention drug.

The reasons I urge this decision are as follows: There is clinical trial medicine and real life medicine and media over-estimation of the benefits of any one cancer drug. There needs to be a higher level of assurance when prescribing a drug that is a known carcinogen in a healthy population or at least no discernible breast cancer. Those of us diagnosed with breast cancer have a different ris/benefit ratio, and tamoxifen may be appropriate.

Clinical trials medicine defines exactly who benefits given their family history of breast cancer, as was done in the NCI trial. Real life medicine has a busy doctor in an HMO whose patient may have no family history or risk factors or the pervasive anxiety about developing breast cancer. This woman would most likely be prescribed

tamoxifen as a preventative. Off-label prescription is common in cancer and is a benefit to most cancer patients, but this may not be the case with tamoxifen as a preventative in a healthy population.

The NCI study does not prove that tamoxifen prevents breast cancer for the life of any one woman. The most that can be said of the NCI trial is that the tamoxifen group appeared to have less breast cancer for the short period of time of the trial, which was an average of 3 years. A woman can develop breast cancer in over a 50-year period. If this drug is approved as a preventative, the insert should say that the drug is only to be prescribed for the length of time of the trial, which was approximately 3 or 4 years.

Other speakers will, no doubt, discuss the British studies which reported no benefit of tamoxifen as a preventative. I am going to discuss the Italian study of Dr. Bianco. At the May, 1998 ASCO meeting in LA, there was a symposium on HER2. Dr. Bianco discussed his 20-year study of HER2 overexpression in tamoxifen use. Bianco and his colleagues found that there was no apparent benefit in using tamoxifen for those who overexpress HER2. All other categories showed a benefit of tamoxifen use.

In addition, the Italian research also showed that those women who overexpressed HER2 and took tamoxifen had an

overall worse outcome. Dr. Bianco stated that his research could greatly affect the use of tamoxifen, and called for further study on this issue.

If, indeed, the Italian studies prove to be accurate, this could potentially mean that 25 to 30 percent of women would have no benefit of tamoxifen either as healthy patients or cancer patients. This could potentially mean that before a woman would be prescribed tamoxifen she would have to be tested for HER2 overexpression. Many other possibilities are also possible.

However, at this time we do not know the answers to these scientific questions but answers are certainly needed. Good science demands more good science. It is well-known in scientific circles that negative studies or non-U.S. studies are routinely not included in drug analysis. I urge that the Italian and British studies be considered carefully in your application.

I urge the NCI to immediately conduct appropriate studies regarding the interaction of HER2 overexpression and tamoxifen use. I recommend these studies be completed before any approval of tamoxifen as a preventative for healthy women. Meta-analyses, retrospective tumor block studies and/or well-controlled trials all need to be done to ascertain if tamoxifen is beneficial to those women who overexpress HER2 in the healthy population and in the cancer

population.

As tamoxifen is already licensed, doctors may continue to prescribe the drug in individual cases, but the FDA and the NCI need to protect the public.

Thank you for consideration of my remarks.

DR. DUTCHER: Thank you. The next speaker is Carolyn Aldige.

MS. ALDIGE: Good morning. I am Carolyn Aldige, President and Founder of the Cancer Research Foundation of America. Additionally, I have the privilege of currently serving a 2-year term as President of the National Coalition for Cancer Research.

The mission of CRFA, cancer prevention through research and education, is fueled by the knowledge that as much as 70 percent of all cancer is preventable. We believe that prevention provides our greatest hope for reducing cancer's deadly impact. We also believe that our organization's focus on prevention is unique among cancer-related organizations. Since 1985 CRFA has directed more than $30 million to promising research, education and early detection programs that turn the promise of cancer prevention into reality.

Before making my formal comments, I should note for the record that CRFA receives support from a number of pharmaceutical companies, including Zeneca Pharmaceuticals,

as well as a host of other corporate supporters and individual donors.

You know the challenge. Breast cancer is the most common cancer among women, accounting for one out of every three women's cancer diagnoses in the United States. Last year approximately 180,000 new cases of breast cancer were diagnosed, and nearly 45,000 women died from the disease. Only lung cancer causes more cancer deaths in women.

In the face of such discouraging news, the prospect of the first effective chemopreventive agent for women at risk for breast cancer, tamoxifen, is heartening indeed.

I would like to thank the Oncologic Drugs Advisory Committee for allowing me to speak today for this is, in fact, the first time I have requested permission to address an ODAC panel. Why? Because this is the first time, to my knowledge, the committee has considered approving a drug to prevent cancer. Heretofore, consideration was given only to drugs that could be used for treatment. In our view, this is a landmark event.

CRFA has long supported the National Cancer's Institute decision to conduct ground-breaking cancer prevention trials. In fact, in 1993 I was pleased to have the opportunity to testify before the Senate Cancer Coalition in favor of continuing the breast cancer

prevention trial.

We believe that the compelling results of NSABP's P-1 study merit approval of Zeneca's application for the use of Nolvadex as the first preventive agent for women at risk for breast cancer. The trial results are, as Dr. Richard Klausner has noted, nothing less than a real advance for women with a family history of breast cancer. Women in the trial taking tamoxifen developed 45 percent fewer cases of breast cancer than those on placebo. There were 85 new cases in the tamoxifen group over 4 years compared with 154 in those on placebo. Women on tamoxifen also had fewer cases of DCIS, as well as fewer bone fractures of the hip, wrist and spine.

We also note that the drug has its drawbacks -- more cases of endometrial cancer, pulmonary embolism and deep vein thrombosis. The risk for endometrial cancer in the tamoxifen groups was more than that of the placebo group, while the risk of pulmonary embolism was nearly tripled. However, these potentially dangerous side effects appear to be limited to women older than 50, and we believe these risks can be managed.

While no one can underestimate the seriousness of these potentially life-threatening side effects, the case for ODAC approval remains a strong one. Approval will ensure that doctors and other health care professionals are

fully aware of the drug's side effects, and can discuss them fully with patients. Approval provides the FDA with the opportunity to capture data about adverse events, rounding out knowledge of the drug. Approval means that patients and doctors will not have to seek the drug off-label prescriptions.

The approval of tamoxifen is a crucial early step in the prevention of breast cancer in American women. We, at CRFA, applaud your taking this step which means so much in the long term to women at risk for the disease and their families.

Thank you again for the opportunity to speak today.

DR. DUTCHER: Thank you. We also have two letters, and Dr. Somers will read the letters.

DR. TEMPLETON-SOMERS: The first letter is from Dr. Samuel Epstein, who is a Professor of Environmental and Occupational Medicine at the University of Illinois.

Zeneca's Nolvadex NDA for preventing breast cancer in healthy women "at high risk of cancer," including all women over 60 years old, is primarily based on NCI's April 6, 1998 summary report, "Breast Cancer Prevention Trial, BCPT, Shows Major Benefits and Some Risks."

This report was unsupported by a peer reviewed scientific publication and was qualified by the admission

that "further analyses of the data are under way." No further data have yet been released, nor has the report yet been published. Additional evidence is derived from tamoxifen's partial protective effects in rats and mice against the induction of breast cancer by 7,12-dimethylbenzanthracene, DMBA, besides other carcinogens. However, those DMBA-induced cancers which were not suppressed were hormone independent and highly aggressive.

NCI's report announced that the BCPT had been terminated prematurely on March 24 in view of "clear evidence that tamoxifen reduced breast cancer risks." As indicated in the Table -- and for this I will have to refer the committee to the tables in their packets -- based on data cited in the report, tamoxifen reduced the incidence of both invasive and non-invasive breast cancer in women of all ages. However, the short term duration of the trial precludes determination as to whether the drug prevented cancer or merely delayed its onset by treating small undetected tumors.

On July 11, 1998, two publications in The Lancet reported no evidence for the efficacy of tamoxifen in preventing breast cancer. A 6-year trial by the Royal Marsden Hospital, London oncologic team, based on some 2500 women with a family history of breast cancer, and a similar 4-year study by the European Institute of Oncology in Milan,

based on 5400 women, reported no difference in the incidence of breast cancer in women treated with tamoxifen or placebo.

An accompanying editorial warned -- this is a quote -- the failure of these trials to confirm the results of the U.S. study, however, casts doubt on the wisdom of the rush, at least in some places, to prescribe tamoxifen widely for prevention. Longer follow-up of completed and current trials is clearly required to clarify the relative preventive benefits and risks in different populations, and to confirm the BCPT findings. Most importantly, none of these trials provides reliable data on mortality, which should be the ultimate endpoint.

These concerns have been summarily dismissed by NCI -- "the chance that our results occurred by chance was 1 in 10,000." However, The Lancet editorial did not challenge the results themselves, but their interpretation and significance.

Serious short-term complications in the BCPT, uterine cancer, pulmonary embolism and deep vein thrombosis, were increased 2-3-fold in the tamoxifen group. These complications were only seen in postmenopausal women. Among non-hysterectomized women in this age group, the incidence of these serious complications was 2.2 percent in contrast to a 1 percent reduction in the incidence of breast cancer.

It must be recognized that the short term duration

of the BCPT, apart from the absence of any long-term follow-up, precludes recognition of possible further increases in the incidence of already recognized short-term life-threatening and other serious complications, and also of other, not yet reported, long-term or delayed complications. Of concern in this connection is the fact that tamoxifen induces ovarian necrosis and ovulation in a manner similar to clomiphene, a recognized risk factor for ovarian cancer.

More serious still is the high hepatocarcinogenic potency of tamoxifen in the rat, as confirmed in February 1966 by the International Agency for Research on Cancer, at low doses and blood levels equivalent to those in the BCPT. Tamoxifen also binds tightly to estrogen receptors in the human liver, and induces highly stable DNA adducts in 2 rodent species. Risks of liver cancer are not precluded by the absence of such reported complications among breast cancer patients treated with tamoxifen as relatively few such women have taken the drug for over 5 years and followed up for a further 20 years before which the induction of liver cancer would be unlikely.

It should be noted that senior NCI staffer Dr. Leslie Ford dismissed risks of liver cancer on the grounds that no cases were reported in the short term BCPT, and also on the incorrect grounds that carcinogenic effects in rats were only seen at high doses. Ford's logic, however, would

exculpate virtually all recognized human carcinogens. Furthermore, NCI's denigration of the human relevance of the experimental carcinogenicity data on tamoxifen and its failure to warn BCPT participants of this grave risk is in striking contrast to its reliance on rodent teratogenicity data as the basis for warning against the administration of tamoxifen to pregnant women.

It is of further interest to note that while some 25 cases of liver toxicity in tamoxifen-treated breast cancer patients, acute hepatitis, liver failure and deaths and hepatobiliary complications, have been reported in the U.K. by 1992, with similar evidence obtained from the FDA, no such adverse effects were noted in the short term BCPT.

NCI's preliminary April 6 report on the prevention of breast cancer by tamoxifen has still not been finalized and published in a scientific journal. The advisory committee should consider the propriety of Zeneca's NDA submission as it is based, in part, on data which have not been made fully available to the public although the underlying NCI research was funded by the public. Furthermore, the claimed evidence for chemoprevention has been rebutted by two subsequent scientific publications. Of as great concern is the well-documented evidence of short-term life-threatening complications, and also risks of delayed fatal complications, evidence for which has been

trivialized and suppressed by NCI. Based on these scientific and ethical considerations, the advisory committee is urged to deny approval of Zeneca's NDA.

This and the other letters are available for your viewing at the registration table outside.

Our second letter is by Barbara Brenner of Breast Cancer Action. It says: Dear Committee Members, based on the data currently available, both from the NCI and from the recently released European results, Breast Cancer Action opposes approval of the proposed indication for Nolvadex. Women are entitled to expect that any drug approved for the prevention of breast cancer will both actually prevent the disease and carry benefits that outweigh the risks of taking it. As far as we know now, neither is true for Nolvadex. We urge you to "just say no" to this application.

Breast Cancer Action is an education and advocacy organization founded and led by women living with breast cancer, representing over 4000 members throughout the United States and beyond, we carry the voices of people affected by breast cancer to inspire and compel the changes necessary to end the breast cancer epidemic. Since our founding in 1990, we have been calling for research into true breast cancer prevention, as well as research on effective treatments.

The history of the breast cancer prevention trial that led to the application that is now before the committee

is well known. Breast Cancer Action long ago summarized the trials as "bad research, bad drug, bad news for women." But it is not the history of the trial that concerns us today; it is the current state of information about the drug's preventive effects and the risks associated with its use.

The data currently available regarding the use of tamoxifen in healthy women point to far too many known and unknown risks to justify the approval of Nolvadex as a preventive. The risks, as revealed by the BCPT-1 data, are presumably well known to the FDA and the committee. But seeing them listed gives us and, hopefully, the committee members the overwhelming sense that this application is premature in the extreme.

From studies of tamoxifen in women with breast cancer and from the BCPT-1 trial, some of the side effects of taking tamoxifen are known: Endometrial cancer, pulmonary embolism, deep vein thrombosis, eye damage, depression, irritability, vaginal dryness, hot flashes, memory loss and weight gain.

Because BCPT-1 ended before the 5 years for which the trial was designed, because a number of the participants were involved in the trial for far less than 4 years, and because there is no rigorous follow-up guaranteed for the trial participants, there is much we do not know about the consequences of tamoxifen for healthy women at high risk for

breast cancer. Given the recruitment of BCPT-1 participants into the STAR trial, BCPT-2, even the minimal follow-up planned for BCPT-1 participants will be of little or no value in resolving the many unknowns about tamoxifen. Among the most troubling unknowns are these:

Long-term effects of the drug in terms of breast cancer risk or any other risk; appropriate duration of treatment; how long the protective effect of the drug lasts; whether and how benefits and risks vary depending on the race/ethnicity of the woman taking the drug; whether and how benefits and risks vary depending on age of the woman taking the drug; whether and how benefits and risks vary depending on breast cancer risk factors; and whether women who develop breast cancer while on tamoxifen develop a more aggressive form of the disease.

While it will be argued that some of the foregoing information is known, we disagree. Either because of the trial design or because data about the trial has not been made available before now, we simply do not have the answers to these questions. All of these concerns are addressed at length in the lead article in the June/July, 1998 edition of the "Breast Cancer Action Newsletter," a copy of which is attached to this testimony for the committee's convenience.

Last but certainly not least, the data that are currently available clearly indicate that, whatever else

tamoxifen does for healthy women, it does not prevent breast cancer. The BCPT-1 data show only that for some small group of women the drug may delay the onset of the disease. The NCI's conclusions, even in this regard, are undermined by the recently released European results finding no benefit from tamoxifen in healthy women at high risk.

Whatever else is true, if someone taking Nolvadex can develop breast cancer, then the drug is clearly not preventing the disease in any sense that the general public understands. What epidemiologists mean by prevention is not what people who are worried about breast cancer mean when they use or, more importantly, hear the word.

When we finally have a drug that we know will reduce a woman's risk of developing breast cancer, with attendant risks of side effects that are both known and acceptable, we will encourage this committee and the FDA to approve it under an indication of "risk reduction," not "prevention."

But, as far as we know today, Nolvadex is not that drug. For this committee to approve the indication that Zeneca is now requesting would expose millions of healthy women to the known risks of tamoxifen and to potentially grave unknown risks without any guarantee of obtaining the benefits that are being claimed. Only one word can accurately describe such an action -- unconscionable. Do

not let Zeneca's drive for profit divert you from the interests of women at high risk for breast cancer.

Respectfully submitted by Barbara A. Brenner, Executive Director.

As a matter of policy, in order to avoid the fact or appearance of a conflict of interest, Breast Cancer Action does not accept funding from Zeneca or from any other pharmaceutical company.

Thank you and, again, both letters are available for you to look at, at the registration desk.

DR. DUTCHER: Since we do have time later in the morning for other comments and people are scheduled to speak, we are going to proceed with the agenda as it is printed and we will begin with the sponsor's presentation.

Sponsor Presentation

Introduction

DR. LEWIS: Thank you, Dr. Dutcher. Good morning. I am Jerry Lewis, Senior Medical Director of Zeneca Pharmaceuticals, responsible for Nolvadex, tamoxifen citrate.

[Slide]

I have the distinct pleasure today of representing Zeneca, and along with my colleagues from the NSABP, the National Cancer Institute and the FDA, we will present and discuss with you the results of the precedent-setting breast

cancer prevention trial.

This is the basis for Zeneca's supplemental NDA for a change in the labeling -- Nolvadex is indicated for the prevention of breast cancer in women at high risk for developing the disease.

[Slide]

Following my introductory comments, Dr. Jo Costantino, from NSABP, will present the summary of the breast cancer prevention trial results. At the conclusion of Jo's presentation, I will summarize Zeneca's position and then be pleased to take questions from the committee.

[Slide]

There are a number of experts here with us today to help address your questions. From NSABP, Dr. Norman Wolmark, Principal Investigator and Chairperson of NSABP; Dr. Costantino, and Dr. Larry Wickerham, Director of Operations at NSABP. For the National Cancer Institute, Dr. Leslie Ford, Associate Director, Early Detection and Community Oncology Program; and from Zeneca there are a number of scientists that are available should they be needed.

[Slide]

Zeneca is very proud that NSABP selected tamoxifen to be evaluated in the breast cancer prevention trial. NSABP has been involved in cancer research for some 40

years, and has been studying tamoxifen for some 20 years.

In 1991, the NSABP met with the predecessor ODAC to discuss the breast cancer prevention trial. We have with us today here Dr. Bernie Fisher who participated in those deliberations. The ODAC at that point endorsed the trial after they were convinced that the potential benefits outweighed the known risks. The trial was designed to detect a reduction in breast cancer risk of 33 percent in women at high risk.

[Slide]

The trial itself far exceeded these expectations. Tamoxifen for 5 years prevented 45 percent of invasive breast cancers in women at high risk, and no unanticipated toxicities occurred in the trial. For a drug with 10 million patient years of exposure, confirmation of the safety data base should not comes as a surprise.

Today is a milestone for it represents the first time that the advisory committee is gathered to deliberate and vote on a drug for breast cancer prevention and, indeed, for any drug for prevention of cancer. Reaching this point in the review process as quickly as we have has been accomplished by tremendous cooperation between NSABP, the NCI and the FDA.

[Slide]

Let me review this time-line for you. The results

of the breast cancer prevention trial were made known to investigators and, indeed, the world on April 8 of this year. Some 22 days later Zeneca filed a supplemental new drug application and the FDA granted it an accelerated review. And, here we are today, a mere 5 months later, on September 2, to consider the results of this trial and a label change for Nolvadex.

[Slide]

It now gives me great pleasure to introduce Dr. Jo Costantino, Associate Director, NSABP, who will present the data from this trial. These data support our new indication. Thank you very much. Jo?

Summary of the Breast Cancer Prevention Trial Results

DR. COSTANTINO: Thank you, Dr. Lewis.

I am pleased to be here this morning to have the opportunity to provide for you the results of the breast cancer prevention trial.

[Slide]

I would like to begin just by answering the question why tamoxifen? Why did NASBP choose tamoxifen to be the drug to evaluate as a preventive agent for breast cancer? Primarily because of three factors.

First of all, the drug has been proven to be beneficial in the treatment of breast cancer in both advanced and early stage disease. It was also shown to

lower the risk of contralateral breast cancer among those patients. And, there was preclinical evidence demonstrating that tamoxifen inhibits the growth of tumors, and perhaps does this by interfering with both the promotion and initiation mechanisms.

[Slide]

The breast cancer prevention trial was a double-blinded, randomized clinical trial in which women were randomized to receive the planned duration of 5 years of tamoxifen or 5 years of placebo, and 13,388 women were actually randomized to the trial.

[Slide]

The primary objective of the study was to evaluate the effect of tamoxifen on the reduction of the incidence of invasive breast cancer. The study was powered to determine that endpoint.

[Slide]

Other objectives included the evaluation of the effect of tamoxifen on cardiovascular disease, bone fractures, other cancers, mortality and the risks of some other outcomes which were known to be risk factors associated with tamoxifen that we had learned from the treatment trials.

[Slide]

The study was designed to maintain the statistical

power even if the non-compliance was as high as 10 percent per year. This is an important factor because this is something that we had planned for in advance. We anticipated there might be a large non-compliance and we wanted to make sure that we did not reduce our statistical power if there was such a fact.

The analysis was based on an intent-to-treat approach. That indicates that all individuals were included in the treatment arm that they were assigned and that all events were included regardless of whether or not they took the drug.

[Slide]

Women got into the trial based on eligibility criteria, one of which was being at high risk for breast cancer. High risk was defined in this trial as being at least 60 years of age, being age 35 or older and having a history of lobular carcinoma in situ, or being greater than age 35 and having a 5-year absolute risk of breast cancer that was equivalent to the 60-year old woman, and that absolute risk was defined as 1.66 percent in 5 years.

The determination of this breast cancer risk was based on a mathematical model developed by Dr. Mitchell Gail and his associates at the National Cancer Institute.

[Slide]

The factors that went into that model that helped

to determine what the risk of breast cancer was for each of these women included age, first degree relatives with breast cancer, parity and age at first live birth, number of breast biopsies, history of atypical hyperplasia, age at menarche and race.

The original Gail model only incorporated this first set of parameters. It did not include a factor for race. But we worked with Dr. Gail and we developed a factor to include race into the program so that we could also calculate predictive risk for non-white women.

[Slide]

In addition, the original implementation of the Gail model was designed to predict the risk of both invasive and non-invasive breast cancer. In the BCPT we were interested in just predicting the incidence of invasive breast cancer so we made modifications to account for that also.

Almost 100,000 women had their breast cancer risk assessments performed. Of those 98,000, approximately 57,500 women were eligible based on that 1.66 percent in 5 years. Now, among those women who were eligible, there were other medical eligibility criteria that had to be met. If a woman desired to be considered for randomization, she went on to be screened and ultimately 13,388 women were randomized.

The data that I am going to present to you today is based on the follow-up as of January 31, 1998. This was the data that was actually used by our data monitoring committee when they decided that the trial had met its objectives and that the trial should be disclosed.

As of that date, January 31, 1998, follow-up was available for 13,114 women, and the average follow-up time was 44 months. About 73 percent of the women at that time had been followed for more than 3 years. Almost 60 percent had been followed for more than 4 years, and 21 percent had been followed for 5 or more years.

[Slide]

I would like to start just by quickly reviewing some of the baseline characteristics related to risk that the population had.

[Slide]

I will begin with age, and 39 percent of the women were in the age range of 35 to 49 at the time they were randomized; 31 percent were in the age range of 50 to 59; and 30 percent were 60 years of age or older.

[Slide]

In terms of number of relatives with a history of breast cancer, 57 percent of the population had at least 1 relative with a history of breast cancer; 16 percent had a history of 2 relatives with a history of breast cancer; and

3 percent had a history with 3 or more relatives with breast cancer.

[Slide]

In terms of the 5-year absolute breast cancer risk predicted from the Gail model, 25 percent of the women had a risk of less than 2 percent in 5 years; 31 percent had a risk in the range of 2-3 percent at 5 years; and 17 percent had a risk of 5 or more in 5 years.

[Slide]

A significant number of women entered into the trial with a history of LCIS and a history of atypical hyperplasia. Over 800 women in the trial, about 6.2 percent, entered the trial reporting a history of lobular carcinoma in situ and about 9.2 percent, approximately 1200 women entered into the trial with a history of atypical hyperplasia.

[Slide]

Now I would like to begin with the results, the primary endpoint of invasive breast cancer.

[Slide]

This plot is a plot of the cumulative incidence of invasive breast cancer that occurred among the participants in the trial. The black line represents the cumulative incidence for the placebo group. The red line represents the cumulative incidence for the tamoxifen group.

As you can see, the cumulative incidence for the placebo group was substantially greater than it was in the tamoxifen group. In fact, there were 154 breast cancers which occurred in the placebo group compared to only 85 in the tamoxifen group. This represents a cumulative incidence of 32/1000 compared to 17.9/1000, representing a reduction of about 45 percent in the risk of breast cancer. This difference was highly statistically significant with the p value being less than 0.00001.

A couple of things to note in this plot are that the difference appears to show itself very early on, and it does sustain itself throughout the whole 5 years of the plot.

[Slide]

Similar findings are noted for non-invasive breast cancer. This is the same type of plot only now we are dealing with non-invasive breast cancer. In the placebo group there were 59 events of non-invasive breast cancer compared to 31 in the tamoxifen group. This equates to a cumulative incidence of 12.3/1000 in the placebo compared to 6.8 in the tamoxifen group. This represents a 47 percent reduction in the risk of breast cancer. Again, you can see that the curves separate rather early, before the first year, and they continue to separate through the entire duration.

[Slide]

This slide reiterates the fact that this finding is consistent across time and has a lasting effect. These are bar charts, and the heights of the bars represent the rate per 1000 of invasive breast cancer by each of the years of follow-up. So you can understand the number of events that went into calculating these rates, at the top of the bars the numbers are given and these represent the number of cases. The yellow bars represent the rate in the placebo group; the red bars, the rate in the tamoxifen group.

If you look across all the years, all the way through year 5, you see there is a substantial reduction in the risk of breast cancer all the way up to year 5 and even a 50 percent reduction is evident at year 5.

[Slide]

To give you a feel for how things look by some of the characteristics of the population, here is the rate of invasive breast cancer broken down by 3 age groups -- less than 49, 50 to 59, and 60-plus. Again, you can see in all 3 age groups that there is a substantial reduction of the rate of invasive cancer in the tamoxifen group.

[Slide]

Here we show the rates broken down by those who reported a history of lobular carcinoma <u>in situ</u> and those with a history of atypical hyperplasia. Again, there are

striking reductions in both of these populations.

[Slide]

This chart shows the rates comparing treatment groups by categories of predicted risk from the Gail model, less than 2, 2-3, 3-5 and greater than 5. Again comparing each of these categories, you can see that there is a substantial reduction in the tamoxifen group, and this magnitude of reduction, seen here at the upper group, is about the same in terms of relative risk as it is in the lower group. Statistically speaking, there was no significant difference between the reduction observed across any of the categories of risk.

[Slide]

I would like to take a few minutes now to describe to you some of the tumor characteristics of the cases that were diagnosed in the trial and how they compared by treatment arm.

[Slide]

The first slide deals with tumor size. What we have here is the rate of invasive cancer by the size of the tumor at the time it was diagnosed, those that are less than 1 cm, 1-2 cm, 2-3 cm, and greater than 3 cm. Again, comparing the bars or comparing placebo to tamoxifen, you can see that there is a reduction in all categories but the bulk of the reduction, the most significant reduction was

among tumors that were less than 2 cm in size.

[Slide]

This graph shows the rates by categories of nodal status, those who were diagnosed with no positive nodes, those who were diagnosed with 1-3, and those who were diagnosed with 4 or more nodes. You will note that there is a really high number of unknowns here, and this is because the majority of these women did not have axillary dissection so the status is in terms of nodes that could not be determined.

If you look at the data, again, there is a striking reduction for those who were diagnosed with no nodes, and also those who were diagnosed with 1-3, but there is no difference in the rates of cancer for those who were diagnosed with 4 or more nodes. This is important to note at this point -- tamoxifen is reducing the rates of disease associated with 1-3 nodes and no nodes; there is no increase in the number of cases being detected with 4 or more nodes; and there is no increase in the number of cases being detected that are larger tumor size. It appears that tamoxifen is culling out the smaller tumors and the tumors that present with less than 4 nodes. So, the theory that cases that occur on tamoxifen are more aggressive is not being demonstrated by the data.

[Slide]

The last tumor characteristic is ER status, and this is an important one because there is an interaction between ER status and the effect of tamoxifen. These two bars represent women who were diagnosed with tumors that were ER positive. You see a very striking reduction in the risk of cancer based on those who were ER positive. On the other hand, there was no difference in the rates of women who were diagnosed with tumors that were ER negative. So, the effect of tamoxifen appears to be affecting tumors that would present themselves as being ER positive.

[Slide]

To summarize the findings in terms of breast cancer, tamoxifen reduced the incidence of invasive breast cancer by 45 percent. Reduction is seen in women of all age groups and at all levels of breast cancer risk. And, tamoxifen also reduced the incidence of non-invasive breast cancer.

[Slide]

I would now like to turn to other cancers that were diagnosed in the trial, starting with endometrial cancer. When we began the trial we were aware that endometrial cancer was a potential risk for women who were using tamoxifen. Indeed, from the world's literature involving treatment trials, we estimated that the risk of endometrial cancer might be elevated about 2-3 fold overall

in the population. Indeed, that is exactly what we found in the prevention study.

In the placebo group there were 14 cases of endometrial cancer diagnosed compared to 33 cases in the tamoxifen arm, for a relative risk of about 2.5. When this was broken down by age group, there was really no difference evident at this time between the treatment groups for women who were less than 49 years of age at the time they entered the trial. On the other hand, for women who were greater than 50 years of age when they entered the trial there was a substantial difference, 6 versus 26 cases.

[Slide]

It is important to note that all except for 1 of the cases in the trial were diagnosed at an early stage. All of them were FIGO stage I, 13 on placebo and 33 in the tamoxifen group. There was 1 case that was a stage IV, and this occurred in the placebo group.

It is also important to note that most of these cases were picked up by a mechanism which included annual pelvic exams and every 6 months a questioning of the individuals regarding gynecologic symptoms, and stressing to the individuals that whenever gynecologic symptoms occur they should report them immediately and have them followed up.

About 3 or 4 years into the trial, in 1995

actually, NSABP began paying for women who wished to have endometrial biopsies as part of their follow-up every 6 months on the trial. Some of the women did participate in that.

[Slide]

Only about half of the women in the trial who were eligible for screening -- and when we say eligible now, we are talking about women who actually have uteri, and I might add that all the rates that we are talking about here for endometrial cancer are based only on women who are at risk, women who had a uterus. About 37 percent of the women who came into the trial, at the time of randomization had a hysterectomy.

So, 67 percent of the women in the trial were at risk for endometrial cancer, and when we calculated these rates these were based only on women at risk. That is why you see on the bottom line that a little over 4000 women in each arm were at risk. This group of women actually participated in endometrial sampling; this group did not. This is the breakdown of the total number of cancers that were detected among the group who were sampled and the group who were not sampled.

As you can see, the rate of detection of cancer was not statistically significantly different, 0.6 percent in those who were sampled compared to 0.5 percent in those

who were not sampled.

[Slide]

To summarize the conclusions in terms of endometrial cancer then, tamoxifen increases the risk of endometrial cancer. Annual pelvic exams, directed questioning regarding gynecologic problems and the prompt reporting and evaluation of symptoms can be successfully used to detect endometrial cancer in early stage. The use of endometrial biopsy did not significantly improve the rate of cancer detection, and the small difference in detection does not justify the use of endometrial biopsy as a screening method.

Consistent with these findings, when we are planning our next prevention study we are not recommending that endometrial biopsy be included as part of the routine follow-up.

[Slide]

Turning now to other cancers, cancers other than the breast and cancers other than endometrial, this table summarizes the complete experience of the trial. Overall, there were 88 other cancers in the placebo group compared to 85 in the tamoxifen group. You can see here the distribution by all the different cancers.

It is important to note a few of these because some of these were suspected as being possibly associated

with tamoxifen and it turns out that they were not. There is no difference in colon cancer. No difference in rectal cancer. No liver cancers. In fact, there is no difference in any cancer at all as you look down the list.

[Slide]

Ischemic heart disease was included in the trial because it was known that tamoxifen reduces levels of lipids and perhaps that would result in a reduction in the risk of heart disease. There were actually 4 different specific ischemic events that were included as endpoints in the trial. These included fatal myocardial infarction; non-fatal myocardial infarction; a category of illness we called severe angina, and that was defined as having angina that required angioplasty or coronary bypass surgery; and the last endpoint that was included was called acute ischemic syndrome, and this included individuals who had changes on the ECG but not necessarily elevated enzymes or chest pain, or individuals who had severe chest pain and required hospitalization but did not have to have surgery.

This table shows the results from those endpoints. First of all, overall there were 59 ischemic events in the placebo group compared to 61 in the tamoxifen group. Dealing with just the myocardial infarctions, there were 27 in each arm. If you were to cull out those that were fatal MIs, the numbers would be 8 versus 7. In terms of the

severe angina, those requiring bypass or angioplasty, 12 and 12 -- the same number in each arm. In terms of acute ischemic syndrome, the numbers were also the same, 20 and 22. So, at this time the results of the trial do not support the contention that tamoxifen does reduce the risk of ischemic heart disease.

[Slide]

Fracture events -- fractures were included as a possible endpoint because of the estrogenic effect of tamoxifen thought to be preserving bone. To evaluate this we included 3 specific endpoints of fractures that we identified a priori which we thought were fractures that would be more likely to represent osteoporotic type of fractures. Those 3 endpoints included fractures of the hip, fractures of the spine and fractures of the lower radial called Colles' fractures.

Overall, there were 61 of these type fractures in the placebo group compared to 33 in the tamoxifen group, for a reduction of about 46 percent overall of these types of fractures. Looking specifically at the types of fractures that occurred, hip fractures were 20 versus 9; Colles' fractures were 12 versus 7; and spine fractures were 30 versus 19. These numbers don't add up exactly to 61 and 33 because there is 1 woman here who had a hip and a wrist fracture. There are 2 women here. One had a hip and spine

and one had a hip and wrist fracture, and they are counted individually in that level.

[Slide]

Vascular events -- as I indicated before, in addition to endometrial cancer we were also aware that there were other potential risks associated with tamoxifen. We learned this from the extensive history that we had with treatment trials. These included thromboembolic events such as pulmonary embolism and deep vein thrombosis.

This bar chart shows the distribution of rates and the number of events occurring for pulmonary embolism, deep vein thrombosis, stroke and transient ischemic attack. In terms of pulmonary embolism, there were 6 cases in the placebo compared to 18 cases in the tamoxifen arm. Three of the cases in the tamoxifen arm resulted in death, and this difference was statistically significant.

In terms of deep vein thrombosis, there were 19 events in the placebo arm compared to 30 events in the tamoxifen arm. This difference was not statistically significant.

In terms of stroke, there were 24 in the placebo compared to 34 in the tamoxifen arm. Again, this difference was not statistically significant, and there really was no difference between the 2 arms in terms of transient ischemic attack.

[Slide]

Ophthalmic events -- when we planned the study there were also reports in the literature suggesting that tamoxifen might have some impact on visual effects. For that reason, we did two things. First, we undertook a special study in one of our that trials, NSABP-14 and, secondly, we included questions in follow-up information in the P-1 trial to help us understand and collect information regarding the occurrence of eye toxicities,

In terms of the NASBP-14 trial, approximately 300 women were called in and participated in very extensive eye examinations to determine if there were problems. The results of that study indicated that there were no problems with the development of retinal crystals -- retinal crystals is one of the things which was theorized to be one of the potential side effects. There also were no problems with macular edema or macular degeneration. However, the results from the study suggested that there might be a problem with cataracts.

[Slide]

In the prevention study we also found that there was no relationship between macular degeneration and exposure to tamoxifen. The actual number of events and the rates were identical between the 2 arms. On the other hand, we did find that there was a difference in the rates of

cataracts.

Of 483 women who came into the trial in the placebo arm without cataracts, developed them during the course of the trial compared to 540 in the tamoxifen arm. This represents about a 13 percent increase in the risk of developing cataracts. Among those women who developed cataracts, 63 out of the 483 went on to have cataract surgery compared to 101 out of the 540 in the tamoxifen arm. This represented about a 60 percent increase in the risk of having cataract surgery.

[Slide]

The next item I would like to talk about is total deaths. Overall, there were 65 deaths in the placebo group compared to 53 in the tamoxifen arm, 5 of the deaths in the placebo group were due to breast cancer compared to 3 in the tamoxifen arm.

There was 1 endometrial cancer death. This occurred in the placebo group, and was diagnosed with a FIGO stage IV endometrial cancer.

In terms of heart disease -- all heart disease not just ischemic, ischemic was 8 versus 7; total heart disease is 12 versus 12. Stroke was 3 versus 4. As I mentioned already, there were 3 deaths due to pulmonary embolism in the tamoxifen arm, and so on and so forth.

If you look down at every single cause, and there

are many causes in here, there are no differences between any cause of death between the arms.

[Slide]

To summarize the findings from the BCPT, first of all, tamoxifen use prevents invasive breast cancer among women in all age groups and at all levels of predicted breast cancer risk, and a similar effect is evident for the prevention of non-invasive breast cancer.

[Slide]

Rates of osteoporotic fractures were lower in the women in the tamoxifen group. The risks of tamoxifen include endometrial cancer, thromboembolic events and cataracts. No difference between the that groups was noted for rates of heart disease, other cancers, macular degeneration or other vision conditions affecting permanent vision loss.

[Slide]

Our conclusions then are that the BCPT was designed as the definitive trial to test the hypothesis that tamoxifen use would reduce the risk of breast cancer. The findings indicate that tamoxifen use can significantly reduce the risk of both invasive and non-invasive disease.

[Slide]

The weight of evidence from the trial is substantial in comparison to the recently published

preliminary findings of the 2 smaller and differently designed European studies. Thus, we conclude that women who are at high risk, as defined in the BCPT, should be considered as candidates for the use of tamoxifen to prevent breast cancer.

Summary

DR. LEWIS: Thank you very much, Jo. Before we open the meeting to questions, I would like to summarize Zeneca's position on Nolvadex in prevention.

[Slide]

Tamoxifen, as given in the breast cancer prevention trial, prevents 45 percent of invasive breast cancers in women at high risk. Benefit was seen in all age groups and at all levels of risk. The safety was as anticipated from earlier trials, and is covered in our current label. The definition of who is at high risk is as described in the label and in the trial. This information has been incorporated into our current label.

Having identified a woman who is at high risk of breast cancer, it is appropriate for that woman to have discussion with her health care provider to determine if tamoxifen is right for her. This discussion should include the necessity for medical care follow-up because tamoxifen is not a substitute for good medical care but an addition to it.

[Slide]

It is our believe that good medical care for all women includes regular examinations, mammography and pelvic examinations, and follow-up of any abnormal signs and symptoms.

[Slide]

Finally, we believe these data support our claim that tamoxifen is indicated for the prevention of breast cancer in women at high risk for developing the disease.

Thank you very much for your attention, and I would be pleased to take questions from the committee.

Questions from the Committee

DR. DUTCHER: The company has given us half of their time to ask questions of them. So, we appreciate that. Dr. Albain?

DR. ALBAIN: Thank you, Dr. Dutcher. I think it goes without saying that we congratulate the sponsor and NSABP for conducting this landmark trial.

It struck me in the data again, presented this morning, about the courage of the over 13,000 women who consented to randomization in this trial, as well as the extensive support this trial received from the start from the lay advocacy community and breast cancer survivors. With that as an opening statement, I would like to take the discussion right away to one of the major topics of

discussion out there since the data was released in May at the ASCO meetings, and that is the admittedly short follow-up at this stage for the endpoint of preventing cancers.

I was wondering if you or NSABP could comment on some of the data that is out there that has much longer follow-up, those breast cancer survivors who received tamoxifen for an adjuvant therapy indication, who have now been followed much, much longer than NSABP-14 or perhaps the worldwide overview data that supports a 45-50 percent reduction in risk of second cancers. Is the maturity of that data in any way supportive of this particular indication?

DR. LEWIS: I would like to call on Dr. Wolmark to make some comments on the NSABP trial itself.

DR. WOLMARK: Thank you. I would like to echo your remarks on acknowledging the role of the 13,388 participants in this trial, without whose courage and perseverance and dedication and selflessness we would not be here today.

Relative to your questions as far as the mean time on study and the duration of the effect of tamoxifen, Dr. Costantino showed you the reduction in relative risk over the period of years of follow-up, and that reduction was durable throughout the five years and now into the sixth year. So, even beyond the discontinuation of tamoxifen we

still see a reduction.

Relative to the data from B-14 where we used the contralateral breast as a surrogate marker for prevention, there too we see that the effect is not a transient one but durable. Those differences that were noted at five years were still very much apparent at ten years of follow-up. That is also true for cumulative analyses of all the NSABP trials relative to the contralateral breast, and is entirely consistent with the overview analysis relative to the contralateral breast, indicating that this is not a transient effect but a durable one.

DR. ALBAIN: To follow that up, what are the confidence intervals like out at the 4- and 5-year parts of your annual hazard curve that you showed and just alluded to? We didn't see those on the slide.

DR. WOLMARK: Yes, confidence intervals are a reflex response for me to call upon the statistician.

[Laughter]

So, perhaps Dr. Costantino would like to look up the confidence intervals to precisely address your question, and perhaps you might have another one as he is looking those up.

DR. ALBAIN: I have the same question for the reduction in risk of invasive cancers by your predefined risk strata by risk.

DR. COSTANTINO: I don't have the exact confidence limits here with me, but I can tell you that --

DR. WOLMARK: It was an excellent question nonetheless!

[Laughter]

DR. COSTANTINO: -- that the relative risk was about 50 percent. The confidence limits for that individual year approached statistical significance. But there was no indication that there was a difference in the hazard rate over time. I think that is the more important question, were the hazard rates constant over time? And, all the data that we have analyzed, including some of the data that was done independently by the FDA, indicate that the hazards are constant over time. So, there is no suggestion that there might be differences over time.

DR. ALBAIN: And what were those generally, those hazards?

DR. COSTANTINO: Well, about 6/1000 is what it is in the placebo group and about 3.4/1000 in the tamoxifen group.

DR. ALBAIN: Thank you.

DR. DUTCHER: Dr. Sledge?

DR. SLEDGE: I have several questions I want to ask. If one looks at the hazard rates for endometrial cancer -- I would echo my esteemed colleagues on what a

wonderful study this is in terms of its design and development, but I will tell you, as a practicing medical oncologist who takes care of breast cancer patients, I pretty much felt I knew the answer before the study was started in terms of a chemoprevention effect. I think many of us who have worked in this field for many years felt that tamoxifen was a chemopreventive drug before the trial was ever started. So, this primarily comes down to the risk-benefit questions rather than the true scientific question of whether or not it can prevent breast cancer.

If you allow for that, I think a number of important questions come up. Let's start with the endometrial cancer question. If I am reading the numbers correctly, 37 percent of the women had a prior hysterectomy and 31 percent of the women were premenopausal. The figures that we were given in terms of hazard rates are hazard rates for the general population of women in the trial but, of course, if I go out to the clinic next week with a woman who is postmenopausal with a uterus, the general hazard rate from the trial is pretty useless in terms of me speaking to that patient. So, what is the hazard rate for a postmenopausal woman who has an intact uterus of getting endometrial cancer in any given year?

DR. COSTANTINO: Actually, I did indicate that these are the hazard rates based on women with uterus

according to their age. So, these hazard rates you see are exactly what you are asking for. So, it is 3.21/1000 women who have a uterus.

DR. SLEDGE: Postmenopausal?

DR. COSTANTINO: Over age 50 or under age 50. We used age here as a categorization for menopausal status, as an approximation.

DR. SLEDGE: Okay, thank you. The second question again relates to the question of risk. The proposed indication is for women with the risk of a 60-year old and, yet, the average risk of the women entering the trial was considerably higher. Since this is largely a risk-benefit issue, what do we say to a woman who doesn't have quite as high a risk as the woman who entered the trial in terms of whether she should go on tamoxifen or not? I looked in the package insert, and the package insert basically says women went into the trial based on the Gail model. It gives us a number of scenarios in terms of who should be considered for tamoxifen, and then after all the scenarios are given it says that these scenarios only account for 17 percent of the women who went into the trial. How is the average general internist or OB-GYN out in the community supposed to decide who is going to go onto this trial?

DR. WOLMARK: Well, I think obviously the information presented today is only relevant for those

individuals who met the criteria of increased risk as defined by the BCPT which was, in turn, a modification of the Gail model. I think it is incumbent on us to define whether that individual is, in fact, at increased risk and meets the eligibility criteria for entry into the BCPT protocol.

There have been a number of actions that have been taken to widely disseminate this information, to make it user-friendly, and also to be readily available to both the physician or to the individual who is considering the use of tamoxifen. Perhaps Dr. Leslie Ford could comment on what these efforts have been up to this point.

DR. FORD: The NCI has obviously been very interested in the issue of how we communicate breast cancer risk to women, both in the context of this trial and in other work that we do. One of the things that we have been working on since the April announcement has been a user-friendly way of assessing a woman's risk of developing breast cancer based on the Gail model, and it has gone through some very early data testing but we are about to start distributing what we call our breast cancer risk assessment tool. It is available by request through our cancer trials web site.

We will also be sending copies to the major medical societies, and announcing its availability in the

newsletters of the major advocacy organizations and medical societies for distribution. The NSABP will also be distributing these risk assessment tools so women and their physicians can, in a sense, plug in their risk factors and determine what their 5-year time risk is of developing breast cancer and whether it was similar to the women that participated in the study.

DR. SLEDGE: I think that is absolutely crucial for a drug like this because I can tell you, looking at the package insert, it is definitely not user-friendly in terms of trying to determine --

DR. WOLMARK: Is there a package insert that is?

[Laughter]

DR. SLEDGE: I think most package inserts are pretty simple. I think for this drug, if we are talking about adjuvant therapy for breast cancer, it would be a lot easier to describe.

DR. HONIG: May I make a comment? I would just add also that in addition to those tables of risk that are in the label as it stands now, if you add in the other categories such as preceding diagnosis of LCIS or age, it actually accounts for a little over 50 percent of the profiles of the women who went on the study. It is not 100 percent, obviously, but it is a little over half.

DR. SLEDGE: And that is not clear in the package

insert. If I am reading the results correctly, tamoxifen is not eliminating the largest tumors; it is not eliminating the most node-positive tumors; and it is not eliminating the estrogen receptor negative tumors, the ones that we typically think of as bad actors from a survival standpoint, which I think is what patients should be interested in, in the long run. This might suggest a lesser long-term survival advantage.

DR. WOLMARK: Well, I am not sure that we are not eliminating the larger tumors, or that we are not eliminating tumors with four or more positive nodes. I mean, these are the characteristics of the tumors that we see that are evolving on tamoxifen.

As far as what the ultimate outcome is going to be, I think if you can eliminate breast cancer at some point in its evolution, I think we have no way of knowing whether that breast cancer would go on to become virulent and eventually kill the patient. So, I don't think that we can really comment with any degree of accuracy on what the ultimate effects are going to be vis-a-vis perhaps a less than expected impact on survival. I think the fact that we can reduce it by 45 percent will ultimately translate into a prolongation in overall survival.

I don't think that there is any evidence that we are selecting out a more virulent variety of breast cancer

as a result of the use of tamoxifen, and I think that we have to emphasize the fact that there has been I think a very clearly defined reduction in the overall rate of invasive and non-invasive cancer. Beyond that, I think we can't speculate.

DR. DUTCHER: Miss Cassel?

MS. CASSEL: I am here today as a patient representative since I am considered high risk and a target population should the drug be approved. How long would you prescribe the tamoxifen for me, so to speak, and at what age? If I have been high risk for the last ten years, at what age would you prescribe it? At forty? At fifty? And for how long?

DR. WOLMARK: The duration of tamoxifen that was used in this trial was for a period of 5 years, and we think that is an appropriate interval to use. Of course, the question that comes up is how do you know that 10 years wouldn't be better? Well, the answer is we don't know since that clearly was not tested in this trial.

But we do have some information from NSABP protocol B-14, where we did compare 5 years versus 10 years of tamoxifen in patients who had a personal history of breast cancer who were negative, and whose breast cancers were receptor positive. There, it was demonstrated, to our surprise, that 10 years was not only not better than 5 years

relative to the index cancer but was slightly worse. But of greater significance, addressing your question, is that there was no additional incremental benefit to the contralateral breast for the additional 5 years of therapy. So, we believe that 5 years is the optimum time until data to the contrary appear. So, I would suggest 5 years.

As far as when it should be started, I mean, from my perspective, I think it should be started as soon as it is known that the risk is such that it would make the patient eligible. If one has a 35-year old woman who is of such risk that she would fit the eligibility criteria for the NSABP study, I think that would be the time to initiate 5 years of tamoxifen. I see no virtue in waiting an additional 5 years to let the risk increase to start at a certain arbitrary time in the future.

MS. CASSEL: I am also concerned, in talking to some of the target population, that women have a feeling that is a false safe feeling -- I have the drug, almost as a birth control pill, and I can just take it and not worry about it. I am afraid that they will forget their self-breast exam, their mammogram. This is the feeling of some of the women.

DR. WOLMARK: Well, I think we have to be very cognizant of that, and I think that we have to indicate very clearly that this is not a substitute and that we have to

continue to exercise the standard of medical care and the standard of screening.

DR. DUTCHER: Dr. Raghavan?

DR. RAGHAVAN: I have just a couple of questions. I always get a little nervous when two-thirds of the deaths on a list are listed as "other." I recognize that the other deaths from placebo are more common than from tamoxifen, but would you give us a little more information about that broad category?

DR. COSTANTINO: I believe a complete list is included in the document that you were provided, but to give you some examples -- let's see, we talked about the breakdown of the cancers -- I am not sure how much detail you want me to go through. We have about 20 different causes, but these are deaths due to brain cancer, 3 versus 1; breast cancer 5 versus 3; colon, 1 and 1; endometrial 1; lung cancer 10 and 8; ovarian cancer 1 and 2; lymphatic system 4 and 1; pancreas 6 and 2. Of course, the first is the placebo arm.

Moving down to heart disease, ischemic heart disease 12 and 12; stroke 3 and 4; pulmonary embolisms 0 and 3; unknown causes 4 and 4. Then there were 9 and 7 miscellaneous causes, which accounted for 11 different categories which, from the top of my head, I don't really know. But there was no indication that there was any type

of cause of death which was predominant arm more than in the other.

DR. RAGHAVAN: And was there a systematic requirement for autopsies where possible?

DR. COSTANTINO: There was no requirement for autopsy. We did obtain the death certificates and we did obtain information from autopsy if it was performed, but there was no requirement that autopsy be performed. In other words, this is a community-based study. So, we had to accept whatever standard of care is going on in the community.

DR. RAGHAVAN: You commented that there was really, I guess, an anticipated absence of ocular problems and, in fact, maybe a reduced level compared to what was expected. Did you have a mechanism where the participants were actually routinely examined by physicians looking for specific indices?

DR. COSTANTINO: There was no routine examination. Our follow-up consisted of at every visit there was a series of questions that the women were asked. The first question was "have you had an eye exam since the last time you visited our clinic, and if you did, what were the findings from that eye exam?" There was also a series of questions specifically aimed at determining vision changes, asking them specifically "have you noted changes in your vision? Do

you have more difficulty driving at night?" or different types of things which were included in the questionnaire. So, we have all these screening types of things.

Also included as part of our follow-up was that the institutions were required to obtain discharge summaries documenting the diagnosis for all incidents for inpatient and outpatient visits. So, from these types of things there is another mechanism for us to identify women who might have had eye surgeries or eye problems that required some type of inpatient or outpatient care. But we did not have a routine eye exam.

DR. WOLMARK: The data from protocol B-14, the that trial where some 303 patients were evaluated for eye changes, that too was a tamoxifen versus placebo controlled trial. That was done in a definitive manner with ophthalmologic examinations, and there I think it was noted prospectively that the changes in the retina, or crystals, or edema, or macular degeneration was not in evidence.

DR. RAGHAVAN: My final question, Norm, if you look at your Gail model, the results are really very impressive for the 5-plus group, and there clearly is a difference with low level of risk, and I am also struggling a little in terms of the hazard ratios in the less at risk group. Can you talk about that a little bit?

DR. WOLMARK: Well, Jo showed a slide based on

risk categories, and in each category there was a reduction. How does one translate that into clinical practice? I think the report from the FDA to ODAC which summarizes our view, I think, very clearly is that it really boils down to an individual choice and an interpretation of risk and benefit, and not every individual will do that in the same way. I think we have to provide the potential participant with a clear overview of the information, given in a very definitive manner, and then I think it becomes a matter of individual choice, particularly for those areas that you allude to, where the risk is below the 5 or the 6 that you allude to.

DR. ALBAIN: Just to follow that up, and then I have a new question. At least in your briefing book the hazards do cross the confidence intervals around the hazards, cross 1, in some of these other subsets. Your predefined strata for risk that you put into the randomization were a bit different than these that appear here. Could you comment on what the hazards actually are for the confidence intervals?

DR. COSTANTINO: When we stratified at randomization we used relative risk. Those are categories of relative risk. Actually, the relative risk was defined as your 5-year risk relative to an individual of the same age and race but who did not have any risk factors. The

reason that we decided to use absolute risk as the categorization is because absolute risk is a much cleaner mechanism to do that. Two people could have the exact same relative risk but have absolute risks which are totally different. Therefore, when we did the analysis we wanted to control for that factor, and the easiest way to do that is to stratify by levels of absolute risk.

DR. ALBAIN: Then I would like to turn to some other populations at risk, in particular DCIS and the African-American population. Certainly, you were not choosing DCIS as a primary endpoint but your results are intriguing, and we are also aware you have another trial that has addressed that specifically prospectively. Do you feel that the data are robust enough in P-1 to add DCIS to the labeling, or must we wait a bit longer, and how much longer for your other study?

DR. WOLMARK: I think we must wait, and I don't think we will be waiting too long. DCIS was not an entry criterion for this trial. So, I think we have to rely on the data from B-24 and B-17 prior to that, which I think will probably require a different session of this group.

DR. ALBAIN: But you did show prevention of DCIS that was quite striking.

DR. WOLMARK: Yes, I think to prevent DCIS --

DR. ALBAIN: That is what I mean.

DR. WOLMARK: -- based on the entry criteria that we utilized in this trial, very much so. I think it decreases the rates of non-invasive breast cancer, predominantly DCIS. I completely agree with that.

DR. ALBAIN: And then the African-American population, you tried very, very hard prospectively to accrue minority communities. Could you comment on that effort, and then how you feel these results could be translated to that population?

DR. WOLMARK: I would like to ask Dr. Wickerham to comment on that.

DR. WICKERHAM: Dr. Albain, you are right. This is an effort that the NSABP has taken very seriously from the start of the trial, and during the study we spent considerable effort to try to increase accrual from these various populations. Our goal at the outset of the trial was to have a population to reflect women at risk. Despite these efforts, we were not fully successful at that. Only about 3 percent of the women entered are women of color. That really doesn't allow us to make definitive statements relative to these results in those populations. But you should be aware that in our that trials we were more successful in entering women from those groups, 10-12 percent, 15 percent in some of our trials. B-14, which in many ways forms the basis for the prevention trial, has been

evaluated and analyzed relative to response to tamoxifen in these populations, and we clearly see no difference in the outcomes.

DR. DUTCHER: Dr. Ozols?

DR. OZOLS: Getting back to the risk again, the 2 major side effects, endometrial cancer and thromboembolic disease, and the 3 deaths in the that group with the pulmonary emboli, can you get any better profile on which women, you know, may be at risk for those 2 toxicities? The traditional risk factors associated with endometrial cancer -- diabetes, hypertension, obesity, are those heightened by tamoxifen? Likewise, can you identify anybody who may be at higher risk for developing pulmonary emboli?

DR. WOLMARK: Well, we obviously examined that, and we are not able to come up with a profile that would identify a subpopulation that would be at inordinate risk, such that they could be eliminated from entry into this trial. We did, however, a priori eliminate those individuals who had a previous personal history of deep vein thrombosis or pulmonary emboli. But examining the actual data of the population that was entered we could not define characteristics that would be associated with increased risk for those events.

DR. DUTCHER: Just to follow up on that, about 25 percent of people who were screened and met eligibility

actually entered the trial, and a comment was made about medical reasons for exclusions. Was it medical exclusion or was it logistic exclusion? What was the drop-off between those that met the eligibility and those that actually entered the study?

DR. WOLMARK: Following the risk assessment, those who were eligible from the eligibility and those who were actually randomized.

DR. COSTANTINO: I think the biggest reason for the drop was that women were not interested in participating in the trial. They did not go forward to have the full-fledged medical evaluation. A little over 14,000 women actually went to that level to be medically evaluated to come into the trial, and out of that 14,000-plus 13,388 were actually randomized. So, the major reason for the drop from 57,000 down to the 13,000 was because women were just not interested in being a participant in the trial.

DR. MARGOLIN: I have what I think will turn out to be 3 questions. The first one is sort of a biology question and it pertains to the question that Miss Cassel asked earlier on about the best timing for intervention in patients who are identified as subjects at risk. It is just hard to imagine that 5 years of that at basically any time in a woman's life is going to infer a permanent change in her likelihood of developing invasive or non-invasive breast

cancer.

I am wondering, based on preclinical models or based on any biology that anybody knows, whether, say, early treatment and then some period of time off therapy and then reintroduction of therapy, or if we can somehow improve on what we are trying to do here to prevent breast cancer.

DR. WOLMARK: I think we are really limited by the data that we have, unfortunately. I mean, we would like to know where tamoxifen acts in this situation. We would like to know what the molecular mechanisms are. Yet, this was a clinically driven trial and we are left with clinical data.

Is there an optimum time at which the intervention should be undertaken that would be better than just starting it when the relative risk becomes apparent? If one were to undertake such a trial clinically, it would require enormous numbers of participants with an enormous amount of support from the agencies, to whom we are forever grateful -- the NCI and Dr. Ford -- and I don't think at this time it is a practical endeavor. I mean, we would much rather go on and determine if we can find drugs that perhaps have the same efficacy with fewer side effects which would make that issue moot to a certain extent because they could be given longer and with greater degree of definitive intervention.

DR. MARGOLIN: Thank you. My second question is I believe the study was noted as being insufficiently powered,

or at least was closed at a point where it was insufficiently powered to detect survival differences. Is it expected that after a certain number of events have occurred, after a certain follow-up, that we will be able to see a potential survival difference, or is that just not going to be possible with this database?

DR. WOLMARK: If we were to have primarily done a survival endpoint, I think we would have required an additional 10 years of follow-up and a considerably greater sample size, but I would like Dr. Costantino to comment on what it would have taken to have configured this trial for a survival endpoint for breast cancer.

DR. COSTANTINO: We never did design the trial to be able to have the power to detect a survival difference because it would have required doubling the sample size and much longer follow-up, as Dr. Wolmark indicated. We do plan to continue following those women. We will learn more information about survival benefits, but it is highly unlikely that we will ever have statistical power to show a significant difference in survival. It requires larger numbers and a longer follow-up period.

DR. MARGOLIN: I have one additional question, whether there are plans to go back and do some genetic studies of subjects enrolled in order to detect potential interactions with BRCA 1 and 2 or other genetic risk

factors.

DR. WOLMARK: Yes, that is I think an important commitment and those trials are about to be launched. Certainly, that is a very important issue. We have collected serum and lymphocytes from the women who participated in this trial, and we will start to analyze BRCA 1 and 2. Mary Clare King will be doing this in the very near future. We will be able to determine definitively what the benefit is in those individuals who have BRCA 1 and 2 abnormalities. Additional comments?

DR. SCHILSKY: A quick comment and a question. It is striking to me that the leading cause of cancer death in this study is lung cancer. It is too bad tamoxifen doesn't prevent that.

DR. WOLMARK: Oh, there wasn't a reduction in that?

[Laughter]

DR. SIMON: The question I guess has to do with how the participants in the study have now been informed of the results, whether women who were randomized to placebo have been advised to take tamoxifen and, if so, how might that confound the future interpretation of the results with continuing follow-up?

DR. WOLMARK: We have a covenant with the participants that they would be among the first to know the

data, and we did not want to repeat the unfortunate events of some of the earlier episodes that affected this trial where the participants learned what was going on from the newspaper. Despite our diligent efforts to avoid that, we were not entirely successful in this trial since the data were previewed in a well-known newspaper prior to the time that we were able to transmit that information through a widely publicized press conference that I believe took place on April 4.

The participants have been formally apprised. That process was in place as the data were being disseminated, and those individuals who were on placebo are given the opportunity to go on 5 years of tamoxifen. Zeneca has been very gracious in providing that medication to these participants. Also, those individuals who did not complete the 5 years of tamoxifen who were randomized on this trial will have the opportunity to complete the full 5 years of tamoxifen.

As far as what does that do to our ability to continue to monitor the differences between tamoxifen and placebo, clearly those are attenuated in that this trial has been unblinded and that we will now have crossovers, but to what extent we do not know as yet. We will obviously continue to follow these patient cohorts and, certainly, those that are on tamoxifen will continue to provide data,

and we believe we can continue to model the events in the placebo arm. So, I think it will provide useful information but the primary endpoint of the trial is obviously affected by the unblinding.

DR. DUTCHER: Dr. Simon?

DR. SIMON: I have several questions. One, several people have noted the concern about the limited follow-up. There is not a whole lot that can be done about that, but you have basically presented data that was available to the data monitoring committee last January. Can you give us updated data on number of events in the placebo and tamoxifen group for the 3 age groups for invasive breast cancer?

DR. WOLMARK: Obviously, you know, the data provided to this committee are the data that are going to be utilized so I would rather not go into the data for the updated analysis, only to tell you that the differences are even more compelling.

DR. SIMON: Why do you not want to give us the updated data?

DR. WOLMARK: I think that we had a cut-off that we all agreed to a priori; that this was submitted to this committee for their review; and I think that is the data set that is going to have to be used to make the decision.

DR. SIMON: Well, typically, you know, when you

present data to a data monitoring committee that is not up to date to that minute anyway. You know, there is a distribution of time since patients were last seen and evaluated. So, that data actually may be a year old at this point really in terms of what it represents in terms of when patients were last seen.

Well, let me go on to my next question. Do you have information about the hazard rate over time for the ER-negative cases, particularly in the tamoxifen arm?

DR. WOLMARK: Jo, the hazard rate for the ER-negative cases in the tamoxifen arm?

DR. COSTANTINO: Over time?

DR. WOLMARK: Over time.

DR. COSTANTINO: I don't have that with me.

DR. WOLMARK: The answer was no, he does not have it with him, and he wondered why you were asking the question.

DR. SIMON: Well, because really, you know, one question is whether you are treating with tamoxifen in subclinical cases that might have materialized as ER-positive tumors -- by the selection process will materialize as ER-negative tumors, and whether you will see that there is some trend of that happening in later periods of follow-up.

DR. WOLMARK: Jo?

DR. COSTANTINO: I can tell you that we didn't see that kind of trend. If you consider that the ER-positive tumors were 80 percent of the tumors and we did see hazard rates over time that were constant, we would suspect that just taking out those majority of things is not going to change the pattern, but I didn't see the type of pattern that you were suggesting.

DR. SIMON: I have a couple of other questions. One is that I have some concern about what we are supposed to conclude in terms of what group of patients these results apply to. One, it is one thing to say what the eligibility criteria were and that is not to say what patients actually entered the trial. In terms of communicating these kind of results in terms of who these results apply to, it is really not an issue of even simplifying in a user-friendly way the Gail model. The real issue is what women went into this trial, because there may be women who were eligible according to the Gail model but if they are not well represented in this trial then we probably can't have much confidence that the results apply to them. I guess I haven't really seen a clear explanation of what the women looked like who went into this trial.

I guess the second issue is that it is one thing to say that the risk of breast cancer of a woman is equivalent to that of a 60-year old woman, and it is

something else to say that the results actually apply to a 60-year old woman. Most of these women, I think two-thirds of them or something like that, were under the age of 60 and they got into this trial because they had other risk factors. So I think we have to be somewhat careful in assuming that because the Gail model said that their risk factor was at least the risk of a 60-year old woman that the results actually apply to a 60-year old woman. The only basis we have for that is, you know, where you break it down by age. You know, that is a relatively small subset. It looks like the effect is just as great for them as it was for the other women. But I think we really have to be very careful in trying to sort out who the results apply to. That is sort of a comment, not a question.

I do have one other question, and I would like to sort of get your general medical interpretation of it. There were 69 fewer cases of invasive breast cancer on the tamoxifen arm, but there were 19 additional cases of endometrial cancer. There were 39 more cases of vascular events on the tamoxifen arm, and there were 38 more cases of cataracts requiring surgery. So, how do you make that risk-benefit equation?

DR. WOLMARK: Well, I don't think it should be up to me nor any other physician or someone who delivers health care to compel anyone to go on tamoxifen or not go on

tamoxifen. I think that it becomes an individual decision after the risk and benefits are thoroughly reviewed and after that information is transmitted in a very clear and well-defined manner.

Having said that, and since you asked for an opinion, I think that there are categories that, from my perspective, clearly fall out where the benefits unequivocally outweigh the risks. I think those subsets would include those women who are under 50 years of age where the excess of adverse events is small; those women who are over 50 years of age who have had hysterectomies, and in our patient population that accounted for a substantial proportion; those women who have had a personal history of lobular carcinoma in situ; and those women who fulfill the eligibility criteria and also have atypical hyperplasia. I think in those instances, from my perspective, the benefits clearly outweigh the risks.

I think in the other categories it boils down to an issue of personal choice and personal decision. I think what some people would consider as inordinate risks others would gladly accept.

DR. DUTCHER: Miss Beaman?

MS. BEAMAN: Would you reference the data that you have for the women who were taking tamoxifen and developed breast cancer as to whether this cancer was of the more

aggressive type?

DR. WOLMARK: I think in the slides that were presented relative to the distribution of women who did develop breast cancer while they were on tamoxifen there certainly was no evidence, from a nodal standpoint as well as a tumor size standpoint, that the tumors that developed on tamoxifen were more aggressive or more virulent than those tumors that developed in women who were taking placebo. So, there is no evidence that tamoxifen culls out a more virulent subset of breast cancer while suppressing the more benign forms of breast cancer. I think that appears in the slides that you have in the handout.

DR. DUTCHER: Dr. Johnson?

DR. JOHNSON: Actually, I want to follow-up, if I may, on what I think Dr. Sledge addressed earlier. Certainly, nodal status is one of the most important, if not the most important, prognostic factors and size as well but there is no mention about tumor grade here which clearly has an impact. If all 154 tumors that appeared on placebo were low grade and all 85 on tamoxifen were high grade tumors there might, in fact, be a difference in outcome even though the other factors were identical. I wonder if maybe you have some data regarding grade. I didn't see any of that information.

DR. WOLMARK: No, we have no data on grade. I

think it would be nice to know what the HER2 status of the tumors was, and is, and will be, but we don't have that information.

DR. JOHNSON: Is that information that we can expect will be forthcoming in the future, or is it simply something that won't be followed-up upon?

DR. WOLMARK: We are collecting slides and blocks, which the protocol has mandated, on all events that occur in this study and, hopefully, that information will eventually be forthcoming.

DR. JOHNSON: And, if I may follow-up with one further question, the death rate from breast cancer, as has been pointed out, is really rather small in the trial overall and it is similar in the 2 arms which, actually, is sort of interesting given the fact that the number of overall cancers is twice as great on the placebo arm. So, do we have any information about the status of those women who have developed breast cancer at this juncture? Again, just to take the extreme, if all 85 of the women on the tamoxifen arm now have stage 4 disease and all 185 on the placebo arm have stage 1 disease there may be an indication of a difference in the aggressiveness of the tumors. Do we have that data?

DR. COSTANTINO: We are collecting information regarding recurrence, and we do have that but it is not

complete at this stage. Dr. Paik is in the process of reviewing all the pathology slides as we speak but we do not have that information accumulated as of yet.

DR. WOLMARK: But, David, why would you think that there would be that disparity?

DR. JOHNSON: Well, because unlike George, I don't have the ability to see the future.

[Laughter]

He predicted that this drug was going to work and I just didn't realize it was going to work. So, I was really happy that the study was done. So, you know, data is what really drives my decision-making, or I like to think it does. So, I don't believe that is the case. Just because I asked the question doesn't necessarily mean I believe that is the answer. I think I would like to know, and I am sure everyone sitting over here as well as in the audience would like to know those data as well. And, if it were to turn out that way, then it would be disturbing.

DR. WOLMARK: George, perhaps you could save us a lot of time by telling us raloxifene versus tamoxifen for the STAR trial?

[Laughter]

DR. SLEDGE: I would be glad to tell you that afterwards.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: I have one question and one comment. The question is that -- unless I have missed it and it has already been presented -- we have heard at various times well before this meeting that the subjects who were accrued or registered to this trial turned out to have higher at least relative risk of breast cancer than was expected and was planned for the original accrual. I am curious to know, at the end of the trial, at least based on the placebo arm data, whether the incidence of breast cancer reflected what was expected based on that revised accrual estimate.

DR. COSTANTINO: Indeed, it did. It was about double what we expected.

DR. MARGOLIN: Thank you. My comment is that if the drug is approved for this indication, and I think that the world, certainly the U.S. but the world really worships what the NSABP says and does, and the NCI as well, and it would be very crucial that very firm guidelines be given in terms of selecting subjects for that with this type of intervention.

DR. ALBAIN: I have a question for the sponsor. Your choice of wording in the indication, using the word "prevention." Typically, when that word is used you have the luxury of long-term follow-up, in particular like we do in B-14 and the worldwide overview for prevention of

contralateral breast cancers. Would you consider perhaps softening that statement to say reduction in risk of occurrence of first cancers because that is really what we have seen quite dramatically by this data?

DR. SIMON: Right. Actually, that is what was seen in the overview also in the contralateral breast, and we would agree with you. I think "prevention" means it doesn't occur and it also means risk reduction. What we are looking for here is a way of getting the message across to the average person. It means something to us. The trial was called prevention; Dr. Leslie Ford's group is prevention. We are not preventing all breast cancers. Clearly we are not. But this is a major step forward, and I would like to think that we could retain the term "prevention," describing it as it was described in the manuscript which states that it is a reduction in the number of breast cancers that are anticipated.

DR. DUTCHER: Dr. Simon?

DR. SIMON: The women over the age of 60, were they a representative group of women or did they have high risk features?

DR. COSTANTINO: Actually, if you look at the hazard rate in the placebo, you can see that their risk of breast cancer was among the highest of all the women in the trial. So, it is true that being over 60 was an eligibility

criterion and so you got in, so your risk could be as low as 1.66 theoretically but, indeed, the rate and the hazard in the placebo group was over 7/1000. So, they were essentially comparable in risk to the women in the other groups. As far as being representative, I think you mean representative of the general population?

DR. SIMON: Right.

DR. COSTANTINO: I don't think any of these women are representative of the general population because they have been selected out to be at high risk for breast cancer.

DR. SIMON: So, how do we know --

DR. COSTANTINO: They volunteered for the trial.

DR. SIMON: So, how do we know that these results apply to a typical spectrum of women over the age of 60 in the United States? How do we know who these results apply to?

DR. COSTANTINO: We know the results are consistent across all categories or risk --

DR. SIMON: No, but you say age and you show over 60, but these are not a representative group of women over 60.

DR. COSTANTINO: That is true of any clinical trial. I think the best we can say is that within the trial we were not able to demonstrate any population which did not show benefit from the treatment; that we can think of no

reason to conclude that the women in the trial, as far as effect is concerned, would not represent the general population. So, I don't see that we can do more than that.

DR. SIMON: So, what is your proposal for who you are recommending this for in terms of an indication? Is it women whose risk would satisfy the Gail model? And, if that is the case, that would include all women over the age of 60 but we don't really have any indication that these results apply to typical women over the age of 60. So, I find that a real inadequate specification of who these results apply to. Can you clarify it for me?

DR. COSTANTINO: I just don't understand your argument, Richard.

DR. SIMON: Well, maybe I can clarify it. You have a study of high risk women and this study seems to have shown a benefit of tamoxifen for this group of women, and now we are trying to figure out who this group of women are before we wind up recommending this drug, with its side effects, for all women. If we recommend it for all women whose risk is at least equivalent to that of 60-year old women, then we recommend it to a large group of women over the age of 60 in this country who probably may not have been represented at all in this clinical trial. You may have gotten a result that worked because of some genetic features that these women had that gave them other high risk features

that really don't have anything to do with your typical --

DR. COSTANTINO: The eligibility criteria for this trial was simply being over 60. It had nothing to do with the Gail model. We are recommending that those same type of criteria be applied to women who are considered candidates for the drug. Simply being over 60 makes you a candidate so that you can go forth and make these kind of comparisons of the risks and benefits and decide. For women who are under 60, we are recommending using the Gail model just as it was applied as eligibility criteria. So, our recommendations are pertaining specifically to the exact same type of women who were deemed eligible for the trial.

DR. SIMON: Well, that is what I was saying. There is a difference between being eligible and who actually got into the trial. I think when you make recommendations as to who the results of the trial apply to, you have to look at who was in the trial, not who was eligible for the trial.

DR. WOLMARK: Richard, I really agree with Jo on this. I think that this is an inherent problem in every clinical trial you do. You set out the eligibility criteria and whoever actually enters the trial may or may not, you know, fulfill the entire spectrum of the eligibility criteria but that does not justify anyone from going back and retrospectively culling out a subset to say that this is

more representative of those individuals who actually entered the trial. We don't have the power to do that, from my perspective and, more importantly, I don't think we have the right to do that.

DR. SIMON: I am just trying to figure out whether the results of this trial apply to the typical woman over the age of 60 who doesn't have other high risk features.

DR. DUTCHER: Dr. Honig?

DR. HONIG: We were concerned about that also with that particular age group, and I don't have the numbers with me but we looked at women over 60 to see if, for example, all of them had positive family histories, or a significant proportion had LCIS or atypical hyperplasia, and that was not true. At the time though we did not have the risk disc so we couldn't run the Gail models, but most of them appear to have a combination of the other factors that went into the Gail model, if that helps answer your question in part.

DR. WOLMARK: Yes, I think we apply, you know, what we believe and we will be using the criteria for the next NSABP trial, the study of tamoxifen and raloxifene as they were used for the BCPT, with the exception that this will be limited to postmenopausal women.

I think it would be a mistake and somewhat disconcerting to try and fine-tune the characteristics of patients who would benefit from tamoxifen based on a subset

analysis of the NSABP population. I think we should use the criteria as they were applied to the BCPT.

DR. LEWIS: I would just like to comment that there was one other criterion that was left out, and that was a discussion with the patient, and we plan, working with the National Cancer Institute, to stress this as a critical part of a decision for a woman which empowers the woman to elect to take tamoxifen. Certainly it is not Zeneca's intention to take all women at 1.66 and say that tamoxifen is right for them. As a matter of fact, in our label there is a sentence which says tamoxifen is not right for all women at high risk -- something to that effect, and we do plan to handle that responsibly.

DR. DUTCHER: Dr. Sledge?

DR. SLEDGE: I would like to get back to Dr. Albain's comments a few minutes ago. On this question of prevention, I think it is reasonable to ask whether what we are seeing in this trial is true prevention. If we look at the risk ratio by year, a great point was made that it was pretty consistent over the first 5 years. It is real hard for me to believe that what I have always thought of as chemoprevention, that is to say, the transition from an earlier to a later place along the stage of development of cancer is what you are seeing when you don't see a cancer in the first year of a trial, and I think we have to assume

that what we are dealing with in the early years is chemosuppression of existing invasive tumors rather than true chemoprevention.

DR. WOLMARK: I would have no argument with that. And what are we seeing in later years?

DR. SLEDGE: Well, presumably the later out you get, the more likely you are to be seeing chemoprevention. I don't think there is any argument about that, but I think to say that all of these early cases where we are seeing a difference represent chemoprevention just simply probably isn't true.

DR. WOLMARK: Yet, the ultimate effort is to reduce the incidence of invasive cancer, reduce the incidence of non-invasive cancer and its clinical consequences.

DR. SLEDGE: I think we can agree on that.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: I would like to know whether the data on the effect of tamoxifen in this cohort reduced the expected risk of breast cancer down to that of an age-adjusted woman with no additional risk factors, or if it is still higher by some relative risk.

DR. WOLMARK: Jo, do you want to comment?

DR. COSTANTINO: Let me make sure I understand your question. Your question is --

DR. MARGOLIN: Does tamoxifen normalize the risk of breast cancer?

DR. COSTANTINO: Did it bring it back to essentially no excess risk? I have not specifically done that analysis to compare the women on the tamoxifen arm to what would be expected, but without having done that I can say I am sure it did not take it all the way down because in general the rate on the tamoxifen arm was about 3.4/1000 consistently across all ages, and I know that is not the baseline rate for women who don't have any risks.

DR. MARGOLIN: So, that information would be a necessary part of the counseling in terms of the subjects on this treatment.

DR. WOLMARK: It reduces it 45 percent overall in this analysis, but not back to baseline.

DR. DUTCHER: Dr. Albain?

DR. ALBAIN: It is not preventing ER-negative cancers essentially, among a few others probably.

DR. WOLMARK: I think one can theorize that is the case.

DR. DUTCHER: What is the long-term follow-up plan on this study?

DR. WOLMARK: We will continue to follow these patients as long as we and they continue to agree to be followed.

DR. JUSTICE: I would just like to follow-up on that question. I think there was perhaps some mis-communication about the updated data. I think I agree with what Dr. Wolmark says, that we don't want the updated data presented today. We will certainly ask to see it, and we will certainly ask to see follow-up data on both efficacy and safety, but we haven't actually seen the updated data and we don't want a lot of different numbers floating around. So, I think that is the hesitation Dr. Wolmark had, not that he is not willing to provide us with it.

DR. WOLMARK: I think that was very elegantly stated.

DR. DUTCHER: Are there any other questions for the sponsor? If not, we are going to take a 15-minute break. We will be back here at 10:20.

[Brief recess]

DR. DUTCHER: We are going to begin the FDA presentation.

FDA Presentation

DR. HONIG: Thank you. I will be presenting the FDA analysis of tamoxifen for prevention of breast cancer in women at high risk.

[Slide]

In every FDA presentation you see a slide similar to this one, but I would like to emphasize that for this

review in particular it was truly a collaborative effort to be able to review this much material, on this many patients in such a short time frame.

I wish I had time to detail everyone's contributions but I would particularly like to mention several people. Donna Griebel, another medical reviewer in our Division who reviewed and analyzed the case report forms for stroke; Karen Johnson who, prior to her departure from FDA, reviewed all of the case report forms for invasive and non-invasive breast cancer; and Alison Martin, who analyzed and reviewed all the case report forms on the endometrial cancer patients in this study.

I would also like to spend a minute talking about the administrative time line because it was certainly a challenge for everyone involved in the application to be able to process and submit this much data, and also to review it in a timely fashion.

[Slide]

As you have heard, on April 2 the NCI and FDA were notified that there were significant efficacy results in this trial. On April 23, there was a pre-sNDA meeting designed to facilitate the submission of the application in a timely fashion.

Along those lines, FDA agreed to accept the report that had been prepared for the ERSMAC committee and the BCPT

technical report in lieu of a study report, and also asked that the draft manuscript of P-1 be submitted as soon as possible to us. Of course, the NSABP was busy with a number of other commitments, as well as trying to write that manuscript which was submitted. We waived the requirements for the integrated summaries of safety and efficacy, and it was agreed that the data would be submitted electronically. On April 30, 1998 the SNDA was submitted and, as you can see, we are here 4 months later at ODAC to discuss the results.

[Slide]

When we initially received the electronic database tables, it was clear that there were some limitations. We didn't have primary data which is usually the type of data that we review. For example, the primary endpoints were at first listed yes/no without dates, and we didn't have any of the characteristics of the breast or endometrial cancers that occurred on study, and we didn't have a complete list of risk factors. But we had multiple discussions with NSABP. We ironed out some of the technical problems in transferring the data and, as you can see, we, in fact, worked out a way for these to be submitted.

[Slide]

We got the first additional set of requested elements on July 23, and the last set of data was submitted

to us on August 4 so that we were able to go through the majority of this data in time for ODAC.

[Slide]

As is usual in a clinical trial, we requested specific case report forms on participants in the trial. We requested those for participants who had died during the study, who had developed both invasive and non-invasive breast cancer, endometrial cancer, DVT, PE and stroke. With those listings we received approximately 625 that were submitted and reviewed in detail by the members of our team.

[Slide]

What I would like to do during this presentation is cover the following topics. I don't want to go over details that have already been presented by the applicant, and I would like, instead, to concentrate on areas that perhaps we have a slightly different interpretation of or some additional information.

[Slide]

As you have already heard, NSABP P-1 is a large randomized, double-blind, placebo-controlled trial of tamoxifen for 5 years. Again, you have already heard about the number of participants on study. Most or the data are with reference to this denominator, however, 13,118 had additional follow-up and this is the denominator for certain of the adverse events, such as hot flashes, that we will be

discussing later.

[Slide]

I want to spend just a few minutes on the requirements for trial entry because this has a bearing on how this drug will be used in clinical practice if it is approved.

In the trial a multistep procedure was required for entry. In the recruitment phase women were first seen and given information about the trial and had the opportunity to ask some questions about the study. Then if they chose, they could fill out a risk assessment form that listed the risk factors for breast cancer that would be entered into the Gail model.

This risk assessment form was then forwarded to NSABP, and in a separate second protocol eligibility assessment the participant returned, having read materials at home, was able to ask and have more questions answered, and was able to discuss the actual risk assessment form generated by NSABP. If at that point she wished to continue with study entry and she was eligible on the basis of breast cancer risk factors, she signed an informed consent and then proceeded with the staging studies required for entry.

It is worth noting that all eligibility factors were reviewed by the NSABP as well as by the local institution, and that includes both breast cancer risks and

medical conditions.

[Slide]

In a third, separate visit at the study enrollment phase, the results of the studies were reviewed. If the participant were still willing to go on study and eligible, her informed consent was reaffirmed, and she was then randomized with a number of prospectively specified stratification factors.

So, this was a multistep process. There were at least 2 institutions involved in ensuring that the participant was informed and eligible, the NSABP and the local site. I mention this only because it is unlikely in a busy clinical practice that practitioners are going to be able to devote 3 separate visits to this level of detail. So, it is very important that we all develop patient education materials that will allow women to make an informed choice about whether they wish to take tamoxifen or not.

[Slide]

There were many protocol amendments during the course of the study, however, I would say that there were probably 2 major protocol amendments and you have heard about some of these already. One was that on September 24, 1994 a requirement for baseline and annual endometrial screening for newly randomized participants was added.

Participants who were already on the trial were offered screening but they could decline and continue on study.

Also, in October of 1996 there was a formal decrease in the sample size based on the higher than expected number of events. This had been prospectively specified in the protocol though. It had called for an interim analysis to calculate sample size.

[Slide]

In terms of on study conduct, the protocol said that you could be unblinded and know your treatment assignment if you developed invasive breast cancer, or if your physician felt that there were medical conditions that warranted knowing the treatment arm.

As you might expect, there were some non-protocol specified unblindings. However, whether these occurred because the participants wished to know or the physicians wished to know based on a variety of medical conditions, these were all balanced between the 2 arms. The "other" category is not other medical conditions but, rather, a separate category and you can see overall that there was really no difference. We have examined all of these reasons in detail. They were supplied by NSABP. And, there was no difference.

[Slide]

In terms of non-allowed medications on study, this

is the information that the NSABP had in its database. Hormonal medications, which was an accumulated group of estrogen, progesterones, androgens, as well as a full complement of hormone replacement therapy. They also collected information on oral contraceptive use; the use of open-label tamoxifen and raloxifene. No one on study used raloxifene.

I really wanted to spend the time on the top line. As you can see, if you look at the women on placebo and the women on tamoxifen who are listed as using hormonal therapy at any time during the study, the number looks large. But if you really restrict it and look at the number of women who used it while they were taking the study drug, it is a relatively small number. Less than 1 percent actually used these medications. This is in distinction to the European studies, which we will talk about later, which allowed the use of hormone therapy in various forms.

There were a few limitations of the database that I will review. We did find some instances in the case report forms where women used hormonal therapy that were not in the database. These were relatively few instances. Also, the database was designed to capture the date of the first use of these medications. So, we don't have duration of use and we don't have multiple events of use.

Overall, our impression from looking at the case

report forms is that it was still a relatively small number of women who used these medications for short times. I think a good example would be women who had episodes of dysfunctional uterine bleeding who took short courses of Provera several times, for example.

[Slide]

Compliance, as you have already heard was very high. For women who started their therapy and subsequently discontinued therapy, the most common reasons are listed here -- hot flashes, anxiety, vaginal discharge. The hot flashes and vaginal discharge are consistent with what is already known about tamoxifen and its side effects.

[Slide]

I am going to move on to the endpoints of the study. First, it is important to note that all events in all participants were reported unless the participant withdrew consent or was lost to follow-up. In oncology treatment trials I think we frequently think about events being reported on drug or within 30 days of stopping drug. This is not the case here. Overall, participants who were followed had all of their events recorded in the database.

In our review of case report forms we could find potentially 1 breast cancer that was perhaps not captured in the database. We are still discussing this with NSABP. The NSABP also set the rules up prospectively that the worst

event per participant would be recorded. So, if you had angina and then subsequently had an MI, the MI would be recorded but not each individual related event. Similarly, if someone had a TIA and a CVA, it would be the stroke that would be reported in the database.

This was true for nearly everything except fractures. That was in distinction where all of the fractures per participant were reported, not just the first fracture.

[Slide]

So, with regard to invasive breast cancer, you have already heard that there were 154 cases on placebo and 85 on tamoxifen. We looked at the number of cases that were diagnosed on each arm after stopping the study drug, and you can see that there are relatively comparable numbers on each arm. Within the follow-up available to us on the study, there was no evidence of a rebound increase in the number of cases after the study drug, tamoxifen, was stopped.

We also saw reductions in the number of breast cancer cases in all the prospectively defined subgroups, specified by the sponsor. In fact, we found reductions in every retrospectively defined subgroup that we could think of at FDA.

The reductions were seen in participants who had a family history, regardless of the number of affected first

degree relatives. We were able to carry this out for none and then 1 through 4, I believe. We also saw reductions in participants who did not have a family history. At first we were concerned that perhaps all the risk and all the benefit was being seen in a subgroup of women who were at risk because of a family history, and that was not true on our review of the database.

[Slide]

The only subset in which this beneficial effect of tamoxifen was not observed was in women of color. There were 486 non-white women entered on the study despite the really aggressive attempts on the part of the NSABP to recruit more women of color, and there were 9 cases, 3 on placebo and 6 on tamoxifen.

We looked at these women in detail. The risk profile of these women didn't difference from that seen in the general population of women entered on the trial. The characteristics of the 2 groups were not any different either. They were not more aggressive or less aggressive.

At this point, I suppose you could say that it is unknown whether there is a differential effect in non-white women but we would favor the interpretation that overall women of color made up a small subset of the population and had relatively few events, and that we just don't have the statistical power to make any comments about that.

[Slide]

In terms of the case report form review of the invasive cases, we agree that all the cases that were reported were, in fact, invasive breast cancer. We assessed 2 additional cases of invasive cancer on the placebo arm. These had previously been categorized as non-invasive breast cancer, and 1 on the tamoxifen arm as invasive cancer. This was a woman who, after several reviews by NSABP, was ultimately assigned to the category of cancer of unknown primary and after our review we felt it was likely that she had breast cancer.

We also reviewed the assessed tumor size based on the original pathology reports. We disagreed with the assessed tumor size for 3 cases on placebo and 1 on tamoxifen. It resulted in minimal stage shifts for these participants and, as I mentioned before, we may have found an additional case that we are still discussing with NSABP.

Overall though, even with these shifts in cases, it doesn't change the primary conclusion of the sponsor, which is that tamoxifen did result in a significantly decreased number of breast cancer cases on the tamoxifen arm compared to placebo.

[Slide]

This shows you the tumor size and nodal status distributions. You have already seen this so I don't want

to spend a lot of time on it except, again, to reiterate Dr. Costantino's point which was that tamoxifen was most effective in tumors that were less than 2 cm in size and in cancers that were either node negative or had 1-3 positive nodes.

[Slide]

This shows the stage groupings for all of the cancers that were identified on study. As is consistent in the general population, most of the women diagnosed with breast cancer had node-negative disease. Some women had node positive. There were 10 cases of inflammatory breast cancer, and 2 women who had either probably or confirmed metastatic disease at diagnosis but, again, you can see that they were not significantly different between the treatment arms.

[Slide]

Again, you have already seen this slide showing that tamoxifen appears to have the greatest effect in reducing the number of estrogen-receptor positive tumors.

[Slide]

So, overall we would conclude from our review that there was a significant reduction in the number of breast cancer cases with tamoxifen regardless of the subgroup. At the beginning of this trial and throughout the conduct of the study there had always been concern about use of

tamoxifen in younger women. We looked at them specifically. We did not see an excess number of cases in young women, nor did we see more aggressive appearance to the tumors in young women.

We would say that at this point there is an unknown effect in women of color, simply based on the small number of participants in this trial; again, that it appears to have an effect on ER-positive but not ER-negative breast cancers; and we would like to point out that we did not see an excess number of ER-negative cases.

[Slide]

As you have already heard, it is most effective against cancers that were earlier in the course of their development. You saw this information from NSABP, not in my presentation, but we also independently calculated the time to event. We did it by 6-month intervals, and there was a reduction in the number of cases diagnosed in the first 6 months and then within every 6-month block afterwards, including at the 60-month time point.

[Slide]

In terms of the non-invasive breast cancer endpoint, NSABP reported 59 cases on placebo and 31 on tamoxifen. When we reviewed the case report forms for these participants, 28 of these non-invasive cancers were actually diagnoses of LCIS, 21 on the placebo arm and 7 on tamoxifen.

An additional 2 cases consisted of atypical hyperplasia without a component of invasive or non-invasive cancer, 1 on each arm.

[Slide]

When we looked at the women who had been diagnosed with LCIS during the course of the study, 12/28 women on placebo and 6/7 on tamoxifen had a prior diagnosis of LCIS as part of their eligibility criteria to enter the study. The seventh participant on the tamoxifen arm had a diagnosis of atypical lobular hyperplasia at entry. When she subsequently had her biopsy and had those slides read in conjunction with her prior biopsy it was felt that both specimens met the criteria for LCIS.

[Slide]

We would disagree with the inclusion of LCIS as a non-invasive breast cancer event for the following reasons: LCIS is commonly considered to be a marker lesion rather than a precursor. It has a high incidence of multifocality and multicentricity, and sequential diagnoses of LCIS do not change the level of risk that is conveyed by the first diagnosis. There are a number of options for LCIS, including now, we believe, tamoxifen on the basis of the results of this study. Finally, our strongest reason is that we would not use entry criteria as a subsequent efficacy endpoint.

[Slide]

For those reasons, we would instead re-categorize this grouping as DCIS alone. When we do that, there are 35 cases on placebo and 23 on tamoxifen. Remember that there were 2 cases on placebo that we had reassigned into the invasive category. Overall, this showed a 34 percent reduction in risk. Calculation of a p value on this difference was 0.12.

[Slide]

In terms of fractures, it was thought that tamoxifen would prevent the incidence of fractures. In the protocol the hip and Colles' fractures were the prospectively designated sites.

The protocol discussed the inclusion of spine fractures but excluded them because of the following reasons: There is no agreed-upon definition of a vertebral fracture. Many vertebral fractures are unknown to the patient, and the methods for determining vertebral fractures are costly and are not reproducible. We agree with the protocol-defined reasons for excluding spine fractures and we would not consider them to be a reproducible efficacy endpoint.

[Slide]

We made this point before, that all fractures were reported, not simply the first event, and we didn't have any

information on concomitant use of medications that would affect osteoporosis risk, with the exception of calcium.

[Slide]

Overall, there does appear to be a reduction in the number of hip fractures with tamoxifen. There were 20 on placebo and 9 on tamoxifen. Reductions were seen in women under age 50 and over age 50, although we would point out that there were very few fractures, 4 on placebo and none on tamoxifen, that occurred in younger women.

The final FDA assessment of the Colles' fractures is pending review. NSABP is currently reviewing the radial fractures that occurred on study and is going to provide us with the final list that we will review.

We would simply add this particular caveat, that the fracture data in this study were derived from this sole study as a secondary endpoint and that, while it is very important to include this in the risk-benefit assessment of using tamoxifen for prevention of breast cancer, we would not consider this to be an independent indication for tamoxifen therapy solely for osteoporosis prevention.

[Slide]

In terms of deaths on study, as you have already heard, they were relatively well balanced between the arms. We did not see any difference either in the number of breast cancer related deaths on each arm. When we reviewed case

report forms, there was 1 case that had been coded as death from non-malignant respiratory disease and we found that to represent death from a pulmonary embolism in a tamoxifen participant. NSABP agreed with that assessment and, in fact, their database has already been updated to reflect this finding.

[Slide]

Turning now to endometrial cancer, this table summarizes the women who developed endometrial cancer. This lists the number of cases by age at randomization. As you have already heard, all of these cases except 1 represented FIGO stage I disease. This slide breaks it by FIGO stage A, B and C, as you can see. In the next slide I would like to make two additional points about the last two rows on this slide.

[Slide]

First, there were 6 women, 1 on placebo and 5 on tamoxifen, who by case report form review had no signs or symptoms that suggested that they had endometrial cancer at the time of their diagnosis. Of these asymptomatic women, 4/6 were diagnosed during a routine endometrial sampling. The sampling was performed on schedule and it turned out to be positive for cancer. The other 2 women were found to have complex atypical hyperplasia and at their institution that was treated by hysterectomy. Then in the pathology

specimen of the uterus cancer was found incidentally.

In the second to last row of the previous table, we would like to point out that 6 women on tamoxifen and 1 on placebo received postoperative irradiation in addition to their surgical procedure for FIGO stage IB disease. I mention this only because it does have some additional implications for complications of therapy, both short term and long term, and should be considered by women who are thinking about using tamoxifen for prevention.

[Slide]

We have seen some information already suggesting that women under the age of 50 had no excess risk of endometrial cancer on tamoxifen compared to placebo. The average annual hazard rate for these women was calculated at 1.10. That rate is somewhat higher than that reported by SEER data. I think that you can make the argument that women at risk for breast cancer also have risk factors that make them at increased risk for endometrial cancer, and SEER data may not be the best comparative rate. A better group, we thought, might be the placebo group in B-14. For women under age 50 that annual hazard rate was calculated to be 0.2, still lower than what was seen in this study.

[Slide]

But we also noted that if you changed the age grouping you could affect the case distribution. Here is

endometrial cancer by age at randomization, as you have already heard, reported from NSABP. If you changed this category by 1 and instead of saying less than or equal to 49 you say less than or equal to 50, you do see a difference. There is a slight excess number of cases on the tamoxifen arm compared to placebo. If you look at how old the participants were when they were diagnosed with the endometrial cancer, you can see again that the numbers of cases shift. There are a few extra on tamoxifen but relatively few cases overall. If you try to get at the actual biologic menopausal status at the time of the event, which was derived from case report form review, the numbers change again with a few extra cases on tamoxifen.

[Slide]

There are several ways that you can interpret this data. One would be to say that there is no added risk from tamoxifen with respect to endometrial cancer risk in young women. I suppose you could also say that an increased risk of tamoxifen was masked in this study by an unusually high rate of endometrial cancer in the placebo group.

What we really think is the most logical explanation is this third one, that overall there were relatively few cases of endometrial cancer and that they don't really permit a detailed subset analysis that would give us a good idea of the relative risks in these groups.

[Slide]

In terms of ischemic heart disease, when the study was started it was hoped that tamoxifen would reduce the number of ischemic heart events but, as you have already heard, there was overall no difference between the treatment arms. This population was generally healthy. Many of the women really had very few or insignificant risk factors for cardiovascular disease.

In the protocol it was originally written that approximately 10,000 postmenopausal women were required to demonstrate a cardiovascular benefit and a little over 8000 were enrolled. We discussed this point specifically with Dr. Costantino who pointed out that certainly you can't completely exclude a benefit of tamoxifen. On the other hand, this trial did not demonstrate any effect of tamoxifen, and you might have leaned a little bit more on this interpretation if you had seen even a trend towards an improvement on tamoxifen. So, we would leave that where it is. No benefit was seen and I think that is the only conclusion that we can draw about that point.

[Slide]

In terms of stroke, again 1 event per participant was counted and the worst event, TIA or stroke, was counted in the database. On our case report form review though there was 1 participant on the placebo arm and 2 on

tamoxifen who each had 2 separate stroke events.

Overall, there were 24 strokes reported on placebo, 34 on tamoxifen, and relatively few of these women were under age 50 at the time of the event. The majority were postmenopausal. Three were fatal on placebo, 4 were fatal on tamoxifen. We wondered whether the excess risk on the tamoxifen arm could be related to the known increased thrombogenic properties of the drug.

[Slide]

As you know, there were other thromboembolic events noted in the course of the study. With deep vein thrombosis there were 19 cases on placebo and 30 on tamoxifen. One participant who was randomized to placebo had a DVT while receiving open-label tamoxifen. She had subsequently developed breast cancer and was being treated with tamoxifen. She is appropriately listed on the placebo arm in the intent-to-treat analysis but I would just point out that her event occurred on the drug of interest.

[Slide]

The sponsor, again, presented data for the diagnosis of deep vein thrombosis by age at randomization. If, instead, you look at the deep vein thrombosis incidence by the actual age of event, you can see that these risk ratios are really approximately the same, about 1.5 or so for the whole population or for either subset of women by

age.

[Slide]

Our conclusion looking at this is that the relative risk for DVT is likely to be the same in younger and older women, although the absolute number of events is greater in older women.

[Slide]

One thing that I would like to point out, again from our review of the case report forms, is that unfortunately there were delays in the diagnosis of DVT of up to 4 weeks. This was not due to any laxity in terms of monitoring but many of the participants had these vents between the scheduled visits. They then went to their local provider or emergency room and did not always tell the treating physician that they were part of the tamoxifen study. So they were managed potentially more conservatively than they might have been. I think this also has implications for patient education if the drug is approved.

[Slide]

In terms of PE, as we have already mentioned, there were originally 6 reported on placebo and 17 on tamoxifen, 2 fatal. The third fatal case was added here for a total of 18 and 3. If one looks at the time of occurrence of the event, all except 1 which was on the placebo arm, occurred in women who were over the age of 50.

[Slide]

I wanted to make some comments about thromboembolic events as a whole. The reported numbers that we have talked about don't count multiple events in the same participant. On the placebo arm there were 4 women who had 2 or more deep vein thromboses, and there were 3 who presented with simultaneous PE and DVT, not an unusual occurrence in general medical practice. On the tamoxifen arm 1 woman had a recurrent DVT, 3 women presented with simultaneous deep vein thrombosis and pulmonary embolus, and there was 1 woman who presented with a DVT and PE that was separated by a 3-month period of adequate anticoagulation for these events.

[Slide]

There were also complications of these events that occurred. The ones that we saw in the case report forms were all on the tamoxifen arm. Two women who had DVTs had subsequent chronic venous insufficiency. One woman developed a GI bleed in the course of her anticoagulation for her event. She required 5 units of packed red cells and fresh frozen plasma. So, it was a significant bleed. One woman on tamoxifen presented with a very large PE that had blocked the perfusion to her right lung. She was treated with intra-arterial urokinase, was able to have blood flow restored to her lung and was then placed on conventional

anticoagulation. She then developed a large retroperitoneal bleed and required a filter placement for definitive treatment.

[Slide]

There were also some other thrombotic events that occurred. Two premenopausal healthy women randomized to tamoxifen experienced retinal vein occlusions. One of these occurred while the participant was on study drug and the other occurred when she had discontinued study drug for more than a year. One of these women had some permanent impairment in her vision.

When we looked at the women overall with thromboembolic events, smoking and obesity were contributing factors but they didn't account for all of the risk. This echoes one of the questions from the committee, investigators in the past have tried to look at the underlying etiology of the coagulation defect that is associated with tamoxifen. Nothing definite has been found, but it would be helpful, we think, to evaluate this again in these participants. Certainly, if a subgroup of women could be identified who are at risk that would significantly help many women in their assessment of the risk-benefit ratio.

[Slide]

Our conclusions looking at thromboembolic events would be that all women on tamoxifen, regardless of their

age, are at increased risk for thromboembolism. I think it is important to point out to women that if they have one event they are at risk for a second related event, and that they may also be at risk for complications of therapy, and that factors that may predispose to thromboembolic events should be examined.

[Slide]

I don't want to repeat the information on cataracts. You have already heard that presented by the sponsor.

[Slide]

In terms of other ophthalmologic events on study, I have already discussed the 2 retinal vein occlusions. NSABP sent us their data on incidence of macular degeneration, which was comparable between the 2 arms. There was no other information that was systematically collected on the effect of tamoxifen on other eye events. Again, as came out during the question and answer period earlier, the participants were not required to have regular eye exams.

The decision for this was made on the basis of the B-14 data which was derived from approximately 300 women involved in B-14 who volunteered for this sub-study. However, we would point out that overall the incidence of these eye events is rare, and it is possible that B-14 has

not fully captured all of these eye events.

[Slide]

We have spent a lot of time talking about very serious and potentially life-threatening effects of tamoxifen. I think it is important to spend a few minutes talking about the day-to-day adverse events such as hot flashes and vaginal discharge. Overall, as predicted by the known side effects of tamoxifen, women on tamoxifen had a higher percentage of hot flashes and vaginal discharge, and were also more likely to have level 3 or level 4 events. As I said, these were the primary reasons that women stopped therapy, and the most troublesome effects on a day-to-day basis. So, I think it is worth looking at those numbers.

[Slide]

In terms of other events, there was no difference in the incidence of vaginal bleeding or vaginal dryness between the 2 arms, and overall in terms of the laboratory abnormalities, relatively few grade 3 and 4 abnormalities were seen and, as you can see here, there was really no significant difference overall between the 2 arms. There had been reports of tamoxifen's effect on lipid profiles. Lipids were collected only at baseline, not throughout the course of the study, so we can't comment on that.

[Slide]

Quality of life was measured during the study. A

medical outcome scale was used for general physical functioning. There was a sexual activity item and a depression scale.

I am going to talk more about the depression scale in a minute so I would like to spend just a little time describing what that was. This was a 20-item inventory of statements, and participants were asked to rate the number of occurrences that they had during the past week. These were then translated into a numeric score and were categorized in groups. A score of less than or equal to 15 was a normal score. This was collected at each separate visit.

We did not ask NSABP to submit the primary data for this. Instead, we asked them to submit their analyses, and there was no difference at all between the 2 treatment arms for any of these 3 categories. The curves were virtually superimposable. This was reviewed by Tony Kontsoukos, our statistician, and he could not find any problem with the analyses as presented.

[Slide]

We did review the depression data in more detail though because of past reports that tamoxifen might be associated with an effect on depression. In addition to the depression scores that I have already discussed, depression was also assessed with a neuro-mood common toxicity criteria

reporting. When the participants came, in addition to the 20-item list that was translated into the depression score, they also filled out some additional paperwork that reflected their mood. This data was also forwarded to the NSABP. The study coordinators were able to translate this into a CTC grade as non, mild, moderate, severe, suicidal or death.

What we did, we looked at the depression scores and then we looked at the participant assessment of mood by the CTC grades, and then we also looked at events that we derived from our case report form review.

[Slide]

So, in this very informal analysis based simply on selected cases that we had, this is what we found. Out of the 69 women who were reported as having severe depression and, again, equally distributed between the 2 arms, 18 of those had normal depression scores. There were 46 women who were listed as being suicidal on study, again comparable, and 4 of them had normal scores. There were 3 women who did commit suicide on study, 1 on placebo and 2 on tamoxifen. Two of them had grade 4 scores but 1 had a grade 1 score.

[Slide]

As I said, from this very informal analysis we would just like to make the following points, and some of them are obvious: The scores are likely to be accurate only

if they can be obtained at the time of maximum distress. With women being followed every 6 months, it is likely that you are going to miss that time point and then get reporting of events in the past.

The other thing that we noticed is that when we looked at the case report forms, women reported the prescription of antidepressant medications at the time that they had scores of grade 0-2. There are two possible ways to interpret this. One is that our usual system of reporting a grade 3-4 event may underestimate a clinically important change in mood that warrants the prescription of these medications, or that the use of these medications confounds the scoring system, that these women start antidepressant therapy, feel much better and when they come in their scores look fine.

So, overall we would say that while P-1 doesn't show any effect of tamoxifen on depression, we would simply point out that perhaps this was not the best way to capture this information, and that it may still be unknown.

[Slide]

In the course of the review also 2 European studies that were negative trials for tamoxifen for prevention of breast cancer were reported. We would like to comment briefly on these. We did not have primary data for review. This is based on our reading of The Lancet

analyses.

The Italian breast cancer prevention study really did not enter women who were at high risk for breast cancer. It was, instead, designed to exclude women who were at high risk for toxicity from tamoxifen. So, they were eligible only if they had a hysterectomy, and there was another long list of exclusion criteria, and they made no effort to actually enrich for women who might be at increased risk for breast cancer itself. There was a high drop-out rate in the trial that was not considered in the sample size calculation, as it was in the NSABP study, and, in fact, their monitoring committee closed the study early because of this reason. Overall, the authors reported that there was a low statistical power to detect any difference between the arms.

[Slide]

The other trial was the Royal Marsden study. As you have already heard, Dr. Powles is here with us today. He will actually come to the podium after I have finished to make a few comments, and will be available for questions from the committee about his study.

Based on my review of the published article, and not on his data -- he is the only one with the data, I would make these points. The Royal Marsden study was designed initially to enter a high risk population of women. It was

hoped that it would be selected out to include women who were members of a hereditary breast and ovarian cancer family. However, from my reading, I would think that the assumption of the baseline for breast cancer risk in this trial was inaccurate.

There has been a lot of data published recently from a number of risk assessment centers looking at the incidence of mutations in women based on their family history. These reviews have suggested that if you use only a breast cancer family history that you are likely to see mutation in only about 20 percent of those patients. You can increase the likelihood of seeing a mutation if you also include family history of ovarian cancer, or if you extent out your family history and, instead of looking simply at first degree relatives as was done in the Royal Marsden study, you take an extended family history. So, overall, I think although it was intended to enroll women at higher risk, those women were actually at lower risk than anticipated.

The rate of non-compliance was not considered in the sample size calculations. I think these are the primary reasons for the negative outcome. These are additional possibilities -- younger women are likely to have slightly higher rate of ER-negative cancers compared to older women, and we have already seen that tamoxifen is not effective, we

don't think, against ER-negative cancer prevention. Hormone replacement therapy was permitted in the study and about 41 percent of the women in the trial used hormone therapy at some point in the study and that may be a confounding factor. Again, Dr. Powles' input on these issues would be appreciated.

[Slide]

So what can we say overall about the risks and benefits of tamoxifen based on the P-1 study? Well, I believe that form this trial it has been clearly demonstrated in the subgroups, with the follow-up we have, that there were fewer cases of invasive breast cancer with tamoxifen. It reduced the number of cases of ductal carcinoma in situ, not significantly but there were certainly fewer cases. Again, it may prevent hip and Colles' fractures.

[Slide]

We think that there was an unknown effect, based on these trial results, in women of color because of the few number of women entered. There was no information here about women with BRCA 1 and 2 mutations. As you have heard, the NSABP was planning to assay the serum samples and to look for mutations, and those data are going to be awaited with interest by everyone, by the medical community and FDA.

I have included women with known DCIS in this

column. Again, there are early reports that show a benefit with tamoxifen in women with DCIS but, as Dr. Wolmark said, that is pending final review of the NSABP studies that were specifically designed to address this question.

We think simply based on the follow-up data available here that we probably still have an unknown effect of tamoxifen on depression, and a non-cataract ophthalmic toxicity.

[Slide]

There was no effect that was observed on ischemic heart disease, on death from all causes. We also agree that there was no difference in the incidence of other cancers. Again, from our analysis we did not see that LCIS was prevented.

[Slide]

Finally, I think we have spent a lot of time talking about the risks. Tamoxifen increased the risk of endometrial cancer, of DVT and PE, stroke, cataract formation and the need for cataract surgery, and hot flashes and vaginal discharge.

[Slide]

It is important that we all keep in mind what the limitations of tamoxifen are. It does not eliminate breast cancer risk, as we have talked about previously. It also does not guarantee that if a breast cancer occurs it will be

diagnosed at an early stage. It does not affect ER negative or larger tumors.

[Slide]

There are additional complications to tamoxifen therapy, other than the listed risks. Again, remember that some of these early stage endometrial cancers required irradiation therapy in addition to surgery, with potential additional complications; that thromboembolic disease may involve the brain, lung, leg and eye. It can increase the risk of a second event, and there may be complications from treating these events.

[Slide]

We think that all of these findings have labeling implications, and we have asked some of these in specific questions to the committee. Women on tamoxifen, regardless of age, should have regular breast exams, mammograms and gynecologic evaluations. We would agree that endometrial sampling detected endometrial cancer rarely. There is a specific question to the committee on this point. We also believe that women taking tamoxifen should seek prompt medical attention for any signs or symptoms of cancers or thromboembolic events.

There is a question to the committee about whether women on tamoxifen should undergo yearly eye exams based on the cataract data and some of the other issues that we

discussed.

Most importantly, we believe that women who choose to take tamoxifen should inform all care providers, no matter what they are being evaluated for, that they take the drug. We would also say that women with a history of DVT, PE or coagulopathy should not take tamoxifen. This was an exclusion criterion for the P-1 study. And, labeling should provide information about individual risks and benefits. One point that also may seem obvious but I think is worth mentioning is that a premenopausal woman who starts therapy may become postmenopausal in the course of her treatment, and that may result in a change in her risk-benefit assessment and that should be kept in mind.

[Slide]

How do we put this in perspective with the negative European trials? Although the European trials reported negative results, we believe that there were design differences that resulted in lower risk populations being entered into those studies. Overall, the size, the statistical power and the internal consistency of P-1, we think, make its results robust and believable, and we also believe that the results are consistent with all of the other published reports of the ability of tamoxifen in the realm of prevention, most notably preventing contralateral breast cancer. So, we would feel that the weight of the

evidence favors what was observed in P-1.

[Slide]

In conclusion, tamoxifen for breast cancer was effective in reducing the incidence. The reduction in breast cancer incidence for most women appear to outweigh the incidence of serious adverse events but, as we have already discussed, it is extremely important to have an individual risk-benefit assessment and that, hopefully, that can be conveyed in labeling as well as in additional educational tools to allow women to make a truly informed decision about whether to use this drug if it is approved.

Thank you. What I would like to do now is to introduce Dr. Powles who has a few comments, and then both of us will be available for questions.

Comments on the Royal Marsden Study

DR. POWLES: I am grateful -- at least I am not sure I am grateful to have the opportunity to discuss briefly the conflict in the results that occurred between our own program and the NSABP program.

I have to say right from the word go that I thought 12 years ago or 13 years ago when we started the tamoxifen prevention that if I was going to be here, I would be here presenting the results of a positive trial on tamoxifen and I am as surprised as anybody that we actually got a negative result at this stage.

Secondly, I would like to make quite clear that I am absolutely sure that the effect of tamoxifen on the early incidence of breast cancer in healthy women which has been shown by the NSABP is real. The problem is what is the conflict between the two results.

Susan has mentioned the various problems that may arise. The first is that there is clearly a difference in the study population. Our women are younger. Our women are more likely to have a stronger family history. They are more likely to be premenopausal. And, what we have done, in spite of what Susan said, is a complete pedigree analysis of all of the women in our program, all 2500 women, in order to evaluate not just the incidence of primary breast cancer but the age at onset of the primary breast cancer, which is important, second degree relatives with breast cancer, and the presence of bilateral breast cancer and the presence of other cancers.

So, we have been able to estimate using pedigree analysis, and using the Klaus model the likelihood of high risk genes within our own program. Our estimate at this time is that about 36 percent of the women in the Marsden program are likely to have inherited a high risk breast cancer predisposing gene. What is more important is that 60 percent of the women who developed breast cancer at this time are likely to have inherited a high risk breast cancer

predisposing gene. This is going to be substantially more than the percentages in the NSABP program, as best as we can estimate it from the figures of the data that we already have.

So, I think a major difference between our program and the NSABP program relates to the study population, and I think it could well relate to the likelihood of inheriting a high risk gene.

The second point that Susan mentioned was the question of compliance. In fact, our compliance has been higher than we estimated when we originally did our power calculations. The estimate for 5 years was going to be for 70 percent and, in fact, looking at the time of use of tamoxifen within our program, at 3 years we got an 83 percent compliance for tamoxifen and at 5 years we got a 79 percent. I think this is about as high as you are likely to get, and this represents a substantial intervention of tamoxifen in half of 2500 healthy women, 1250 women, and, to my mind, that amount of exposure to tamoxifen with what is going to be a 50 percent effect -- we would anticipate on that compliance that we would be able to see that effect.

The third point that was raised was about the use of hormone replacement therapy. We allowed the use of hormone replacement therapy within our own program because we felt that denying the use of hormone replacement therapy,

as you can see from the NSABP results where women would be withdrawn from the program if they took hormone replacement therapy, in itself would produce a bias if it was not matched. And, 41 percent of our women at some stage have taken hormone replacement therapy. But we are now 12 years into the program, and if we actually look at the amount of hormone replacement therapy that was used in conjunction with tamoxifen or placebo, there was only a 12.6 percent concomitant medication. So, it is really a very small part of the program itself.

The second thing is that we have been unable to identify any interaction between the use of hormone replacement therapy and tamoxifen on bone, on clotting factors and on cholesterol, and we have published this, and it, therefore, seems unlikely that this would occur in the effect on tumor cells.

The third thing is that we can see no difference in the incidence of breast cancer for women on or off hormone replacement therapy who have ever had it or not had it. In fact, if anything, there is a marginal effect for women who have had tamoxifen versus those who have not. So, it is unlikely that we would have confounded our trial in order to make it negative.

Furthermore, the Italian trial has shown the only effect that they could see was the use of tamoxifen in women

on hormone replacement therapy. So, I think it is very unlikely that hormone replacement therapy could have confounded our trial in a way that would have made the trial negative.

The fourth point is whether the trial ever had the power to be able to show this effect. We clearly are a small trial, although we are talking about 2500 healthy women from a single center, which must be one of the biggest single center trials that has ever been mounted on anything. We did do the power calculations in 1993 when we realized that the national program would not be able to start because it had not been approved by the Medical Research Council in England. We did the power calculations then to estimate the numbers of women we would need, the compliance that we would expect on an intent-to-treat basis that would give us a 90 percent power to detect a 50 percent reduction.

In fact, those power calculations were exactly right for the placebo. We were within 1 cancer for the incidence of breast cancer, and it was exactly on point at the beginning of 1998 when we did our estimates. There is only about a 10 percent chance that this trial is negative for statistical reasons. In fact, what is more impressive is the fact that we can't see any difference at all in the incidence of breast cancer for tamoxifen or placebo. There is not even a trend there.

With the Italian trial, that is also completely negative for a different population of women, and the chances of both trials being negative is less than 2 percent. I think probably the reason we are seeing these differences -- they can account for various things that may do this, but one of the main factors in my opinion probably is the fact that we are looking at different populations of women.

As far as the power calculations go, the problem that we have is the problem of multiple outcomes, and this is shown with the power problem in relation to the NSABP trial. In spite of what was said earlier, the primary objective of the NSABP trial in the original protocol was to test tamoxifen's effectiveness in preventing the occurrence of breast cancer and reducing mortality in breast cancer. So, it was originally designed and the power calculations were done for reduction and mortality. It also wanted to look at heart mortality and bone fractures, and benefit-risk ratio as secondary aims.

The trial was stopped early when there were 239 breast cancers. At that time there were only 9 breast cancer deaths and 10 heart deaths. So, there was never any hope that we were going to be able to look at one of the main features of the primary aim, which was mortality from breast cancer, because the trial was so powered to look at

incidence of breast cancer that it wasn't going to allow the secondary outcomes to be seen.

I am obviously concerned that if everything we do in the future is going to be based on early incidence data, will it actually tell us much more than that about the prevention of breast cancer and, in particular, what the clinical benefits may be? I am concerned because when we look at these results at the present time there are only 69 breast cancers at 3.5 years median follow-up, and these are mostly estrogen-receptor positive cancers, less than 2 cm and no nodes or 1-3 nodes. We would anticipate that there would be a cure rate for these 69 cancers of about 80-90 percent. This is particularly so because they are likely to be tamoxifen sensitive because they have been prevented from occurrence by tamoxifen. To achieve this reduction in 69 cancers, 6600 healthy women have received tamoxifen for an average of 4 years, and that, even with compliance, is about 20,000 years of tamoxifen or 300 years for each what I would call good cancer that has been delayed or prevented.

The question that we must ask in any prevention trial is would it have been easier to have treated the 69 cancers versus the 6600 healthy women because prevention trials are a completely different dimension than treatment trials. We are talking about treating huge numbers of healthy women in order to prevent small numbers of cancers.

That is the issue that I am obviously concerned about. I am not sure that at this stage we know enough to be able to say that prevention in many is better than treatment in a few.

In Europe, the Clinical Trials Committee is not satisfied that "prevention" has been proven to be beneficial, clinically beneficial. We would wish to continue our trials to evaluate not just the incidence but all potential long-term benefits and risks that we can, the most important of which is obviously mortality from breast cancer. Furthermore, because of the concerns we have about subgroups and high risk groups, the high risk genes and low risk genes categories, we would like to try to identify the subgroups of those who may or may not gain a benefit, especially the high risk young women who are likely to pay the long-term consequences if there are any problems with tamoxifen.

Approval of tamoxifen for prevention at this time implies that we know its use in healthy women is a clinical benefit and we know who gains that benefit. And, I don't think we are there yet. In spite of this early incidence data which I think is very encouraging, I am not satisfied that we have proven at this time that long-term use of tamoxifen in healthy women is likely to be beneficial over the risks. We are talking about large numbers of healthy women and there are risks.

Thank you.

Questions from the Committee

DR. DUTCHER: Questions for the FDA and Dr. Powles? Dr. Albain?

DR. ALBAIN: Yes, Dr. Powles, could you comment on your choice of duration of treatment in your trial of 8 years of tamoxifen, in particular given the concern that durations beyond 5 years may, in fact, be adverse in terms of tamoxifen-stimulated growth? How many women actually got 8 years of tamoxifen?

DR. POWLES: I think we must distinguish between the treatment trials and the prevention trials. When we are doing treatment trials we are looking at cancer that is there that may go away and may come back. With prevention we are looking at anti-promotion of estrogen by using an anti-estrogen, and the events of the initiation of the tumor can occur at any time.

We had to make a decision in 1991, because we started our trial in 1996, when we reached 5 years about whether we gave more than 5 years or not. At that time it was agreed that we would continue to 8 years. This was discussed with various bodies in the United Kingdom, and that was based on the fact that we were looking for anti-promotion of early cancers and not treatment.

I don't think the results of the adjuvant trials

bear any relationship to anti-promotion. They obviously do if you are only treating occult cancers.

DR. ALBAIN: What percentage of your population took the full 8 years?

DR. ASHLEY: I am Sue Ashley. I am a statistician at the Royal Marsden. Sorry, I don't have the exact figures but I think it was around 160 on both tamoxifen and placebo who have completed 8 years of treatment at the moment.

DR. ALBAIN: And these are women on active treatment? In other words, they hadn't dropped out before that 8-year point. Is there a percent that have already dropped out?

DR. ASHLEY: There is a percent who have already dropped out. These are people who have continued for 8 years.

DR. ALBAIN: What percentage have dropped out, and at what time points of treatment, do you know?

DR. ASHLEY: There was about a 17 percent drop-out in the first year of treatment. After that there was very little drop-out on the tamoxifen arm.

DR. ALBAIN: Thank you. I also have a question for Dr. Honig. Could you just clarify from your review of the data patient events, breast cancer events -- my understanding is they were reported as an event whether they were on study drug or off study.

DR. HONIG: That is correct.

DR. ALBAIN: Okay.

DR. HONIG: That was a mis-communication in my draft, the draft that went to ODAC while we were still communicating with the sponsor. So, that was an error and, hopefully, was corrected in my slides.

DR. ALBAIN: Okay. Then, the patients who had the DCIS event, were those patients continued on tamoxifen?

DR. HONIG: That also was clarified with NSABP. By protocol, they were supposed to continue on blinded therapy and that did not always occur. I am trying to remember offhand the number of women who were unblinded. Jo, you may be able to help me out. I think it was maybe 10 or 12 per arm, a relatively small number compared to the total number of DSCIS events.

DR. ALBAIN: So maybe I should ask the NSABP. Were patients with DCIS, for the most part, continued on their study drug?

DR. HONIG: Please clarify this, Jo, but it seemed like there was a group who stopped drug altogether and then there were some who were unblinded and who may have continued open-label?

DR. COSTANTINO: As you indicated, there were many instances where, regardless of what the protocol stated, the physicians felt they needed to know this information, and if

they insisted upon being unblinded, they were. The exact proportion of women who actually stayed on therapy of the DCIS cases -- to be honest with you, I don't know the exact number but there were women who did and there were women who were unblinded and did not. So.

DR. ALBAIN: Would you comment on the rationale of continuing the drug in the face of the event?

DR. WICKERHAM: I can comment on why the desire was to continue the blinded drug per protocol. At the time the trial began, tamoxifen was not of known benefit for the treatment of DCIS. We thought it appropriate to capture the event to try to maintain the therapy per protocol. As Dr. Costantino said, the majority appeared to do that but there were cases where either the patient or the physician demanded that the patient be unblinded.

DR. DUTCHER: Dr. Sledge?

DR. SLEDGE: Dr. Powles, you are basically telling us that it is too early to know. Could you give us your wisdom in terms of, first, how long you think this trial does need to be followed before we have data that would convince you and, secondly, what specific endpoints would convince you?

DR. POWLES: Yes, I found a reference to a paper that I wrote in 1988, I think it was, where we were looking at how long it took for breast cancers to develop. We know,

for example, from the nuclear explosions in Japan that the increased incidence of breast cancer doesn't start until 14 years after irradiation and it needs endocrine promotion with estrogen.

So, in terms of interfering with estrogen promotion, we made estimations then, which we published, that we felt that it would take 10-15 years to really know what you were doing in terms of preventing breast cancer by using tamoxifen.

Now, the thing that was encouraging is that we were obviously going to have a positive effect on the early incidence of breast cancer by treating subclinical disease, and because that went the right way we estimated that what would happen is that you would have 2 curves that started to go apart and they would continue to go apart, to begin with because you are treating breast cancers, some of which may or may not come back, and later on because you are preventing breast cancers.

What is more important is that most breast cancers are likely to be estrogen-receptor positive very early on in their process. They are arising from a breast cell that is endocrine dependent, and they will use their receptor positivity with time. So, by the time they present clinically only 18 percent of them are likely to be estrogen-receptor positive and only 50 percent of them have

a functional estrogen receptor.

What we don't know is when we are giving tamoxifen early on in the natural history of breast cancer we could actually be preventing a 100 percent of the breast cancers. This is why long-term incidence data and long-term mortality data was going to be very important in terms of telling us what was going to be happening in the prevention scenario.

I can't emphasize too strongly that we are encouraged by this reduction in early incidence, but I still don't think it is telling us very much about the long-term prevention of breast cancer, which is what we need to know before we start getting on to the next agents, the tamoxifen look-alikes.

DR. SLEDGE: So, again, I am sorry --

DR. POWLES: Ten to 15 years of follow-up is what I think you need before you really know what is happening.

DR. SLEDGE: Thank you.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: I have a question about the data from what you call women of color. First of all, is that African-American only or does that include Latinos, Filipinos?

DR. HONIG: A subset were African-American and the others were simply listed as "other" with no racial breakdown.

DR. MARGOLIN: If you look at the chart we got this morning about the effect of tamoxifen in ER-positive tumors, it is about a 67 percent reduction, with the others being equivalent. Just arithmetically, there is about a 2-fold increase, 6 versus 3, the wrong way in women of color. But you didn't tell us whether those patients developed ER-negative tumors, in which case the data are just a wash.

DR. HONIG: No, they were all over the map. We specifically looked at ER status, and I don't have those numbers with me although I think they are in my review, and they were not all ER negative and they were sort of a mixture. I think of 3 cases 1 was ER positive, 1 was I think a mix. Jo, do you have that data?

DR. COSTANTINO: Yes, of the 9 cases which you were referring to, actually 7 were in Afro-Americans. Among those 7, there were 3 ER-positive cases, 2 in the placebo arm and 1 in the tamoxifen arm. So, if you limit yourself to the ER, it went the right away but the numbers are very small.

DR. DUTCHER: Dr. Schilsky?

DR. SCHILSKY: I have a question for Dr. Powles in follow-up to Dr. Sledge's question. I take your comments very seriously although they are reminiscent of comments that were made, I guess, in the 1970s with the introduction of adjuvant chemotherapy when lots of questions were raised

about how many women should get adjuvant chemotherapy to prevent the recurrence of breast cancer in just a few, and it is a similar type of argument that you have made now. I am concerned, I suppose, about the need to wait 10-15 more years to have definitive information, and whether or not such information could be available from the NSABP trial in view of the fact that so many women on the placebo arm are now likely to cross over to receive tamoxifen.

So, I suppose my question is do you feel that the NSABP, as it continues to mature, will be able to provide the definitive information that you are looking for, or are there other trials that are ongoing that will be able to provide that information relatively soon?

DR. POWLES: Yes, I think I need to make it clear that there are two different levels of the question. One is if you really want to know what is happening in prevention you would have to wait 15 years, say, for incidence data. We know how useful, for example, the adjuvant data is, not just the 2- or 3-year data but the 5-year, the 10-year data. I mean, think what a disaster it would have been if we had given tamoxifen to everybody 3 years into the adjuvant trials and we didn't really know what was happening. This is the same sort of situation here.

What I think the caveat is, as far as it goes with the prevention programs, we won't have to wait 15 years,

although one would like to, because you are going to be looking at other endpoints and other outcomes, and the like. I would guess that in order to get sufficient information, in my opinion, if the NSABP hadn't been unblinded we would probably have been in a position with the European trials and with the NSABP to be getting meaningful answers on clinical benefits in the prevention scenario by the year 2000, 2005. That would have been something that we would have then built on for the next generation of anti-estrogens.

As far as the trial goes now, I don't know how much information you can get, now that it has been unblinded and now that tamoxifen and raloxifene will be offered in the control arm. I don't know how much information we will get. I suspect not very much.

DR. DUTCHER: Dr. Honig, you made a fairly strong series of statements about the thromboembolic events. How many of those people actually had or soon after had developed cancer?

DR. HONIG: You mean the thromboembolic events in cancer patients in particular? That is a good point and, without looking at my notes, relatively fewer than developed cancer. Is that correct from your recollection, Jo? The patients with DVT and PE? I should say specifically breast cancer. We looked for any cancer as a contributing factor

to underlying clotting and there were certainly people who had procedures with general anesthesia; there were people who had long trips; there were people who were diagnosed with cancer. But all of that did not account for all of the clotting events.

DR. DUTCHER: Dr. Simon?

DR. SIMON: I have a couple of questions for Dr. Honig. You said you looked at a variety of subsets for examining the relative effect of tamoxifen on lowering the risk of invasive breast cancer. Did you look at women over 60 who had a relative risk less than 2, or women over 60 who had a relative risk of 2-5?

DR. HONIG: We didn't have the information categorized by relative risk, and we didn't have the Gail model until I think the first or second week in August and we really haven't run any of those calculations. But what we did, we looked at the individual risk factors which, granted, is not the same as the Gail model but, anyway, we looked at the various groupings, say, of age at menarche, first live birth, family history -- those sorts of things, and ran a series of queries --

DR. SIMON: That is a problematic way of doing it. In other words, if you need risk factors to get on study, then to look at those univariately is all confounded because those who don't have this one have something else.

DR. HONIG: Right.

DR. SIMON: So, you tend not to see anything.

DR. HONIG: Exactly. I mean, we didn't have the disc so we were looking to see if, by eyeball, we could see if there were one factor that was driving everything. In fact, there wasn't. I think, as you say, it is the combination of risks, and there are many, many combinations.

DR. SIMON: I have a couple of other questions. You showed some data categorizing endometrial cancer cases based on woman's age, and you defined the age in a couple of different ways. It looked, actually, fairly striking to me that the increased risk of endometrial cancer was greatest for women over 50. You wound up concluding that you didn't have enough data to make any conclusion. Did you do a statistical analysis on that?

DR. HONIG: We would say that, you know, you can frame shift everything depending on how you assign the cases, and that you get slightly different outcomes and that, yes, it is true most of the cases were in postmenopausal women but --

DR. SIMON: I mean, you got different numbers and the numbers change but in all of the ways you presented it, it looked like there were many more cases of endometrial cancer in the tamoxifen group. The excess cases of endometrial cancer in the tamoxifen group relative to the

placebo group always seemed to be concentrated in the older age group.

DR. HONIG: Yes. I mean, that is true. We think that most of them were in excess in the older group but to say that younger women are completely immune and that they have no risk other than the general population, we don't feel confident saying.

DR. SIMON: The other thing that I guess I was surprised about is you showed data on number of events of invasive breast cancer after stopping the study drug, either tamoxifen or placebo, and I don't remember the exact numbers but I think it was something like 34 --

DR. HONIG: I think 38 and 32.

DR. SIMON: Something like that, 38 and 32. But that was fairly striking to me because there were only 85 cases of invasive breast cancer in the tamoxifen group. So, 38/85 versus 32/154 for placebo, that suggests to me that it is pretty striking, that the tamoxifen cases are tending to occur after discontinuation of the drug and the placebo cases are not.

DR. HONIG: I think what we found is even if you took those cases out, the number diagnosed on study drug was still less for tamoxifen compared to the number on placebo, and if you stopped study drug you then continued to find breast cancers but at approximately the same rate in either

arm. We were not trying to make too fine a point, except it certainly would have been of interest if you had stopped tamoxifen and then suddenly saw a rebound number of cases that brought you right back up to baseline.

We didn't see that. What we saw is that you get some reduction while you are on tamoxifen and then you continue on at the same rates. I guess the question again is, you know, at follow-up would you still in 10 years see that same difference? How long does the effect of tamoxifen last, and which of the cancers have you interfered with? You know, have you treated some early stage 1, etc? I think those are all valid and open questions at this point with the follow-up that we have.

DR. DUTCHER: Dr. Schilsky, I cut you off. I am sorry.

DR. SCHILSKY: No, that is okay. I really just want to make a comment with respect to the risk for thromboembolic disease. There is a substantial body of literature to suggest that women who clot while receiving hormone therapy or during pregnancy may be carriers of a mutation in the Factor V gene, called Factor V Leiden. I think it would be important to look at whether women who clot on tamoxifen might also be carriers of Factor V Leiden because that would provide a relatively simple screening test to sort out those women who might be at greatest risk

of developing thromboembolic complications while on tamoxifen.

DR. HONIG: Thank you. I think that is one of our questions to the committee.

DR. DUTCHER: Miss Beaman?

MS. BEAMAN: Yes, the doctor did say a moment ago that these are healthy women and they are now possibly tamoxifen sensitive. What exactly did you mean by that, and how might that affect future treatment for those women in particular?

DR. POWLES: That is an interesting question. Yes, I wasn't meaning that. I meant that those who get the cancers are likely to be tamoxifen resistant if they have been on tamoxifen when they get their cancers. So, they will lose the benefit that they would have from tamoxifen. I don't think I understood -- as far as the rest of the population, for women who don't get breast cancer, I think the issue there is what are the long-term effects of tamoxifen, particularly in young, healthy women going out to 20, 25, and 30 years? That is an issue that we can't fully address from the adjuvant trials at the moment.

DR. DUTCHER: I think what he said was that if they were not treated and they got cancer, it would be more likely to be a tamoxifen-sensitive cancer.

DR. POWLES: Yes.

DR. DUTCHER: Dr. Albain?

DR. ALBAIN: For Dr. Powles again. Trevor, I have to come back to your 10-15 years follow-up and that we can't extrapolate from treatment trials. Don't you think that we could perhaps still extrapolate from the overview data in B-14 that does have that 10-15-year follow-up on a solid persistence of the reduction in risk of contralateral breast cancers despite only receiving tamoxifen for 2-5 years?

DR. POWLES: I have a real problem with contralateral breast cancer in its own right. You know, of all of the groups that we are looking at, populations of women that may be the same or different, second cancers are likely to be a subgroup that is special in many ways. Therefore, I have no problem saying that an indication for use of tamoxifen in a woman who has had breast cancer is prevention of her second breast cancer. But taking that to a healthy woman and saying the same thing works in a woman who has never had breast cancer is a big step and you have to be sure that you are talking about the same biology.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: Just a comment to follow-up on that, I think in that trial also we had a very favorable group of patients who were ER positive and node negative. It is a highly select group of patients.

DR. DUTCHER: Dr. Raghavan?

DR. RAGHAVAN: Trev, I am still a little unclear about the difference between the 2 populations. You sounded tremendously confident that you could identify differences, and I guess I missed the point. So, I just want to go back to that. You said you thought they were younger and had a stronger family history and they were more premenopausal. In the NSABP group 76 percent had relatives; 39 percent were 49 or less and about 70 percent, I think, were less than 60. Can you flesh that out a little?

DR. POWLES: Yes, I think the big difference is that if you don't do a pedigree, if you just look at the family history risk itself, then you don't really identify the high risk gene population. You can be as low as, say, something on the order of 20 percent of those women you might identify that would actually be BRCA 1 or BRCA 2 positive based on just the breast cancer history. You really need to do the full pedigree, and there are various models that have been established.

I can't be confident that there are differences between the Marsden and the NSABP because we can't do the pedigree analysis -- we can't, on the data we have on the NSABP data set. All we can say is that we can look at just the numbers of first degree relatives they have with breast cancer, and we can say that there are likely to be big differences in the incidence of high risk genes in the

Marsden population versus the NSABP population. It is a factor of 2 or 3. It is likely to be that different.

DR. DUTCHER: Dr. Ozols?

DR. OZOLS: I am concerned about what additional information we are going to get in the future. We know what the NSABP follow-up trial is. You alluded to some trials that are going to be done in Europe. Do you have data on some of those plans?

DR. POWLES: Well, the Italian trial has 5000 women in it, and it is a different population from the pilot trial, our trial, which has 2500 women in it. The national British trial has 4500 women at the moment. So, between the 3 of them -- I can't add that up in my head but there is 11,000 or 12,000.

One of the concerns we obviously have about this hearing is that we would like to be able to hold those trials together, having those numbers of women. We are still accruing to the British national trial which we would like to take up to a total of 10,000 women. If we can hold those trials together through incidence data, we hope that we will be able to get identification of clinical benefit in those trials.

DR. DUTCHER: Other questions? Dr. Simon?

DR. SIMON: Dr. Powles, what percentage of your invasive breast cancer cases were ER positive?

DR. POWLES: We haven't completed that yet. We are doing it at the moment but we haven't completed that.

Open Public Hearing

DR. DUTCHER: Thank you very much. We have half an hour allotted now for an open public hearing. We have six people who have requested to speak. We ask that they each state their name, identify themselves and their sponsors for participation, and then following the open public hearing we will proceed with the committee discussion and vote. The first person is Ann Fonfa. We would ask you to use the podium if possible.

MS. FONFA: My name is Ann Fonfa. I am a five and a half year breast cancer survivor. I consider myself an activist. I am very glad to be here today because I have a very strong point of view on what we have heard, and much stronger on what we haven't heard.

[Voice on telephone: "Thank you for saving me from breast cancer. Today, I had a pulmonary embolism.]

Survival is what counts for cancer patients. What I heard here today only aggravated the feelings that I felt when I first read the newspaper information and everything that has been published so far about the trial.

Women died of breast cancer who took placebo; women died of breast cancer who took tamoxifen; women died

of pulmonary embolism who took tamoxifen. This pains me because as far as I can see when you are dead, you are dead. It doesn't matter what you died from. I have a great concern about women who come in healthy and die because of something that they take, thinking that it is going to prevent them from dying from something else. There is a real problem here.

Some of my concerns include the fact that for tamoxifen, while we hear that there are hundreds of thousands of hours of follow-up, it is actually not very lengthy in time. And, time I think is what will indicate what may be further problems when healthy women are given this drug.

So, all we have is really a 5-year or less follow-up, and from what I heard today, the follow-up is really very shaky. It is if the women consent, if the company consents, and if we are able to continue to look at what happens. We don't know whether women who are healthy take tamoxifen at this point and whether they benefit for any length of time afterwards. Yes, we can say that there haven't been any cases but how far out are we from the end of the study? We are not even 6 months. So, we are not looking at any long-term follow-up right now to say, yes, there has been a tremendous benefit conveyed; that these women now are safe from breast cancer for the future. We

don't know at all that they are.

So, my point is really that there are endless questions about what is going on, and I think it is way too soon to allow this drug to be in the general population because you know darned well that once doctors are able to prescribe it -- you know, let's face it, we have had very good success in making people aware that there is an epidemic of breast cancer and, therefore, lots of women are going to want it from doctors and lots of doctors are going to give it to the women regardless of their risk-benefit.

Women with cancer and women without cancer are not foolish. They need information. We have presented the trial as being prevention when it has clearly been indicated today that it is not; it is really a risk reduction and that should be made very, very clear to the population and to the physicians. I think that is very important.

And, once it is out in the trenches, which is what I call the world of women who have cancer and the women who fear cancer, they are not going to be able to hold to the standards that are established, and you have to be aware of that in a very serious way. Women will be asking for it; doctors will be granting it. We know they are doing that now with lots of other drugs.

I envision a situation in which you go to see your doctor and the doctor says, "do you want hormone replacement

or do you want tamoxifen?" and, you know, you are on a pill taking care of something that may or may not be useful. We don't know yet. My main point has been questions.

I came here waiting to hear what was presented, figuring I would start my talk based on everything I heard, but I didn't hear anything that actually changed my point of view. There has been no new information. There are still tons of questions.

We are saying women under 49. Women under 49 is a huge category. A young woman in my organization, in New York, has been talking to be about the idea that women under 35 may have different standards. We haven't heard a word about that subset and that is really scary to me. Yet, women under 35 who have high risk, who have family connections, who are fearful of breast cancer -- how are they going to know what to do? We don't have any information. Women of color -- we have no information. We are leaving out all these subsets of populations, saying, well, women over 60, we will just give them tamoxifen if they are not taking hormone replacement, or maybe they will be taking both. There is something wrong with this picture.

I have a very, very strong concern about where this is going to go. Remember that when doctors are prescribing it, when you are out in your doctor's office asking what you should do and talking about your risks and

benefits, there are a lot of blurred lines. It is not going to be clear. However many scientists here are truly clear about what they have heard and what they have found out, it is not going to be clear in the doctor's office. It is going to make a difference. Women will not know what to do. I think we need a lot more information.

I have a concern about the fact that we are saying we only need one trial here, in the United States. That is a concern for me. I don't feel that is a benefit for patients or for healthy women or high risk women. I think we are rushing things in a way which we should not be doing. There is no reason to. It is not even like that many women got breast cancer within the trial. If they are really high risk -- I just don't see this. It is not strong enough for me.

Also, we saw a slide that said the tamoxifen study began in 1978. So, overall we don't even have long-term follow-up to know what is going on. Leslie Ford was quoted in the Journal of NCI, Volume 88, August 28, 1996: Tamoxifen has been available for 30 years. It wasn't until the late 1980s that we found about tamoxifen in the uterus. Again, I say that over time they find things out that we don't find in the hours of use because that is not the same thing. You can have 300 women take it for an hour each and that is 300 hours but it is not the same as having long-term

years out and we need to see those effects.

So, my main point really is that we don't know enough to go forward on this at this time, and I really feel we need more studies; we need more information. That is really about all I have to say. Does anyone have any questions for me? I would also like to point out that no drug company has ever paid me for my opinions.

[Laughter]

DR. DUTCHER: Thank you. The next speaker is Cindy Pearson.

MS. PEARSON: Good morning. I am Cynthia Pearson. I am the Executive Director of the National Women's Health Network. The Network is supported by a national membership of individual and local organizations, and we do not accept money from pharmaceutical companies or manufacturers of medical devices. The Network urges the FDA and the committee that has been asked by the FDA to give it advice not to approve tamoxifen for prevention or even for risk reduction at this time.

Now, how can we take such a strong negative stand when women in the United States and the world have been hearing such positive comments about tamoxifen and the results in the breast cancer prevention trial since April 6? Federal officials, including the Director of the National Cancer Institute, Richard Klausner, and Donna Shalala,

Secretary of Health and Human Services have called the trial and its results and the drug tamoxifen stunning, remarkable and a historic success?

Well, our questions about the trial and the drug, and whether this is the right time for approval for its use in risk reduction -- some of them have already been brought up by Dr. Powles, by Ann and others, but we would like to go over them again so that you and the FDA are aware of the concerns from all the places that are coming to the FDA.

We share the concern that has already been expressed about whether or not prophylactic tamoxifen will save lives. As you saw in the data earlier this morning, as of right now it is not possible to say that a single woman's life has been saved by taking tamoxifen for prevention, as far as we can tell from the breast cancer prevention trial, and it seems more and more obvious that the breast cancer prevention trial will never actually be able to tell us anything about whether or not tamoxifen can save women's lives, tamoxifen taken for prevention.

Dr. Klausner says he only has guaranteed 2 years of funding for follow-up. As you heard earlier, many of the women who were originally on placebo are now taking tamoxifen. But what you haven't heard very clearly is that since April the NCI has publicly announced, and has taken steps to effectuate the active recruitment of placebo women

to the STAR trial which has no placebo group. So, if the NCI's efforts are successful there will be little control group left to follow-up even if there were a guarantee of more than 2 years follow-up. I see someone nodding, whispering, "that's true, actually."

So, why are we stressing so much our concern that we do not yet know if tamoxifen for prevention saves lives and are likely not to ever know it from the BCPT? It is because the early data are troubling. We heard over and over again from the sponsor and the NSABP people this morning that the data at 4 and 5 years show no harmful trends; that there isn't an increase of the ER-negative cancers; that none of the effects that started to be seen at 1 and 2 years changed for the worse at 4 and 5 so that the long-term effect should be as good as the short-term effects.

But that is not true with treatment, and everyone at this table knows it. It took eight and a half years of long-term treatment with tamoxifen in breast cancer for survivors to see that going beyond 5 years actually caused more recurrences and more deaths from breast cancer than stopping tamoxifen treatment at 5 years. So, we absolutely need to know those long-term data, which we are going to have trouble getting. As you cleverly questioned the sponsor this morning, we don't even really know all the

prognostic data on the women who have been diagnosed in this very short period of time.

So, to play out the worst case scenario, we already know that estrogen-receptor negative cancers are not even delayed by tamoxifen for prevention. We don't yet know whether estrogen-receptor positive cancers are delayed, prevented or merely delayed, which would mean we would have no net effect on numbers of cancers. And if, even worse, this early pretreatment of non-detectable breast cancers with tamoxifen results in the same sorts of resistance and aggressiveness that we see with long-term treatment of detected and diagnosed breast cancer, we could have the same number of cancers in women who have taken tamoxifen for prevention but with a worse prognosis and even a harmful effect on mortality. So, this is why we have emphasized it so much, and believe that we just don't know enough now to change the label and tell the women of America that tamoxifen can be used to prevent breast cancer.

Our other concern is if tamoxifen were to be described to women and doctors in the United States as a approved for prevention breast cancer, will more women be hurt than helped? That question is answered primarily by how many women will take tamoxifen and who will they be and what will their level of risk be.

We know that even in the ideal environment of a

tightly controlled research time not all risks can be prevented. We know that if any of you were asked, as I am sure you already have been, for tamoxifen by a woman who hasn't yet been diagnosed with breast cancer, you would give a very reasoned analysis. Some of you would go even further than the Gail model and look to who actually was in this trial -- as we saw, women who had double the risk that the Gail model requires. But do you really think that every primary care doctor and gynecologist in America could give that kind risk? Do you think that the lovely little, nicely designed risk model information, user-friendly description of the Gail model that Leslie Ford held up in her hands is enough? I don't think so. I think that as other speakers have said, busy doctors are going to respond to women's expressed needs. As you know, women already have quite a high concern about the likelihood of being diagnosed with breast cancer. If we add FDA approval to this, we are giving the manufacturer a green light to start direct to consumer advertising.

So, if you add the concern that is already there, and the limited time that most physicians have to have these conversations, if you add in a high powered marketing campaign, we are in for potentially 29 million users of tamoxifen.

I am getting the signal that I need to close up.

We, again, conclude with saying we urge you to recommend against the approval for tamoxifen for risk reduction at this time.

We have appended to our remarks suggested labeling language about how to better educate physicians and women as to who might or might not benefit in the short-term from tamoxifen, and maybe later there will be time to go over that.

Thank you for the opportunity to testify, and I wonder if there are any questions for me.

DR. DUTCHER: Dr. Simon?

DR. SIMON: Could you summarize briefly, based on the uncertainties of long-term benefit and the risks, is there a group of women who your organization believes the risk-benefit ratio might be favorable for?

MS. PEARSON: I think our organization agrees with almost everyone who has addressed that so far today, that women who already have been diagnosed with lobular carcinoma in situ, if -- and it is an important "if" -- if they are fully informed about the risks and benefits, the fact that the positive effects right now are based on one trial that is yet to be confirmed, and the complications associated with it -- if there is good information sharing, that is a group of women for whom even this limited short-term knowledge would be enough; useful.

DR. SIMON: Is that the only group?

MS. PEARSON: That is the easiest group to answer it. In our language, which I know I don't have time to read, we suggest that every woman considering this go through a formal risk assessment. Then we recapitulate the findings of the BCPT based on who actually took part in it, not based on what the entry criteria were, which was that for women over age 50 with a uterus there was no net health benefit. Breast cancer cases were delayed or prevented in the time of the trial but as many, and even slightly more at least as of January 31st, as many other life-threatening events took place.

For women over age 50 with a hysterectomy, there appears to be, based on the short-term data, a net health benefit if the risk of breast cancer is 2-3 times that of the general population of women that age. For women under age 50, it takes 5 times risk compared to the general population of women that age to get a net health benefit.

DR. DUTCHER: I might say that in the handout from her organization there is a copy of those indications you can look at.

MS. PEARSON: Are there any other questions?

DR. DUTCHER: Dr. Raghavan?

DR. RAGHAVAN: Just for clarification, one of the things that I have heard you and Miss Fonfa talk about is

the risk to the people taking tamoxifen in terms of what might happen and deaths unrelated to breast cancer, and so on. Yet, the NSABP figures show that 65 people dies on the placebo arm and 53 on the tamoxifen arm. I understand the numbers are small but any way you cut, slice or dice it, it still means more deaths in the placebo arm. Does that not affect how you view this in some way?

MS. PEARSON: No, it doesn't. That effect is not statistically significant, and it is based on short-term data where we have these troubling hints from the long-term treatment that the use of long-term tamoxifen in breast cancer survivors might indicate that its effect on breast cancer will start to worsen.

DR. DUTCHER: The next speaker is Vincent Li.

DR. LI: My name is Dr. Vincent Li. I am the Scientific Director of the Angiogenesis Foundation, and neither I nor the Foundation have any financial interests in Zeneca.

Breast cancer afflicts 1.8 million women in the U.S. and it is a highly angiogenic tumor. By this, I mean that breast tumors must initiate angiogenesis, new blood vessel growth, in order to grow beyond 1-2 mm in size. This brings oxygen, nutrients and growth factors to the tumor. New blood vessels also provide an escape route for breast cancer cells to metastasize to other sites in the body. The

smallest palpable breast cancer is 1 cubic centimeter and already contains 1 billion cancer cells. To supply the metabolic demands of those cancer cells, between 10 to 100 million blood vessel cells will have already invaded the tumor. Therefore, anti-angiogenic drugs are being developed to cut off the blood supply from established tumors.

This approach is currently in clinical trial for some 26 experimental agents around the world but the treatment of large, established cancers is only one goal. The Angiogenesis Foundation believe that an equally important goal is to develop chemopreventive strategies that can prevent even the smallest tumors from gaining the ability to create a new blood supply.

We believe that Nolvadex is the first chemopreventive drug that may benefit patients at risk for breast cancer through anti-angiogenesis. Tamoxifen is an angiogenesis inhibitor, as well as an anti-estrogen drug. In tissue culture it inhibits vascular endothelial cell growth. It inhibits angiogenesis ex vivo in the chick chorioallantoic membrane assay. In mice implanted with MCF7 human breast cancer cells tamoxifen inhibits tumor angiogenesis as well as tumor growth. When given long-term in animals, tamoxifen suppresses malignancies, and this preventative effect has been attributed to angiogenesis inhibition as well.

The Angiogenesis Foundation is a non-profit organization dedicated to bringing new angiogenesis therapies to the world through education, research and innovation. Each week we receive hundreds of telephone calls from patients, including many breast cancer patients, seeking information on angiogenesis therapies. Patients in remission, as well as women at high risk for breast cancer ask us about chemoprevention.

In 1994, the Foundation identified tamoxifen citrate as a potential anti-angiogenic chemopreventative agent. In that same year, researchers from the National Cancer Institute published a paper in the Journal of Cellular Biochemistry supporting our idea. Based on our analysis of the breast cancer prevention trial, we offer the following insights for ODAC's consideration:

First, there is a sound biological rationale for tamoxifen's use in chemoprevention based upon its anti-angiogenic as well as its anti-estrogen properties.

Second, tamoxifen is still relatively devoid of harmful effects compared to the consequences of breast cancer.

Third, tamoxifen's approval for this indication will stimulate the pharmaceutical industry to develop further generations of chemopreventative drugs, including other anti-angiogenesis agents.

Fourth, tamoxifen's approval may uncover additional beneficial anti-angiogenesis effects when they are looked for specifically, for example suppression of diabetic retinopathy, psoriasis, arthritis, or the suppression of other non-breast cancers.

A few words of caution are warranted, however. Tamoxifen's use for chemoprevention may lead to primary care doctors or nurse practitioners to prescribe the drug to women who do not fall into high risk categories, and this has been spoken about by others, due to pressures from their patients or from a perceived benefit. Our concern is that some women taking chemoprevention may avoid the gold standards of self-examination, routine physician visits and screening mammography.

Long-term use of tamoxifen may also lead to some undesirable side effects of anti-angiogenesis, for example, inhibition of coronary angiogenesis, delayed wound healing after surgery and fetal malformation. The Angiogenesis Foundation is studying this problem because it will be necessary to achieve the desired effect of anti-angiogenesis without disrupting the body's ability to generate beneficial blood vessels.

Finally, tamoxifen is associated with a slight increase in the incidence of endometrial cancers, and there is an angiogenesis base of mechanism for this as well.

Animal studies have shown that tamoxifen can up-regulate mRNA expression of the angiogenic factor VEGF, vascular endothelial growth factor, in uterine tissues, and this may be a concern for women at high risk for endometrial cancer.

In summary, tamoxifen is an estrogen blocker with anti-angiogenic properties. Its therapeutic effects are likely due in part to inhibition of breast cancer angiogenesis. If Nolvadex is approved for breast cancer chemoprevention, we emphasize the need to educate women on the continued importance of self-examination, regular checkups and screening mammography. Prescribing doctors must watch for possible harmful effects, as well as any additional beneficial effects, of long-term anti-angiogenesis in women.

Thank you very much.

DR. DUTCHER: Thank you. Our next speaker is Helen Schiff.

MS. SCHIFF: My name is Helen Schiff. I am a breast cancer activist and survivor.

When you look at the results of the breast cancer prevention trial, the reduction of breast cancer incidence of 45 percent is stunning. I remember thinking when I first read the newspaper that there probably is a group of ultra-high risk women for whom the benefits would outweigh the risks. I was happy some women might be helped. But the

more I studied the results of the trial, the more I read the pros and cons, the more I thought about it, the more I began to worry -- worry about giving tamoxifen to a healthy population.

I would like to share my worries with the advisory committee and with the FDA, and hope that they worry about them too. I worry that the prevention trial was designed to look only at breast cancer incidence. Shouldn't incidence of other life-threatening diseases caused by tamoxifen, such as uterine cancer and deep vein thrombosis and pulmonary embolism be weighed too? Further, isn't death really the most important endpoint?

I worry that even though there is less breast cancer incidence in the tamoxifen arm, will there be less breast cancer mortality? I am not the only one who worries about this. Dr. Ken Osborne, a leading breast cancer researcher and clinician was quoted in the June issue of Oncology Times as saying, and I quote, tumors that develop on tamoxifen have a somewhat poorer prognosis than those that develop on placebo, suggesting that there is a treatment effect on an established tumor. Over time, mortality between the 2 groups may not be that different.

I worry that the trial was too short to know if we are preventing breast cancer or holding it in check for only a short time, after which a tamoxifen-resistant tumor

develops that does not respond to hormonal treatment. Again, it is not just me. Dr. Osborne says, and I quote, a major question is whether these drugs affect only preclinical breast cancer or are true prevention agents. We don't know if these drugs block cancer at earlier stages. We may learn from the longer European studies.

I worry that the trial is too short for all side effects to emerge. Is that why premenopausal women on the tamoxifen arm showed no bone loss, contrary to the results of all previous trials?

I worry that the average length of time on the treatment arm is shorter than the overall 4-year average because over 30 percent of the drop-out rate could have been unequally distributed between each arm, and we just heard today that it was.

I worry that the reason we don't know what the distribution of the drop-out rate was is because the trial has not been published in a peer reviewed journal, as the Italians and British trials were. I worry about what else we don't know because the trial was not published in a peer reviewed journal. As was brought up toady by one of the panel members, we don't know at how high a risk the actual participants in the trial were.

I worry that we don't know if tamoxifen works for women with BRCA 1 and 2 mutations, the very population most

likely to want it.

I worry about the long-range effects on tamoxifen blocking estrogen receptors in the brain, causing memory loss and other cognitive deficits.

I worry that using the breast cancer treatment trials to validate prevention trials is like comparing apples and oranges. They are two different populations.

I worry because I learned in Project Lead, the National Breast Cancer Coalition program for breast cancer advocates, that you need more than one trial to validate results, and we don't have that. In fact, we have two trials that don't validate the results.

I worry that if the drug is approved women's exaggerated fear of breast cancer, couples with advertising publicity, will cause irreparable harm. This drug will mainly be prescribed by primary care physicians and gynecologists, not oncologists.

I worry about approving a drug with life-threatening side effects for a disease that a large majority of the indicated population won't get, and those who do won't die from it. Breast cancer is not an automatic death sentence. The relative survival rate is 50-60 percent out to 15 years. We need more data and longer trials to make an accurate risk-benefit analysis. We want prevention for our daughters, sisters and mothers and for all women. We want

answers but we are willing to wait for them to make sure they are right.

I just have one question to ask, if there was any breakdown done on premenopausal women younger than 40, the 35-40 age group or for the 45 age group down.

DR. DUTCHER: Thank you. The next speaker is Mary Ann Napoli.

MS. NAPOLI: I am Mary Ann Napoli, from the Center for Medical Consumers in New York. We are a public interest advocacy organization. In the 21 years we have been in existence, we have never sought nor accepted pharmaceutical industry money.

The Center for Medical Consumers strongly urges the committee not to approve for the new indication. My organization has long been concerned about the growing trend in this country towards treating a risk factor as if it were a disease. Direct to consumer advertising of prescription drugs to prevent bone loss, to lower cholesterol and so forth reinforces the idea that common manifestations of old age must be treated at menopause, and that people, particularly women, couldn't possibly live a long, healthy life without the aid of protracted drug therapy.

As an example of distorted ads to the public, I have brought one along from Good Housekeeping magazine. Though Bristol-Myers Squibb is selling cholesterol-lowering

drugs to women without heart disease in this ad, it stands as an example of what is ahead for us if tamoxifen is approved as a preventor. The woman in this ad -- you are going to have to take my word for it because you are all so far away, but the woman in this ad looks to be about 40. The lone study to support this ad claim did, in fact, have female participants but their average median age was 63. Women entering middle age, rather than elderly women, are a favorite target audience of drug companies, and that is for good reason -- they tend to be more receptive and they have a longer life span ahead in which to take drugs.

To show that misleading ads to the public are not confined to the consumer, I have brought Merck's ad to doctors for fosamax. This ad appeared repeatedly in Annals of Internal Medicine in 1996. Next to the woman's face it encourages doctors to prescribe no matter what her degree of bone loss. Here too you are going to have to take my word for it. She looks like she is no more than 50. At the time of this ad campaign, the only evidence to support the drug's ability to prevent bone loss was entirely confined to elderly women.

We don't know whether Zeneca is going to be a irresponsible in its advertising, but we already know that there is a precedent for allowing it to happen. You add to this precedent the fact that this is a country in which

breast cancer awareness activities have caused younger women in particular to vastly overestimate their odds of getting breast cancer. Middle aged women are very familiar with that laundry list of risk factors for breast cancer that frequently appears in the lay media, and that laundry list tends to emphasize the woman's reproductive history. In fact, I can't think of a single list that told women how important being over 60 is.

Misleading ads and overestimation of risk makes for a worrisome combination. Any drug billed as a preventive to the public is likely to be taken literally. Even if physicians confine their prescribing of tamoxifen to women who are truly at high risk, keep in mind that most of these women will not die of breast cancer. More likely, they are going to die of heart disease. Scientific data, by definition, can be replicated. Obviously, the U.S. tamoxifen trial's most significant benefit has not been replicated, nor has it been published in a peer reviewed journal. For these two reasons alone, the advisory panel should not approve it for the new indication.

While the equal number of deaths in the tamoxifen and the placebo groups may not be statistically significant, it is certainly a red flag that indicates caution in approving tamoxifen on the basis of the trial that only lasted four and a half years. When long-term drug therapy

is contemplated for healthy people, it becomes imperative for the panel to be even tougher on the supporting evidence than you would be if you were assessing evidence to support a drug given to people with an established illness.

Here is a drug known to increase the risk of cancer and potentially fatal blood clots. Prescribing physicians who want to help a woman who is fearful of developing breast cancer would want to be sure that they are not causing her more health problems. They would want the panel's assurance that the consequence of their prescribing would be more than simply changing what it says on her death certificate.

Thank you.

DR. DUTCHER: Thank you. The next speaker is Sharon Batt.

MS. BATT: Madam Chairman, members of the committee, thank you for the opportunity to testify today. My name is Sharon Batt, and I am a breast cancer survivor. I am here on behalf of Breast Cancer Action, Montreal, a public interest organization representing women with breast cancer, their families and friends.

About 700 Montreal women took part in the breast cancer prevention trial. While the outcome of this hearing will not directly set policy in Canada, the FDA's decision will affect Canadian public opinion and will influence

regulators in Canada and elsewhere.

We ask the FDA not to approve the application for the preventive use of tamoxifen. The 600 million dollar question addressed in this trial was whether tamoxifen can prevent breast cancer. Despite the statistically significant difference in breast cancers between the 2 groups, the trial did not answer the question that was its raison d'etre, and other people have discussed that and made that point very well so I won't belabor it.

Even if tamoxifen prevents breast cancer, the rationale for approving the drug is tenuous because the risks are considerable. We simply don't have enough information to effectively steer women from serious harm. Even with the careful efforts to screen women at risk for life-threatening events, deaths occurred. Outside the protected confines of a trial, they will surely occur more often.

Several people have mentioned the BRCA gene, and the fact that this population is probably the one that is most motivated, will be the most motivated to take tamoxifen for prevention. Yet, we don't know if women carrying a mutated BRCA gene are more likely to benefit from tamoxifen or less. The British study suggests that these women may not benefit at all.

It is commendable that the NSABP is planning to

proceed with testing for this factor but surely drug approval should await results of the BRCA testing so that the women from this key high risk group can make an informed decision about prophylactic tamoxifen use.

I haven't heard any comments about the issue of pregnancy. We have no data on pregnancy and tamoxifen to my knowledge. This drug has only been used by women who have breast cancer or women in a clinical trial. If the drug is approved for widespread preventive use, surely some women on tamoxifen will become pregnant and carry those pregnancies to term. Although data on risks to a human exposure of tamoxifen in utero is lacking, animal experiments show deformities.

Everything about this trial has progressed "pedal to the metal." The urgent need of women has been incessantly invoked, first to launch the trial, then to stop it, then to go public, and now to take the drug to general use. Surely, it is time to pause, take our collective breath and reflect on what course would truly benefit women.

In 1992, the FDA ruled on another controversial product concerning women. Dr. David Kessler announced that silicone implants would be available only through controlled clinical trials until questions about their efficacy and safety were answered. I ask this committee to recall the principles behind that decision.

The first was that manufacturers, by law, must prove their products to be both efficacy and safe before they may be distributed and used.

The second was that the FDA has a duty to mediate between the vested interests of manufacturers and the interests of patients. The rationale for FDA intervention is greatest precisely in cases where vulnerable members of the public are hoping against hope for a medical solution to a deeply felt need.

Finally, Dr. Kessler argued that meaningful data was needed to answer the outstanding question about safety and efficacy of breast implants. The only way to assure that this information would be collected was for the FDA to restrict the product's availability to clinical trials.

I urge this committee to uphold the standard of this previous ruling and to protect the public interest. The interest of science and sound medical practice will benefit as well.

Thank you.

Committee Discussion and Vote

DR. DUTCHER: Thank you, and I want to thank all of the public for coming and expressing their views and demonstrating a high level of involvement. I think many on the committee have expressed some of the same questions and concerns, and I think we have to decide whether we feel we

can safely generate guidelines, or where we stand with this. So, we are going to have to go ahead with discussion.

The first page of the questions to the committee describes the trial -- prospective, multicenter, randomized, double-blind, placebo-controlled trial of tamoxifen versus placebo for 5 years in women at increased risk for breast cancer as determined by age, prior history of lobular carcinoma in situ, or 1.7 percent risk of developing breast cancer in the next 5 years as predicted by the Gail model. And, 13,388 women were randomized, 6707 on placebo and 6681 on tamoxifen. The objectives of the trial were to test the ability of tamoxifen to prevent invasive breast cancer, mortality from cardiovascular disease, and bone fractures, and to assess the toxicity and safety and effects of tamoxifen in this patient population.

The results of the trial, per FDA review, are summarized in the following table. Events have been categorized by age at diagnosis of the event rather than age at randomization. So, I will give you a moment to look at the table.

The first question, is the NSABP P-1 an adequate and well-controlled trial demonstrating the efficacy of tamoxifen for the prevention of breast cancer in women at increased risk as defined by the study? Dr. Sledge, do you want to discuss it?

DR. SLEDGE: Well, I guess I would have to say I agree with most of the statement but not all of it. The concern that I think both Dr. Albain and I raised is with use of the word "prevention." This is a trial of very short follow-up. Everything we know about breast cancer is that it is a disease that takes a long term to go from a premalignant to an invasive, malignant state. Here, we are seeing effects within a year of starting the drug. While those may be beneficial effects in and of themselves, they are not prevention in the way that scientists understand the word prevention.

So, I would have to say that while I would be comfortable saying that we have demonstrated risk reduction with this very well-controlled, very well-performed trial, I don't think it has met the bar of what a scientist would consider a chemopreventive effect.

DR. DUTCHER: Dr. Albain?

DR. ALBAIN: Those were almost exactly my words too. It is clearly a well-controlled trial, and there has been a very significant reduction in events at this time. Regardless of what we think about the biology in patients who have already had one cancer versus this population, it is remarkable how much it agrees with the reduction of contralateral breast cancer in patients with one cancer.

I think our concerns is with this word

"prevention." I don't think we are seeing that yet. I hope that we will see it as this trial is followed but we haven't had the time to say that we can use that word. In particular, as was just pointed out earlier in the discussion, after the study drug is stopped there is a higher rate of cancers reported in the tamoxifen group than the placebo, at least by the percentages that were shown by the FDA review, 46 percent, 39/85, occurred after the study drug was stopped versus 34/154, 22 percent, in the placebo arm. But there is a very encouraging cumulative curve that we saw that as this trial is being followed the curves are not coming together; they are staying apart and that is what we would expect from contralateral breast cancer data as well. So, again, we need some more time to be certain that we are seeing prevention.

DR. DUTCHER: Dr. Simon?

DR. SIMON: I guess I have one additional concern with it as it is written -- prevention of breast cancer in women at increased risk as defined by the study. I think the study demonstrated either something like risk reduction or delay of diagnosis in a group of women at increased risk. One of my big problems is I am not very sure as to what that group is but I don't think it has demonstrated it in women in general at increased risk, or even using the risk as defined in the protocol. I think there is a group of women

who are at increased risk who had fewer invasive breast cancer events over this time period, but I think there is a problem with categorizing who they are.

DR. DUTCHER: Dr. Justice?

DR. JUSTICE: I think your points about the terminology are well taken, and we would be happy if the committee would like to rephrase the question and subsequent questions to use terminology that is more appropriate, such as was mentioned -- reducing the risk for the duration of the trial.

DR. DUTCHER: So, let me give it a try and see what you think. Is NSABP P-1 and adequate and well-controlled trial demonstrating the efficacy of tamoxifen for risk reduction of breast cancer in a group of women at increased risk for the duration of the trial, or do you want a duration on this? Dr. Margolin?

DR. MARGOLIN: I think it was the issue of how to define the population, and something to the effect of rather than as defined by the study entry criteria, it was as defined by those who were studied, or, you know, something of that nature -- women who are like the ones who were studied.

DR. JUSTICE: Let me try it again. How about saying for the reduction in the risk of breast cancer in women who were studied on the trial?

DR. DUTCHER: Good.

DR. JUSTICE: Or women with characteristics.

MS. BEAMAN: And, exactly how would that transfer to "Woman Q. Public?"

DR. DUTCHER: That is down the road here I think. That is to be defined, you are absolutely right.

Is NSABP P-1 an adequate and well-controlled trial demonstrating the efficacy of tamoxifen for reduction of breast cancer in a group of women comparable to those studied in the trial?

DR. ALBAIN: Reduction of risk of breast cancer?

DR. DUTCHER: Risk reduction.

DR. SCHILSKY: How about reducing the risk of developing?

DR. DUTCHER: Demonstrating efficacy of tamoxifen in reducing the risk of breast cancer?

DR. ALBAIN: We can also say reducing the incidence of breast cancer.

DR. DUTCHER: Risk? Incidence? Risk? Is risk okay? The risk in a group of women comparable -- well, in the women studied in the trial. That is what it was really demonstrating.

DR. SIMON: I mean, the most accurate thing would be reducing the short-term incidence of breast cancer.

DR. RAGHAVAN: We should put a time frame on it.

DR. DUTCHER: Okay, reducing the risk of breast cancer, the short-term incidence. Okay, demonstrating the efficacy of tamoxifen in reducing the short-term incidence of breast cancer in the women entered in the trial.

DR. ALBAIN: In women comparable to those entered in the trial?

DR. DUTCHER: Well, I mean, we will have to make a recommendation of the patient population, but basically the trial demonstrated in the patients that were in the trial. Carolyn, you are not happy?

MS. BEAMAN: I guess I am not really clear on who they were. Who were they?

DR. DUTCHER: Well, I think what we are trying to say is that in the patients as entered in the trial, and when Dr. Honig presented her analysis of the subgroups it seemed that every subgroup demonstrated a reduction. We will have to decide the risk-benefit ratio, which we are not talking about in this one. Do you want to look at the tables again?

DR. SIMON: I mean, I guess I don't believe that every subgroup demonstrated a reduction just because they were looked at one at a time. But I think if we word it this way we are not really saying it is for every subgroup. We are just saying there was a group of women who were studied on this trial -- we are going to have to grapple in

the following questions with who they were and who the risk-benefit is appropriate for. Basically the women who were on this trial, within this time frame they had a reduction in the incidence of breast cancer.

DR. DUTCHER: So, let me read it again omitting a few more words. Is NSABP P-1 an adequate and well-controlled trial demonstrating the efficacy of tamoxifen in reducing the short-term incidence of breast cancer in women entered in this trial, which could be all or some. Is that acceptable language?

All those who would vote yes?

[Show of hands]

Eleven yes.

All those who don't know?

[No response]

Zero.

The next table is to discuss adverse events. I will give you a moment to look at that. The mortality, breast cancer-related mortality, and occurrence of other cancers were not significantly different between the two arms. The table points out invasive endometrial cancer, DVT, pulmonary emboli, stroke, cataract surgery, hot flashes, discharge.

Does NSABP P-1 demonstrate that tamoxifen has a favorable benefit-risk ratio for the short-term reduction of

breast cancer in women -- well, I will read it as it is and then we can change it -- a favorable benefit-risk ratio for the prevention of breast cancer in women at increased risk as defined by the study? If the answer is no, can the committee identify a subpopulation in the study for which the benefit-risk ratio is acceptable? Does this demonstrate a favorable risk-benefit ratio for prevention of breast cancer in women at increased risk as defined by the study?

DR. SIMON: I guess in this situation I am not sure we should -- it is really does the treatment in this population of women provide a favorable benefit-risk ratio. You know, there may be certain benefits and there may be certain risks. Here, I don't think we can change "prevention" to short-term incidence because it is asking a broader question.

DR. DUTCHER: Okay. Do you want to comment on the question?

DR. SIMON: Well, I guess my own feeling is the answer is no. I guess I have two concerns. One is that there is some uncertainty as to what the population who actually achieved short-term benefit is. The second concern is I think this incorporates -- when you are talking about risk-benefit you have to think in terms of long-term effects. I think there is great uncertainty in terms of what the long-term mortality benefits are given that many,

if not most of the tumors that are being prevented or delayed are going to be curable by surgery plus tamoxifen. I think you have to be concerned here when we talk about the risk ratio. There are many women who could be included in this trial who would satisfy the eligibility criteria for this trial, for example, being 60 years old with no risk factors, for whom I think the risk-benefit ratio was not favorable. I think the long-term benefits are probably relatively small and the risks are large, and the risks apply to all of the women and the benefits only apply to a small subset.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: I happen to agree with Dr. Simon, but the real reason I wanted to speak is that I think if we are going to remove the word "prevention" -- I think we agree that this drug does not prevent breast cancer, or at least there is no evidence to date. So, for consistency we would still have to reword the question: A favorable benefit to risk ratio for the short-term decrease -- for reducing the short-term incidence of breast cancer. That actually makes it a little bit easier to accept the risk-benefit because we are not being asked to say, yes, we agree that it prevents breast cancer but only that it reduces the short-term incidence, which is pretty obviously the case.

DR. DUTCHER: Dr. Justice?

DR. JUSTICE: I just want to clarify what we mean by "defined by the study." We are talking here about the patients who were actually entered on the study, not the patients who would necessarily have been eligible for the study, because that is the data we have.

DR. DUTCHER: Okay, well, that is what we want to use. Can we just say as defined by the study population?

DR. JUSTICE: Sure.

DR. OZOLS: Do you want to make another comment about the length of follow-up? Do you want to perhaps address the issue of the limited follow-up available? Does NSABP demonstrate that tamoxifen have a favorable benefit, because as Dr. Simon pointed out, it is a long-term thing. I mean, with the data available now you are actually, I guess, asking us for the short-term follow-up.

DR. JUSTICE: That is fine.

DR. JOHNSON: I actually think this is very important because we are talking about two different things. If we are going to talk about prevention, and the way the question is worded, I think many committee members -- and I am projecting now, would vote one way as opposed to if we changed the wording here. I think it is important to understand what we are voting on, and I would personally argue that we should at least vote on the issue of prevention, and then we can modify later, if you would like,

because I think that will have a bearing on some subsequent discussion that takes place.

DR. DUTCHER: So your proposition is to vote on the question as it stands and then modify the question?

DR. JOHNSON: Right.

DR. DUTCHER: Is that all right?

DR. SCHILSKY: I think we have already sort of agreed by consensus that there is limited evidence for prevention so why go through that exercise?

DR. JOHNSON: Well, it may be a subtle, and it may seem like an arcane point but I think it is an patient point, and I think maybe people have discussed or attempted to discuss that throughout the course of the morning, not only on the panel but the applicant and members of the public.

I personally think it is a very important issue, and I think Dr. Simon's point that he has come back over and over again is the crux of the issue. That is, what population was treated here? If we understand that population very clearly, then we can judge more definitively the risk-benefit ratio, at least for short-term. Prevention is quite different. We have acknowledged that, and I think that is why it is important. I think people may go away, if we don't definitively address the issue of prevention, thinking that we just used a code word for prevention.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: Well, I think we had better be very careful about putting too many extra words also in the question. Somebody suggested, you know, talking about does it do it just for the short term, to the extent that the study was followed, or something like that. When we commit to putting a woman at high risk on an intervention we are committing to whatever happens to this woman for the rest of her life, and her life doesn't stop at the same time that the follow-up was reported or when we took this vote.

DR. DUTCHER: All right, I think we should vote on the question as it stands and then we will modify it. Does the NSABP P-1 demonstrate that tamoxifen has a favorable benefit-risk ratio for the prevention of breast cancer in women at increased risk as defined by the study population?

All those who would vote yes?

[No response]

All those who would vote no?

[Show of hands]

Eleven no; zero yes.

If the answer is no, can the committee identify a subpopulation of the study for which the benefit-risk ratio is acceptable? I guess if the answer is no, can the committee identify where the benefit-risk ratio is a benefit?

DR. SIMON: I guess the way I interpret that is the benefit of administering tamoxifen for 5 years with the intention of having some anti-breast cancer effects. Is there is a set of women that we can identify with that fact that is likely to outweigh the risks entailed by treating that group of women?

DR. SCHILSKY: It seems to me that the intent of this question as modified is that I think we pretty well agreed that as yet there is not compelling evidence for prevention of breast cancer. There may be as time goes by but as yet there is not compelling evidence for prevention. There does seem to be compelling evidence for short-term reduction in incidence.

So, the issue then is can we identify one or more populations of women for whom the risk-benefit ratio favors use of tamoxifen to reduce the incidence of breast cancer?

DR. SIMON: I think when you are talking about risk and benefit you can't stay with the short-term incidence of breast cancer --

DR. SCHILSKY: It will change over time.

DR. SIMON: You know, if we don't think that is likely to translate into some mortality benefit, then how can we weigh that? You know, then it becomes a less meaningful thing. So, the way I view this question is that there are some women who were able to at least delay,

possibly for a very long time, possibly for ever, the incidence of breast cancer. And, we have to treat a whole lot of women and expose all of them to risk in order to prevent a certain number of breast cancers in whatever population we are trying to identify here. When we think about the risk-benefit, then we have to take into consideration that some of those things that we are going to be delaying or preventing, whatever it is, are going to be curable anyway. Therefore, since I think that the reduction in mortality is likely to be small, the reduction of breast cancer mortality is likely to be small, that means that we need to be focusing on a quite high risk population or a population who are not so subject to some of the risks.

DR. SCHILSKY: But the pragmatic issue is, is there any group of women to whom tamoxifen should be given today? I think that is what we are being asked to address here.

DR. SLEDGE: I voted no on this question because of the word "prevention" because we have not discussed risk-benefit in any meaningful sense here so far. We all know what the risks are. I think the study and other studies of tamoxifen give us a pretty good idea of the safety profile of this drug and I think that is unlikely to change over the next decade or two.

So, the real question to me here is the question

of how do we define benefit. Do we define benefit in terms of short-term incidence? Do we define benefit in terms of a survival advantage? If we are going to set that bar then, to be honest, we are going to have to go back as a community and develop an entirely new set of studies, and kind of pretend for the next 20 years that we don't have the results of P-1. That, frankly, is a very difficult proposition for the oncology community. I think that is a real problem that we have to be concerned with here.

DR. SIMON: We know something about the survival rates of node-negative, ER-positive breast cancer.

DR. SLEDGE: I will tell you that having buried several women with ER-positive, node-negative breast cancer I won't take quite as blasé a view.

DR. SIMON: I am not saying it is 100 percent; I am saying we know something about what it is.

DR. SLEDGE: We know it is better than having lots of positive lymph nodes. But, you know, kind of the impression one gets from hearing this discussion is that if we add up thromboembolic events and add up endometrial cancer and add up cataracts, and then add up the breast cancer cases that you can do some sort of mathematical equivalency.

Real life is that when one goes into the clinic with a woman who has a multi-generational history of breast

cancer with her sister, her mother and her aunt who died of breast cancer, that patient may well be willing to accept a different level of risk than your 60-year old who has no risk factors.

I guess the question comes down to really how do we define benefit here, and to what extent do we remove that from the bedside?

DR. MARGOLIN: I think in trying to identify a subpopulation of patients at risk to whom we can apply this data we have to be careful to be aware that this identification of risk factors is a rapidly moving target. BRCA 1 and 2 issues are still to be determined. The patient you just described may be at risk of an ER-negative, node-positive tumor, or may be BRCA 1 positive or not, and we can't extrapolate too much from what little is known about the actual risk factors that were used in this study.

DR. ALBAIN: I think too there is another side we haven't heard today. We haven't heard the advocacy community on the other side of this question, and I would defer to our two members here. The trauma of being diagnosed with breast cancer -- I don't think you can weigh it the same way as getting a pulmonary embolus even though you may, in fact, survive both of those events. I wanted your comments on this issue because it is really difficult to try and put that into the proper perspective. I had

hoped, actually, to hear from the advocacy community on the other side because they were very involved in this trial's development.

MS. CASSEL: I know in my risk population, having a mother and a grandmother that were diagnosed with breast cancer, ER positive, and today I hear you talk about, you know, mortality really isn't any different, but it is your quality of life of life now and you are living now. From the population that I have spoken to in my similar circumstances, these women want a choice -- let me go to my doctor. Yes, we have pulmonary emboli; yes, we have cataracts; yes, we have hot flashes; yes, we have endometrial carcinoma but let me make that choice. As long as I am well-versed and the physician is well-versed and is honest, let me make that choice. Let me, my family and physician make this choice.

To me, personally, I guess if you are talking about endometrial cancer, I can handle that personally. And, that is just me. Maybe someone else can't. I feel I can have more control of that by going for endometrial samplings, GYN visits, etc. But it is more personal, and I think you need to give the women a choice.

But I am afraid, on the other end, that you will have this woman who says, "oh, okay, well, here's my magic pill; this will protect me. I don't need to do my self-

breast exam. I can miss my mammogram. I don't have to follow routine." That does frighten me. So, it is a mixed bag. I don't think there is going to be an easy answer.

MS. BEAMAN: One of my great concerns -- I certainly agree with Debbie -- is that when we leave here today we need to have a clear-cut definition of who was helped by this. Who is this population? Where can we run a reference and say, when we are talking to "Jane Q. Public" that you fall into this risk of even short term and, therefore, you would be a candidate for taking the tamoxifen for the 5 years?

I am also very concerned about the fact that there is a high incidence of breast cancer after that preventive run of tamoxifen in women who did not have cancer before taking the drug.

Maybe we can't clear this up today but we should certainly not mislead anyone by voting in a positive way here today and leaving here, having women all over think that there is that magic pill and it does all of this that the papers have noted up to this point.

DR. JOHNSON: It may be that this is simplistic thinking on my part, but of the patients who did develop invasive breast cancer on the placebo arm -- I am sure NSABP has analyzed that group of women, and what do we know about them? Are there any characteristics that stand out in

that group that, in fact, developed invasive tumors as opposed to the other 5850 women in that arm? I mean, was there something unique about that group that may have identified them as a higher risk, and how did that relate to the 86 women on the tamoxifen arm?

DR. COSTANTINO: There really is no differentiation between the level of risk of the women who got breast cancer and those who did not get breast cancer on the placebo arm.

But I really feel that we need to correct something that has been misstated here twice. The misstatement is that the rate of breast cancer was greater in the tamoxifen arm after the drug was stopped. That is not correct. The rates were the same in the 2 arms after drug was stopped. There was no rebound effect. There was no additional preventive effect but there was no rebound effect.

DR. JOHNSON: And just for clarification, if I may, when you say that there is no difference in these 2 groups, that is not looking at BRCA 1 and 2.

DR. COSTANTINO: That is correct. BRCA 1 and 2 was not included. We do not have that information as of yet. It is based on the factors that went into the risk profiles.

DR. ALBAIN: Since I have apparently misstated

something here, I think it is very important that we have this clarified because we have been given data that states that 34 cases on the placebo arm were diagnosed after stopping the study drug versus 39 on the tamoxifen arm. That is 39/85 versus 34/154. Is this incorrect data?

DR. COSTANTINO: When you are calculating the risk of disease, it is based on the total of women who were at risk not just the number of individuals who got disease. So, it is 39/6000 versus 34 out of approximately 6000. So, that is why the rates are exactly the same.

DR. ALBAIN: Okay, thanks.

DR. DUTCHER: Do you think we can define a population, or should we go on to another question and try to come back to this?

DR. JUSTICE: Well, I mean, that is the question.

[Laughter]

I just want to clarify. Dr. Johnson wanted to vote separately on the prevention question. Do you also now want to vote on the overall population, reducing the short-term reduction in risk? Is that what you would like to do overall, and then, if the answer is no, do that for a subgroup?

DR. JOHNSON: Well, I am having a difficult time, based on the information that has been provided to us, to come up with a subpopulation. I don't see how any of us

could. It would be speculation on our part. I am sure the applicant is going to do a number of analyses over the next several months as they go through these data. It seems to me the only thing we can do is vote on whether the population that was entered into the trial is appropriate for the indication or not. That seems to me to be the only thing that we can do. I think that is going to be a difficult vote but that is my view.

DR. DUTCHER: Dr. Raghavan?

DR. RAGHAVAN: I think we are sort of beginning to set a different standard from the deliberations of the committee over the last few years. In a way, maybe you could say that is okay because we are dealing with prevention issues as opposed to treatment issues. But the way we have approached drugs coming through the committee over a period of time is that we have made our decisions based on the data available.

I have been sitting here, scratching my head for the last three hours, trying to figure out what the rush was to come to this committee because there is a wealth of information there. I mean, this is a fantastic trial. It has been done by one of the best groups in the world. If we turn down the application I think it would be a real shame for anyone to interpret in any sense that it reflected on the NSABP. It reflects on the judgment to come to the FDA

at this time; it has nothing to do with the quality of the data as they stand.

I think the reality is that we are all experts in the field but, unlike Dr. Sledge, we don't have a prescience and --

[Laughter]

-- therefore, we can only look at the data and even Dr. Sledge wouldn't try to influence this committee on his knowledge of what will come down the pike -- quoting his own words back at him.

So, I think one of the problems with the questions is that they were framed in advance of the meeting and we are now wrestling, trying to fit them into a mold that really we can't fit.

I think one of the much more interesting issues that we should come up with today is the question of do we think that another trial needs to be done? Do we have to go back to square one? I personally think not. Or, do we need more data to be extracted from the trials that are extant? You know, we have quoted journal reports. We are fortunate to have Dr. Powles here. But essentially we have not had raw data to look at. The advocates who have spoken, have spoken as if there is something magical in the peer reviewed published press, and there isn't. I mean, the peer reviewed published press will often have less information than we

have heard today.

So, I think all we can do in the context of where we stand is look at the data that are on the table. I don't think we should from now on for the rest of the discussion ask the members of the NSABP to data dredge to try to help us. I think the data are on the table. We can either make decisions based on those with a frame of reference that says we have this information out to this point. I think the NSABP knows as well as we do that curves come together. I think we all have a hunch that these curves won't because breast cancer generally doesn't adopt a zig-zag course but the reality is that we don't know that for a fact.

So, I think instead of trying to fit molds of questions that really may not be appropriate now, after all we have heard, I think we just have to look at the data that are available rather than trying to extract more bits of information in an ad hoc fashion.

DR. DUTCHER: So, we could rephrase the question into does the study demonstrate that tamoxifen has a favorable benefit-risk ratio for a reduction in the short-term incidence of breast cancer, and that becomes the question. Is the benefit-risk ratio sufficient for the reduction in breast cancer as observed?

DR. SIMON: I guess I am a little confused as to what that would mean, in other words, to look only at the

incidence and not worry at all about that might translate into or not translate into. I don't know, I have a little trouble with that.

I guess the other thing is the issue we are supposed to be talking about, "as defined by the study population." You know, I think we haven't received a whole lot of information, at least for the women over 60, in terms of what that study population really looked like.

DR. DUTCHER: Well, we can deal with the information that we have -- I mean, that is what we have to do, and decide whether the benefits to this group of people outweigh the risks as demonstrated in the study. We have, certainly, the short-term risks and we have the short-term benefits.

DR. MARGOLIN: I think that would be consistent with how we chose to vote on question one, and it would be a logical follow-on to our vote on question one. It is just, you know, in women at increased risk as studied in P-1. We have already given up on trying to define the subpopulation.

DR. SIMON: Well, at some point I think you have to take cognizance of the fact that if you are going to say something has a favorable benefit-risk ratio, then it is for some defined group of women and you want to make sure you understand what that definition is and try --

DR. DUTCHER: But I don't think we have enough

information to do that. I mean, I think we really are going to have to go back and look at each subgroup.

DR. JUSTICE: I think that is our job, to get that information from NSABP, but what we are saying is based on the trial results, when we get that all sorted out, what is your recommendation?

DR. RAGHAVAN: Richard, you are torturing us, as only a statistician can.

[Laughter]

You know, the reality is that this group took 13,000 courageous volunteers and, at the end of a lengthy period of time, demonstrated that those people who were exposed to tamoxifen for 5 years and less had less breast cancer, which is a good thing. And we have asked them, and we have shaken them, and we have said tell us which ones you think are the best players, and they said, "we don't yet know," I think the operative word being "yet." Maybe from this data set they will never know, but the answer for us now is "yet." And, you are setting us to a standard that makes us prestigiate because the data just aren't there.

DR. SIMON: I mean, a prevention trial is different than a therapeutic trial, and basically it is different because relatively few proportion of women who get the drug benefit but, yet, everybody is subject to the risk. So, when you say is it worthwhile to treat all of these

women for this benefit, it is more important than typically in a clinical trial, a therapeutic clinical trial, to sort of assess who really was subject to the risks and who really got the benefit, and were there women who just weren't studied enough, with enough numbers, to know whether they got the benefit or not. If so, then you probably wouldn't want to believe that you really knew whether it was appropriate for them.

DR. DUTCHER: Go ahead.

DR. MARGOLIN: I hate to torture the discussion even further but in answer to Dr. Simon's concerns, we could only legitimately do that on pre-stratified factors anyway because subset analysis is not something we want to rely on retrospectively in any case when those factors weren't pre-stratified. And, you can't pre-stratify for factors about the cancers that hadn't developed at the time that patients were enrolled.

DR. SIMON: I mean, I really wasn't looking so much for looking at every subset that benefited. I really was more looking for just a clear description of who were the women who got in the trial and, for example, for the older women who were they in terms of how may risk factors they had, and that sort of thing, to make sure that we have enough evidence that they were represented in this trial and that they would then be included in a recommendation.

DR. RAGHAVAN: The way you could get around that is that you could potentially vote in the affirmative in the phraseology that Dr. Dutcher portrayed, and then put in a caveat that at the present time the specific women likely to benefit have not yet been identified. That could be made as a caveat to the vote, or you can vote no. But you can't do more than that because the data just aren't there. You can't speculate.

DR. DUTCHER: We could put something in saying for women with 5 times the risk. No? You don't like that? We could also ask the question does it demonstrate a favorable risk-benefit for reduction of incidence of breast cancer for women at increased risk as defined by the study population? Then, the second question could be can you define the exact population for which the greatest benefit exists?

DR. SLEDGE: I think we get into real danger when we subset. I agree entirely with Derek. We have a study population. The study was not designed to look at the subsets with any statistical precision. We don't have long enough follow-up to make those judgments even retrospectively. I think we either vote it up or down for the study, not for the subsets.

DR. DUTCHER: Okay. With the limited follow-up available, does NSABP P-1 demonstrate that tamoxifen has a favorable benefit-risk ratio for decreasing the incidence of

breast cancer in the patients in this study population?

All those who would vote yes?

[Show of hands]

Nine. Nine, yes.

Those who would vote no?

[Show of hands]

Two. Two, no.

The next question is dealing with the comparison or at least the evaluation of the other trials, the Italian trial and the Royal Marsden trial. There are a couple of tables to look at.

What effects should the results of the Royal Marsden and Italian tamoxifen breast cancer prevention studies have on the approvability of the indication that the applicant is seeking? If they do not affect approvability, should the results be addressed in the tamoxifen package insert and patient package insert?

Any comments? Dr. Simon?

DR. SIMON: Well, I think the Royal Marsden trial just highlights the fact that there are some women who benefit and some women who don't, and we don't know really at this point -- there is some population that is benefiting from this intervention but it is not really clear what it is.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: Those trials were not scrutinized or reviewed by the FDA reviewer the way the P-1 study was, and I don't think they should be allowed, you know, other than for discussion.

DR. DUTCHER: Dr. Schilsky?

DR. SCHILSKY: I guess I just have one question about the wording. Since the indication the applicant is seeking is use of tamoxifen for prevention of breast cancer, based on our discussion up until now, are we assuming that the wording of the indication would be changed or not?

DR. JUSTICE: Yes.

DR. SCHILSKY: We are assuming that?

DR. JOHNSON: Let me just ask a question and make a comment. I mean, I have heard the comments made by many of the public speakers and our advocates on the panel, and repeatedly the comment has been made that we need information. These are two studies that have, in fact, appeared in the peer reviewed press, although perhaps not as heavily scrutinized as they might have been by the FDA and I will grant Dr. Raghavan's comment that the peer review process may not be quite as stringent as the FDA ODAC process, certainly not as tortuous, but, nevertheless, they have been reviewed and I do think those are data that, at least if I were thinking about going into a trial onto a drug, or if my wife were or my daughter, I think it would be

good for them to have that information. So, the fact that it is in peer reviewed literature would certainly make me comfortable including it. I don't feel impelled to include it but I think I would feel comfortable including it.

DR. JUSTICE: We would certainly characterize it as having been reported, not as having been reviewed.

DR. DUTCHER: I would also like to say I agree with Dr. Simon's interpretation which just focuses more clearly that we don't know who to treat, even if we think there is something positive happening here.

DR. JOHNSON: Well, I think that is what these data show. Distinctions are made in this type of table. Admittedly, it may be fairly sophisticated for the average physician, let alone the average lay person, to try to distinguish all of this information but, nevertheless, it is there. One can refer to it; one can compare and contrast, and understand that there, in fact, is a difference. Furthermore, I think it gives a lot of credibility to the P-1 trial based merely on the size of the trial. I mean, there is so much there that is useful, it seems to me, that it is worth including it.

DR. SLEDGE: I would agree with David. I don't think this alters the approvability or non-approvability but I think it is certainly reasonable information to include in the packet.

DR. DUTCHER: All those who would vote yes on question three?

DR. SLEDGE: Which part?

DR. DUTCHER: We want a yes/no question. Should the results of the Royal Marsden and Italian tamoxifen breast cancer prevention studies have an effect on the approvability of the indication that the risk reduction of breast cancer indication --

DR. JOHNSON: I wonder, rather than voting on this, if it might not be worth just getting the sense of the panel? My personal view is that I think we have heard from Dr. Powels, and we have seen and read these two manuscripts from the published data, I think as has been pointed out earlier by someone we were asked to address the data presented to us. We have not scrutinized these data nearly to the extent that the data that we are currently deliberating has been reviewed.

So, in my view the answer to the first part should be no. I don't think it should have an impact unless we had that data set to review in the same kind of detail.

The answer to the second part, however, is given the fact that these data are in peer reviewed press, it seems to me it is appropriate to include them as information, as Dr. Justice has pointed out, in the package insert.

DR. JUSTICE: Yes, I think if that is the sense of the committee, it is fine with us.

DR. DUTCHER: Fine. Question number four, should tamoxifen be approved for the prevention of breast cancer in women at increased risk as defined in the study or as identified in the answer to question two?

Do you want to vote on this or do you want to get rid of "prevention?" We are going to get rid of "prevention."

Should tamoxifen be approved for risk reduction of short-term incidence of breast cancer in women at increased risk as defined in the study?

DR. ALBAIN: Would you read that again?

DR. DUTCHER: Should tamoxifen be approved for risk reduction of short-term incidence of breast cancer in women at increased risk as defined in the study?

DR. SIMON: Could we change to as defined by the study population rather than in the study?

DR. DUTCHER: All right, as defined by the study population.

DR. SIMON: And, I guess that puts an onus on the FDA to figure out what that is.

DR. DUTCHER: Well, it seems to me that this is a question where we could also put in something about defining an appropriate study population. I think we are back to

where we were.

DR. JUSTICE: I think what we would like you to do is vote on the overall question and then, if the answer is no, if you think there is a population that you can vote yes for, cope with that.

DR. DUTCHER: Either a population or level of risk.

DR. JUSTICE: Either.

DR. SIMON: I mean, I personally am very comfortable with your proposal that we say something about for women at high risk, or even to put in a relative risk.

DR. SLEDGE: Again, this gets back to the subsetting issue. I am very uncomfortable about subsetting on this.

DR. SIMON: It is not an issue of subsetting. It is an issue of saying there is an overall effect but, if your relative risk isn't high, then the risk-benefit ratio is not favorable.

DR. SLEDGE: I understand, but we don't have the data to give us a cut-off. I mean, are you going to use 2.1 percent, 3 percent? If you have that data -- I haven't heard it today -- that would allow me to make that decision.

DR. JOHNSON: George and I may agree on this. Even though we are not sitting next to one another, we are not sending secret signals to one another. I agree. On the

other hand, it also suggests that I have a knowledge of the risk that I am not subject to that would allow me to decide to take the drug. In fact, it seems to me that an individual who is being asked to take the drug has to decide whether that is an appropriate risk or not. Therein lies the conundrum that we are faced with. What the data have said is that at least at this level of risk and beyond, whatever that might be, in the totality of the way the study was conducted there was a reduction in the incidence of breast cancer. So, beyond that it is very difficult for me to distinguish now, and my risk of getting shot walking down the street in Nashville is probably a little less than somebody walking down the street in New York. I am not banging New York --

[Laughter]

-- the point is they are different. I accept that risk and some people accept that risk living in New York.

DR. DUTCHER: In the Bronx.

DR. JOHNSON: Yes, okay, it is higher.

DR. DUTCHER: But on the other side of it, if we can't decide making a patient decide or a subject decide isn't fair at all. And, if I am going to be giving them cards that tell them what their risk for breast cancer is -- I mean, I don't think that is fair either. I think we have to somehow, in our own minds, be able to say, you know,

"here's where you fit into this spectrum, and here's your risk of PE and here's your risk of breast cancer."

DR. JOHNSON: No, we are exactly agreeing. My point is I don't think we can do that. George has pointed out that we have a tremendous amount of information about the side effects of this drug and that this trial, if anything, confirms our knowledge of the side effects of this drug. So, that was good. We didn't find something totally unexpected. There was nothing here that wasn't known about this drug vis-a-vis side effects.

What we did find, however, was that in a group of women at a level of risk or beyond there was a reduction in the frequency of breast cancer. We did learn that. There were certainly lots of side effects. There were side effects in the placebo arm as well. I think all we can say is that for that level of risk or beyond we can approve this drug or not for that indication.

Now, if we want to go further and say, well, in my mind you have to have not 1.66 but 3.0 or 5.0, well, that bothers me. I mean, as a committee we have decided many times before that we want to give full information to the patient, allow the patient and the physician to make the decision at what level of risk he or she may wish to take this medication. It seems to me that we should not artificially set that bar. We should use the data that has

already set the bar, for whatever reason that was selected, and use that and then allow the patient to have that information.

DR. DUTCHER: Dr. Schilsky?

DR. SCHILSKY: Yes, I agree with David. You know, I think the problem is that at any point where we would set the bar would be artificial. If you go around this table and ask people to define which population you think has the optimal risk-benefit ratio, you are going to get a different answer from each of us, undoubtedly. That just reflects the fact that there is going to be a different ratio in every doctor-patient encounter when this is brought up for discussion.

So, I think it is probably unwise for us to try to specify in the context of this discussion some ratio. You know, I am very sensitive to many of the remarks that were made by members of the community at large about concerns that busy doctors are not going to have time to adequately discussion these things with patients, and that hysterical patients are going to be out there demanding tamoxifen, but I think, nevertheless, it is incumbent on the medical community, on the patient advocacy groups, and all who are involved to devote their energies to educating patients and physicians about how to determine risk and benefit in this sort of circumstance, and then let those discussions between

doctors and patients go forward.

DR. DUTCHER: Dr. Ozols?

DR. OZOLS: I agree that I think this is not unique to this drug or this situation. I think physicians very frequently discuss risk-benefit ratios for all sorts of treatments, and it ultimately comes down to a decision between the patient and the doctor. I think we aren't going to be able to say that at some level you must take this drug because that is not going to be the case. So, I think we need to have that option for the patients and the physicians to be able to discuss that and then come to an individual decision.

DR. DUTCHER: But I also do think, as was brought out, that physicians in different fields have different perspectives on the risks. For example, if you talk to a gynecologist about hormone replacement or an oncologist about hormone replacement therapy you may get two different perspectives. So, I don't know that oncologists, in terms of assessing risk-benefit or discussing it are going to be the people that will be discussing it with subjects or with people that would get tamoxifen, frankly, and I think that is where the educational aspects have to come in, in terms of people that have cancer phobia, saying everyone should get a drug that has clearly a risk-benefit ratio that varies with the patients or the subjects that are getting the drug.

DR. SCHILSKY: I do think that is a critically important point because I think essentially all of us around the table are medical oncologists. In fact, you know, we may be participating in counseling some patients but we are not likely to be prescribing this drug for this indication a whole heck of a lot because, you know, the candidates for this are people who don't have cancer. So, they are not the ones who are coming to see us with great frequency, and they are going to be seen in the community by private practitioners, by generalists, by OB-GYNs and so on, and their perspectives and the importance of educating them about this issue I think has to be paramount. So, we need to just send the message that we think the risk-benefit is beneficial for women who are at high risk of breast cancer.

DR. SLEDGE: Actually, I would like to add something to what Dr. Schilsky said. I generally think this is a drug that should be approved because I think doctors and patients should be allowed to decide this issue on an individual basis.

Having said that, I am tremendously concerned about how it is going to be used, and I think for a chemoprevention drug, however so defined, there probably should be a higher bar in terms of doctor-patient communications, specifically in terms of the onus on the company and on the NCI's chemoprevention branch to provide

information to patients about this. I suspect this has never been done, but I would be quite happy making my recommendation dependent upon real evidence that the NCI and the company are going to put real resources into patient education and doctor education on this issue.

DR. ALBAIN: I was just going to say the same type of thing. The sponsor has an incredible and exciting challenge here to be the first out there with this type of approval for breast cancer prevention, and really doing this education process, getting out to the primary care societies, to the gatekeeper physicians who will be seeing this type of patient.

DR. RAGHAVAN: As a coda to that, I think there is a very substantial responsibility to develop a mechanism for following these patients as well because that is clearly what we are all worried about, and that is what the advocacy groups have said. They don't want, and we don't want to see any patients developing a whole series of complications late.

Now, that puts a big responsibility on the sponsor because that sort of thing costs money. I guess what that says is that the FDA, the sponsor and the NCI chemoprevention branch need to figure out a mechanism. That is not our role here. I think our role is to identify what the problems could potentially be, and I think we all

recognize the benefits that NSABP have shown out to 5 years.

We are stuck with the fact that there is a whole alternative lobby out there who never bring their products to the FDA that patients in this situation use every day of the week. We, as a group, probably underestimate outrageously some of the products that have really substantial complications. So, we don't want to set the bar to a level where tamoxifen, with FDA, NCI, NSABP and anybody else's blessing is being kept away from patients when all sorts of other more dangerous products are available. At the same time, we don't want to sanction this and then in 20 years say, "boy, have we got a lot of complications that we've only just discovered!" So, there needs to be a mechanism for monitoring I think if we let this through.

MS. CASSEL: What I envisioned was going to my primary physician, and a decision is made to take the tamoxifen. I envision then being put into a database with the sponsor, being followed up with adverse events that the physician and the patient knew were serious or questionable and then being given follow-up newsletters periodically. So, you are kept in a database and that you are well versed.

DR. DUTCHER: You envision this because you thought it was a good idea or someone told you this would happen?

MS. CASSEL: This is what my blue-sky vision would

be for this compound.

DR. DUTCHER: Has the sponsor considered a registry of tamoxifen prevention people?

DR. JOHNSON: Where I live people try to avoid being in databases like that.

[Laughter]

MS. BEAMAN: I think that it would, indeed, be a blue-sky event. I am a representative of a population that when there is a breast exam or a gynecological evaluation the patient goes to see the OB-GYN. Then, when that happens and you tell them that, you know, "my mom had breast cancer and I know that now I can get it," or, "I've heard of it," and a prescription is written.

DR. DUTCHER: Period.

MS. BEAMAN: That is it. There is no follow-up. There is no nothing. And we are going to see a major blow-out; a major blow-out in that particular population. There is no database. There will be no follow-up. Sometimes the follow-up doctor visits can be the difference between paying rent or not following up on something that could be a very positive indication of uterine cancer or something. But, at the same time, who are the people who were helped? If we clearly define that, then those are the people who will benefit from this particular data.

DR. DUTCHER: Dr. Justice?

DR. JUSTICE: I would just like to comment that we have clearly gotten the message that an extra special education campaign needs to be undertaken, and we will work with Zeneca to see what they are willing to do if you vote yes on the question.

DR. DUTCHER: If what?

DR. JUSTICE: If you vote yes on the question, obviously.

DR. DUTCHER: Okay. Are you ready to vote? No?

DR. SIMON: It says increased risk. Can we say high risk?

DR. DUTCHER: But we haven't defined high risk.

DR. SIMON: Increased means anything greater --

DR. DUTCHER: No, it says increased risk as defined by the study population.

DR. JUSTICE: Yes, I think our intent is to characterize the risk in that population and put it in the labeling, and so it will be indicated.

DR. DUTCHER: You will put tables in?

DR. JUSTICE: We will put as much information in there as we can fit.

DR. DUTCHER: Should tamoxifen be approved for risk reduction of the short-term incidence of breast cancer in women at increased risk as defined by the study population?

All those who would vote yes?

[Show of hands]

Nine. Nine, yes.

Those who would vote no?

[No response]

Those who abstain?

[Show of hands]

Two.

Okay. Question five, in the study participants were required to have a history and physical examination, blood tests including CBC and chemistries, renal function and liver function, gynecologic exams including pelvic and Pap smear, at baseline. Women were required to have had a normal mammogram within the past 6 months. After study entry, a physical examination, breast examination and blood tests were performed at 3 and 6 months and then every 6 months. yearly mammograms and gynecologic evaluation, as defined at baseline, were required.

Does the committee recommend that the package insert and patient package insert should include all of the above protocol-specified monitoring?

Go ahead, Dr. Ozols.

DR. OZOLS: Yes, I think the gynecologic exam and physical exam certainly should be continued. I don't see any indication that you need all the blood tests.

DR. SLEDGE: And a mammogram obviously.

DR. JOHNSON: Unless the applicant tells us that they have looked at that data and they have seen something that would be unique for that study -- presumably no.

DR. DUTCHER: Do you want us to actually vote on that question?

DR. JUSTICE: You don't need to vote.

DR. DUTCHER: Okay. Revised question six, endometrial sampling at baseline and annually was added as a protocol amendment. Four thousand three hundred forty-five women were screened from 1 to 5 times; 26/47 women with endometrial cancer had at least 1 endometrial sampling. One comparison that could be made is shown below. You can see the table.

The detection rate on a per patient basis, not per sampling, was similar with or without endometrial sampling. Twelve women, 0.28 percent of women with sampling, were found to have endometrial cancer on sampling; 4 were randomized to placebo and 8 were randomized to tamoxifen. Six of these women, 0.14 percent of women with sampling, had no antecedent signs or symptoms and diagnosis of their endometrial cancer might have otherwise been delayed. Four of the 6 were found to have endometrial cancer on routine sampling, and the other 2 were found to have complex atypical hyperplasia, which was treated with hysterectomy

and endometrial cancer was found incidentally during pathology review.

Based on the information from this study, should the package insert and patient package insert recommend that women who take tamoxifen for the short-term reduction of breast cancer incidence undergo yearly endometrial sampling?

DR. SLEDGE: No. This is the "OB-GYN employment act of 1998!"

[Laughter]

DR. DUTCHER: What do you think is sufficient?

DR. SLEDGE: My review of the literature is we have nothing other than the patient's symptomatology that really represents a reliable indicator of whether or not the patient is likely to have endometrial cancer, and to mandate a procedure that is of unproven benefit I think would be enormously expensive and would not save any lives.

MS. CASSEL: You don't think it should be done as screening as entry criteria?

DR. SLEDGE: No, I do not. I mean, we are talking about a low -- you know, this is given as a per patient rate. The real question is on any given sampling what is the likelihood of finding endometrial cancer, and the answer is that it is infinitesimally small. So, you are doing a huge number of samplings to get a very tiny benefit, if that benefit is real in terms of early detection of endometrial

cancer, which we don't know.

MS. CASSEL: Unless it is you --

DR. SLEDGE: I have no objection to a patient requesting it, and I have no objection to someone ordering it. I am saying to mandate it in the absence of any data that it is beneficial I think would be very unfortunate.

DR. RAGHAVAN: Yes, I agree with George, and I think the NSABP presentation gave some data, as I recall, a couple of days ago when they first started to speak --

[Laughter]

-- that they were, (a) dropping it from their future protocols and, (b) it was a rationally-based decision that had to do with the pick-up rate from the procedure. They may want to comment on that now but that was my take from either Dr. Wolmark or Dr. Costantino, that didn't influence staging.

DR. DUTCHER: All right. So, all those who would vote yes on question number six, that women should undergo yearly endometrial sampling?

[No response]

Zero.

All those who would vote no?

[Show of hands]

Nine, yes.

All those who abstain?

[Show of hands]

Question number seven, in the P-1 trial, women on tamoxifen had a higher incidence of cataract formation and a higher rate of cataract surgery. Information about non-cataract ophthalmologic toxicity was not collected. Should the package insert and patient package insert recommend that women who take tamoxifen for the prevention of breast cancer undergo yearly eye examinations?

DR. SLEDGE: Again, no. I mean, first, I didn't get a good sense from the data about when these cataracts developed, how many years you had to be on study, or whatever, for the average cataract to develop. Secondly, we are not talking about someone losing their eyesight here; we are talking about someone needing cataract surgery in a small percentage of the cases. You know, the indication for cataract surgery in many cases is that the patient notices a change in vision, not just simply the development of cataracts, as was clear in this trial where, I guess, a fifth of the patients who had cataracts actually went on to cataract surgery.

DR. DUTCHER: Dr. Albain?

DR. ALBAIN: There was additional data from the B-14 population too that did show an increased incidence of posterior lens opacity, which is a rare type of cataract, and I am just wondering if we ought to consider recommending

at least a baseline eye evaluation before women go on the drug.

DR. DUTCHER: You want that in the package insert?

DR. ALBAIN: Yes.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: Just as a modification of that, even though the numbers were hugely higher in postmenopausal women, that is where the p value was highly significant, and since postmenopausal women have a higher incidence of any kind of eye problems maybe it would be prudent to recommend at least a baseline eye evaluation, and then p.r.n. in that population of patients.

DR. DUTCHER: Dr. Schilsky?

DR. SCHILSKY: I guess I am not convinced that it is worthwhile to put this in the package insert. You know, if the postmenopausal women in this study are anything like my mother, they go to the eye doctor about every three weeks, anyway. But I think that the real issue in my mind is whether you are going to take any action based on the test results. You know, if you have a baseline test that shows some cataract formation, I don't know whether that would influence a decision whether to go ahead with the treatment or not. Furthermore, if you had a follow-up test that showed cataract formation, I doubt that would result in your discontinuing the therapy. So, I would feel

comfortable making the risk known without making the recommendation for the exams to be done, and just basing the need for exams on symptoms.

DR. DUTCHER: I don't think we can actually legislate when people go to a physician before they start a medication, and it may add an expense that is unnecessary. But I do think that the awareness should be there that it is a potential problem and that people need to know that they have to evaluate new changes in their vision or other factors.

All right, we will vote. Any other comments? All those who would recommend putting a baseline ophthalmologic evaluation prior to starting tamoxifen in the package insert?

[No response]

All those who would vote yes?

[Show of hands]

All those who would vote no?

Ten. Abstain?

[One hand raised]

One.

Question eight, does the committee have any other recommendations for monitoring the safety of women taking tamoxifen for short-term breast cancer risk reduction?

I think we have made a lot of recommendations in

that respect, and I think seriously people are very concerned that we are sort of opening Pandora's box here but it may be a beneficial opening for several people, and others have to be aware. So, I think we want a strong recommendation for an educational program for both primary care physicians as well as subjects.

Any other recommendations from the committee members? Any specific testing you think should be required? I guess part of that is that we would definitely like some further teasing of the data. Yes?

DR. RAGHAVAN: One test that may just bear a moment's discussion -- I don't want to prolong the agony -- was raised by one of the advocates, the issue of pregnancy and tamoxifen. In general terms, I think once you are on tamoxifen, if one is looking at level of risk, the chance of becoming pregnant is relatively small. But the one issue that might be worth considering is that before starting tamoxifen in a woman of child-bearing years it may be appropriate to consider a pregnancy test before that medication is started. Certainly, if it were one of my family I would feel more comfortable if that were done.

DR. DUTCHER: Any other suggestions?

Question nine, should FDA ask for a Phase 4 commitment to further study participants with thromboembolic events for possible predisposing factors, such as Factor V

Leiden, as Dr. Schilsky mentioned?

DR. SCHILSKY: Sure.

DR. DUTCHER: Yes. How many officially yes?

[Show of hands]

You want to ask a question?

DR. MARGOLIN: It probably doesn't belong here, but is it true what one of the patient advocates said, that patients from the placebo group of P-1 are being routed into the STAR trial so that we are going to lose the follow-up in those patients? Because that sort of affects the answer to this question about follow-up on a large captive group of patients. It would be hard to get Factor V Leiden on a bunch of patients off-study who were being followed, despite Miss Cassel's fancy.

DR. WICKERHAM: We will, indeed, be allowing women who choose, rather than going on tamoxifen off trial, the opportunity of entering a follow-up prevention trial where they would have the opportunity to receive either tamoxifen or raloxifene depending on the randomization and, thus, contribute to that trial as they have contributed to the P-1 study.

DR. SCHILSKY: Kim, just a point of information, the CALGB is about to begin a case-control study looking at frequency of Factor Leiden in women who clot and don't clot on tamoxifen, and would be happy to look at samples from

women who participated in the breast cancer prevention trial as well.

DR. WICKERHAM: Indeed, Dr. Schilsky, Dr. Garber and her associates have already made that offer to us and we have it under review, and plan to move forward with it as soon as possible.

DR. ALBAIN: Could I ask a question just in general about the further study and the participants? What exactly is the follow-up that is funded so far? Is there a chance for longer-term follow-up perhaps, given some of the comments that we have made today? What is the current follow-up planned?

DR. FORD: The current follow-up plan is to follow the women in the trial for another 2 years at the level of follow-up that they have had for the first 5 years, which includes every 6-month visits and the rest. We had made a commitment from the beginning to attempt to do lifetime follow-up but for that, of course, you have to get into more of a passive follow-up mode. We will be discussing that as this trial winds down, the other one starts, and what information we continue to get from that follow-up. But we are committed to following these women for as long as it is possible to follow them.

DR. DUTCHER: And they will be in the NSABP database so there will be follow-up, telephone follow-up,

whatever.

Were there any no responses on question number nine? All yes? Anyone abstaining?

Number ten, should FDA ask for a Phase 4 commitment to further study women on tamoxifen for non-cataract ophthalmologic toxicity, which could be incorporated into a subsequent trial?

Comments?

DR. SLEDGE: I don't have a good sense of this, other than I thought I heard the data presented earlier today to say that there wasn't an increased incidence.

DR. DUTCHER: What are you referring to in this question?

DR. HONIG: I think the question was that in this trial the follow-up specifically collected for cataract-related events and also macular degeneration, but other eye events were not collected, especially because the participants weren't specifically followed for other eye events.

DR. SLEDGE: I am sorry, macular degeneration was followed?

DR. HONIG: Right. Incidence of macular degeneration on study was collected.

DR. SLEDGE: It is hard to have an ophthalmologist look at your macula without noticing some other things. So,

I guess the question is what other examinations are you going to ask them to do?

DR. HONIG: Well, the question was that since it wasn't required, participants filled out a form. So, you were dependent on, you know, hopefully, that they reported those visits but if they were simply told by their ophthalmologist that everything was all right you could potentially miss various events. The question is, you know, do you think the trial is large enough, with the other published data from B-14, that this is really not an issue any more, or do you think there should be more information systematically collected on other eye findings?

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: Could you clarify the last part of the question? Would a retrospective sub-study be just to cull more information from the eye exams of those participants who had them, because otherwise those patients are crossing over or otherwise going on intervention.

DR. JUSTICE: Clearly crossover is a problem. You know, I don't have a study design in mind.

DR. MARGOLIN: So, you are looking for just getting more data onto the case report forms --

DR. JUSTICE: Right. Susan can correct me, but I think the data we have in the database is primarily cataracts and macular degeneration. We do not have the

actual data from ophthalmology exams. I assume that NSABP has but we haven't clarified that yet, I don't believe, have we, Susan?

DR. HONIG: No. We asked NSABP. There were places on the form were participants could write in other problems or other therapies. So, that was on the form but it was our understanding that was not put in the database. Is that correct?

DR. COSTANTINO: Actually, the nurses were asking the participants and they were filling out the forms for them, but that is correct. There are places where other things are written in and, actually, the information was coded according to diagnosis of ICADA codes and we didn't see any differences in some of these other things. The information was collected routinely on all participants and we felt that the information we had was adequate to address the question.

DR. JUSTICE: But just to clarify, we don't have information on the actual eye exams.

DR. COSTANTINO: No, we do not. We did not require documentation of physician reports. We did require documentation of the surgeries but not of the actual eye exams.

DR. DUTCHER: All those who would feel that further ophthalmologic evaluation is necessary of the study

participants, please raise your hand.

[No response]

All those who would vote no?

[Show of hands]

Eleven, no.

I think the Phase 4 information that we want is the long-term follow-up data, and the data in the various subsets, and perhaps what happens to younger patients that are taking tamoxifen, which wasn't really discussed. We would like that information to be followed up.

DR. JUSTICE; I would just like to thank everyone for dealing with this very difficult application.

DR. DUTCHER: Thank you for an excellent trial. All right, we are going to have a very quick lunch. Can we do it in half an hour -- 2:45.

[Whereupon, at 2:05 p.m., the proceedings were recessed, to be resumed at 2:45 p.m.]

AFTERNOON PROCEEDINGS

Call to Order and Introductions

DR. DUTCHER: I appreciate everyone's patience; we have had a long morning. We are discussing Herceptin this afternoon so we have a large number of new people at the table so we are going to again introduce the members of the committee.

I am Dr. Janice Dutcher, from Albert Einstein Cancer Center, in New York, medical oncologist.

DR. O'LEARY: Timothy O'Leary, Armed Forces Institute of Pathology, and I am a pathologist.

DR. MARGOLIN: Kim Margolin, medical oncologist, City of Hope, Los Angeles, California.

DR. MILLER: Carole Miller, Johns Hopkins, consultant from the CBER advisory committee.

DR. SCHILSKY: Richard Schilsky, medical oncologist, University of Chicago.

DR. DOROSHOW: Jim Doroshow, medical oncologist, City of Hope, Los Angeles.

DR. TEMPLETON-SOMERS: Karen Somers, Executive Secretary to the ODAC, FDA.

DR. WEISS: Jim Weiss, from Johns Hopkins. I am a cardiologist and a consultant for the committee.

MS. ZOOK-FISCHLER: Sandra Fischler. I am a patient rep.

DR. VOSE: Julie Vose, from the University of Nebraska and Chair of the FDA Biologics Committee.

DR. LIPSCHULTZ: I am Steve Lipschultz. I am a cardiologist at the University of Rochester.

DR. STEIN: Katie Stein, Division of Monoclonal Antibody, CBER, FDA.

DR. JERIAN: Susan Jerian, a clinical reviewer, FDA.

DR. KEEGAN: Patricia Keegan, Division of Clinical Trials, FDA.

DR. SIMON: Richard Simon, National Cancer Institute.

DR. SEIGEL: Jay Seigel, Office of Therapeutics, FDA.

DR. DUTCHER: We have a conflict of interest statement to be read.

Conflict of Interest

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been

reported by the participants present no potential for a conflict of interest at this meeting, with the following exceptions:

Dr. Robert Ozols, Dr. Kathy Albain and Dr. David Johnson are excluded from participating in today's discussions and vote concerning Herceptin. In addition, Dr. Derek Raghavan, Sandra Zook-Fischler, Dr. Kim Margolin, Dr. Victor Santana, Dr. James Doroshow and Dr. James Weiss have been granted waivers which permit them to participate fully in all matters concerning Herceptin.

A copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office, Room 12A-30 at the Parklawn Building.

In addition, we would like to disclose for the record that Dr. Derek Raghavan and Dr. Richard Schilsky have interests which do not constitute a financial interest in the particular matter within the meaning of 18 USC 208 but which could create the appearance of a conflict. The agency has determined, not withstanding these interests, that the interest of the government in Dr. Raghavan's and Dr. Schilsky's participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Dr. Raghavan and Dr. Schilsky may participate fully in today's discussion and vote concerning Herceptin.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous involvement with any firm whose products they may wish to comment upon. Thank you.

DR. DUTCHER: We would also like to note that Dr. Trevor Powles is going to be joining us at the table as a consultant for this particular topic.

As I mentioned this morning, we have extended the open public hearing to include speakers before the presentations and one speaker after the presentation by the FDA so that we can give as many interested parties as have requested to participate time to participate. We are going to begin this afternoon's open public hearing. We are going to be alternating letters with speakers, and I will let Dr. Somers let you know who everybody is.

Open Public Hearing

DR. TEMPLETON-SOMERS: The first letter is from Alice Hamele, from Farmington Hills, Michigan.

Because I cannot travel to Rockville to be present

at the September 2 meeting, I send these comments and ask that they be read and included in the docket for the meeting.

I have metastatic breast cancer and tested highest positive for the HER2 abnormality. After carefully reading the National Institutes of Health booklet on clinical trials, and after carefully reading the Genentech informed consent, I was randomized into the Genentech trial on February 24, 1997 to receive the HER2 antibody as well as the Adriamycin. Within four months a MUGA scan revealed damage to my heart muscle, and heart dysfunction had been noted symptomatically prior to the scan.

There was some small suggestion of heart risk in the informed consent dated November 21, 1996, which I signed. However, it was suggested that preexisting disease might be the problem. Genentech continued to collect and monitor data and, although these were very serious side effects, and although there must have been increasing indications that the antibody-Adriamycin combination was the culprit, there was no further warning or suggestion of the real problem as of February 24, 1997, when I was enrolled in the trial. I was enrolled and consented on data that were three months old. Genentech did get around to issuing a stronger warning, as an addendum to the informed consent, stating that heart dysfunction was common but, not until May

29, 1997, did NIH declarations state that trial participants will receive ongoing information. It took six months for Genentech to provide ongoing adverse information to participants -- too late for me and, no doubt, for other women.

Breast cancer patients like myself, who entered without complete information, now have disabling heart dysfunction as a cost. And, perhaps a greater cost is that once "poisoned" by the Herceptin-Adriamycin combination, we will never be able to use the antibody agent again to try to extend our lifetimes. We have the worst of both worlds.

I ask that the advisory committee not give approval for Herceptin until such time as Genentech addresses, and agrees in writing, to deal with the costs of all the breast cancer women who have suffered heart damage because complete information was not made available to them when they entered the trial. Thank you for consideration. Sincerely yours, Alice Hamele, Farmington Hills, Michigan.

This and the other letters that have been received from the public are available for you to view at the registration desk. Thank you.

DR. DUTCHER: I will now ask Rosemary Locke to please come to the podium. We would like to ask all speakers to identify themselves and any sponsorship by the sponsor or other organizations for their participation.

MS. LOCKE: Good afternoon. I am Rosemary Locke, a volunteer for Y-Me National Breast Cancer Organization. Thank you for this opportunity to make a statement.

Y-Me is most encouraged by the results from the clinical trials using Herceptin. This is a drug that was developed from the growing knowledge of how cells, particularly breast cancer cells, function. While indicated for only 25-30 percent of all breast cancer patients, Herceptin is the first biological agent to show favorable clinical results in slowing the progression of metastatic breast cancer, but we are also cautious since more research will be needed to answer questions of long-term effectiveness. In addition, we believe further research needs to be done on other indications for Herceptin.

Y-Me was involved with the National Breast Cancer Coalition and Genentech in providing information about the clinical trials to women with metastatic disease. Women would call Y-Me's national hotline and ask specifically about Herceptin and the clinical trials, or they would be given information if their circumstance indicated that they might be eligible for one of the trials. If a woman expressed interest in the Herceptin study, we would refer her to Genentech for eligibility criteria and site location.

We believe that the following quote from Dr. Melody Copely, Director of the Rush Presbyterian St. Luke's

Medical Center, reflects the promise clinicians see in Herceptin that it will make a difference in the lives of women with metastatic breast cancer. She said: The patients who went into this Herceptin trial were in a hopeless situation. I have treated breast cancer patients for nearly 20 years. By the time I treated my third patient with Herceptin I knew that a breakthrough was going on. To see some of these patients resurrect themselves from being totally bedridden to being fully functional was amazing. And, Herceptin didn't cause toxicity. There was no hair loss; no nausea; no vomiting.

In the interest of women with metastatic breast cancer, Y-Me urges the FDA to approve Genentech's application for the drug Herceptin so that it can be made available as rapidly as possible for use in the treatment of metastatic disease.

Thank you. Are there any questions?

DR. DUTCHER: Thank you very much. Next we will read another letter.

DR. TEMPLETON-SOMERS: This letter is from Elaine Doubrava, from Houston Texas.

Next Monday, August 24, 1998, will mark my 95th trip from my home in Houston, Texas to Birmingham, Alabama. These trips started on September 30, 1996 when my name was picked from the HER2 lottery to receive the drug on

compassionate waivers.

I am a 6-year plus breast cancer survivor. My first metastasis was discovered in January, 1995 and I have been in chemotherapy non-stop since then, approximately 43 months. My metastases have been in my liver, spine and brain.

In September, 1996, my liver metastasis continued to grow in spite of aggressive treatments. Knowing my original tumor was HER2 positive, I called the Birmingham location and asked to have my name put in the lottery for the next drawing. I was very fortunate as my name was selected on the first drawing. My first HER2 treatment was October 7, 1996.

My first 12-week checkup was right before Christmas, December 23, 1996. What a gift! My liver lesions had shrunk approximately 73 percent. I was elated and so very grateful to Genentech and Kirklin Clinic.

I realize a cure for my cancer is yet to be found, but Herceptin has certainly afforded me two years of quality time I know I would not have had otherwise. No side effects from Herceptin whatsoever.

I have gone through about 8 different chemotherapy treatments utilizing 14 different drugs. I have been through high dose chemo. After total head radiation, I will probably never have a full head of hair again, but that's

okay, I am alive and I attribute my being alive to Herceptin.

I would like to urge the FDA to approve this drug so that it may get to the many women in need of it as quickly as possible.

I was informed of my first recurrence on my 49th birthday. I never thought I would see age 50. Now, thanks to Genentech and Herceptin I may see birthday number 53. Elaine Doubrava, Houston, Texas.

DR. DUTCHER: Our next speaker is Miss Marilyn McGregor.

MS. MCGREGOR: Thank you. My name is Marilyn McGregor. I am the Administrative Director of the Cancer Support Community located in San Francisco. I have no financial interest in Genentech. The company did not pay for my trip, nor did they read or edit my remarks. The Cancer Support Community received $3000 in 1996 for community support, and a $1000 donation as an honorarium for our board members.

I want to say at the outset that I urge approval of Herceptin and immediate marketing of the drug. It is a great breakthrough and a great chance to extend life for women with refractory cancer. However, women should not have to wait until November for access to this important new therapy. We have waited too long already.

Four years ago this December I, along with two other breast cancer activists, Grace Buflavin and Linda Reyes, under the sponsorship of the Breast Cancer Committee of ACTUP, Golden Gate, held a demonstration of civil disobedience at Genentech's South San Francisco headquarters. Through allies such as ACTUP and Project Inform and other AIDS advocacy groups, and over a long series of meetings we were eventually able to negotiate several major advances for women with breast cancer.

The first was a crossover protocol so that women who showed disease progression were able to get Herceptin. This is a common design in HIV AIDS trials but is not common in breast cancer trials.

Another advance was Genentech's eventual agreement to have an expanded access, compassionate access protocol for those who did not meet the criteria for the various trials. Although modest in number, 200 women over 2 years, the first expanded access trial protocol was a pioneering achievement and the first in the history of breast cancer trials, and Genentech is to be commended for this pioneering effort.

Of course, the National Cancer Institute has always had a variety of compassionate access mechanisms but comparatively few people know of them and utilize these mechanisms. Yet, compassionate access, expanded access is

commonplace in HIV AIDS drug development.

We were pleased that Genentech and NCI finally developed an open-label Herceptin trial for 500 women. But this trial was slow to start up and slow to receive IRB approval in the 40 sites. We had expected the start-up in January-February, but people only began to become enrolled, and the IRBs approved, in June and July. However, at this point women still have to enter a lottery in the NCI-Genentech's trial as there is reportedly a limited supply of drug.

In our meetings with Genentech over the past nine months, the supply issue was reportedly the reason for the continued lottery. Of course, if a company does not a schedule production run there will be insufficient drug. It appears now that the supply of Herceptin is no longer limited.

We have learned that additional Herceptin trials are under way at Memorial Sloan Kettering, M.D. Anderson and in Florida comparing responsive women who overexpress HER2 with women who do not overexpress the protein. Therefore, it is time to end the lottery. All women in the applicant pool should have drug made available to them now. I repeat -- now.

The trial will accrue its full number of applicants and many hundreds of women will have the

opportunity to possibly extend their lives. If this was an AIDS drug that showed the kind of effectiveness that Herceptin has shown, even with the cardiotoxicity, it would have had really fast track approval. Six months is the maximum time for FDA fast track approval. There is no minimum amount of time.

The major labeling issue for cardiotoxicity is in Herceptin. Considering that Herceptin does not have the many other known toxicities of commonplace chemotherapies, this major labeling issue could be resolved in brief focused sessions so that the drug could be ready for marketing in two weeks instead of two months.

I ask that all those concerned about the lottery issue and immediate access contact the FDA or their congressional representatives. The lottery women need Herceptin now.

Thank you.

DR. DUTCHER: Thank you. We have one more letter.

DR. TEMPLETON-SOMERS: This letter is from Dr. Philip Wyatt, who is Chief of the Department of Genetics at the North York General Hospital in Ontario, Canada.

Thank you very much for allowing me to write a letter to be entered into the record regarding the consideration of Herceptin as a possible approved drug.

It would appear from the preliminary research

which is available, the use of the HER2 antibody Herceptin may potentially provide great value in the treatment of certain forms of breast cancer.

Ours is an institution that is involved in seeing a number of women who do have early cases of breast cancer and cases which are advanced and have failed all therapies.

We have been investigating the improved diagnostic capacities of breast cancer and have, as many others, found that the laboratory testing for HER2 overexpression is quite reliable. We specifically use the Vysis-related probes by fluorescent in situ hybridization and we are finding on a double-blinded study that approximately 20 percent of patients who present with breast cancer are overexpressors of the HER2 gene.

It would appear that this is a situation where the technology is advancing over the means by which promising therapies may be introduced. As a result, I am writing the FDA in support of a rapid evaluation and availability for Herceptin.

The dilemma we personally find ourselves in is that we now can accurately and reliably diagnose biological activity which is different in some women who have breast cancer, yet a potential therapy targeted specifically against the biological activity is not available. It creates the dilemma of perhaps not making the test even

available to women who request it or pointing out that, yes, their test is positive but there are no available therapies which are accepted.

I think I truly do appreciate the dilemmas that go on in making sure that appropriate clinical trials are addressed, drugs are appropriately brought to the worldwide health care system in a responsible and well-thought out fashion, and also the complex nature of global health care industries.

One possible solution to deal with these new category of targeted biologicals against gene activities and the like would be a mandated linkage of the companies providing diagnostic laboratory testing, either approved lab testing services or biotech companies, and the pharmaceutical companies producing the Herceptin. A pool of resources could be created from the sale of Herceptin or the lab test, in essence, an FDA tax, and the pool of resources would be used specifically and solely for creating a database and a large worldwide clinical trial investigating the response of HER2 antibody Herceptin for those women who are confirmed to be either HER2 negative or HER2 positive through accredited lab services.

I appreciate the opportunity of at least expressing some of the front-line concerns regarding the changes which are going on in the treatment of breast cancer

and do look forward to receiving a copy of the deliberations of your meetings. Sincerely, Philip Wyatt, M.D., Ph.D., Chief, Department of Genetics at North York General Hospital.

DR. DUTCHER: While the sponsor is setting up the slides, we have Dr. Julie Goldstein who is going to provide an overview.

Introduction of the Issues

DR. GOLDSTEIN: Good afternoon.

[Slide]

I am Julia Goldstein, chair of the CBER committee and product reviewer of the biological license application for Herceptin. The Center for Biologics has been reviewing the Herceptin license application submitted by Genentech which is indicated for treatment of patients with metastatic breast cancers whose tumors overexpress the HER2 receptor. In parallel, the Center for Devices and Radiological Health has been reviewing the immunohistochemistry kit, submitted by DAKO Corporation that, should accompany this product. The indication of the immunohistochemistry kit is to determine patient eligibility for treatment. The immunohistochemistry kit will be presented to an advisory committee next Friday, September 4.

[Slide]

I would like first to acknowledge the members of

the CBER committee: Keith Weber, regulatory coordinator; Susan Jerian, clinical reviewer, and you will hear from her at a later time; Genevieve Schechter, clinical reviewer; Teresa Neeman, statistical reviewer; Dave Green, pharm-tox reviewer; Walter Lange and Lloyd Johnson, establishment reviewers; Debra Bower, bioresearch monitoring coordinator; and Kurt Stromberg, product consultant.

Breast cancer is one of the most common malignancies in women. It accounts for a third of the female cancers in the U.S.A. and remains a serious health care problem. Thirty percent of the primary breast cancers overexpress the HER2 receptor.

[Slide]

During my presentation I would like to briefly describe the following four issues: First, the biology of the HER2 receptor. The second is what is the pathobiological significance associated with the HER2 overexpression. What is the clinical relevance associated with HER2 overexpression, and finally, what is Herceptin and how does it work.

[Slide]

HER2 belongs to the ErbB family. This family is constituted by four receptors. All of them share extensive sequence homology, which suggests similar mechanisms of activation and signaling.

On the right-hand side of the slide are some of the ligands known to bind to each one of these receptors. I want to point out that no ligand has yet been characterized that binds the HER2 receptor.

The current view is that HER2 is the preferred dimer partner for the other three members and functions as a co-receptor, amplifying the signals transduced by the other three.

[Slide]

HER2 is a membrane glycoprotein of 185 kilo daltons. It consists of an extracellular domain, rich in cysteine -- presented in pink, and this will be so throughout the presentation -- a single transmembrane domain and an intracellular domain with tyrosine kinase activity.

HER2 expression has been extensively studied in adult and fetal tissues. Its expression has been shown on epithelial cells derived from three germ layers, in particular, the gastrointestinal, respiratory, urogenic and skin, breast and placenta. It has also been shown to be expressed in neurons, Schwann cells and glia and muscle cells.

The study collaborators have shown that HER2 plays a crucial role in cardiac and central nervous system embryonic development. The mice that carry the null allele die at embryonic age of 11 days due to a dysfunction

associated with a lack of cardiac trabeculation. These mice also had altered development of the neural crest-derived sensory ganglia and motor nerves. These results indicated that HER2 plays a role in mesenchymal-epithelial communications.

[Slide]

What is the physiological role of HER2? HER2 participates in an interactive network of receptor-receptor interactions with a high degree of pathway intercommunications. These interactions regulate cell fate, growth and proliferation.

HER2 acts in a cooperative manner with other ErbB proteins as a shared, low affinity co-receptor for multiple stroma-derived growth factors. Upon ligand binding to each one of these receptors -- and I want to emphasize here, again, that HER2 is in pink -- the tyrosine kinase phosphorylates. The complex of ligand-receptor now heterodimerizes with HER2 which transphosphorylates. The tyrosine kinase now becomes docking sites for multiple substrate and docking proteins, and these culminate in MAP kinase activation and, finally, in the regulation of proliferation, cell survival or differentiation. In other words, this oncoprotein acts as a shared signaling subunit of primary growth factor receptors, prolonging and enhancing signal transduction specifically through MAP kinase.

[Slide]

What is the pathobiological significance associated with HER2 overexpression?

[Slide]

In vitro studies have shown that HER2 overexpression is an important component of neoplastic transformation. Tumors that overexpress HER2 lead to constitutive activation of the receptor, and this translates into an increased proliferation rate and increased resistance to TNF-alpha, decreased expression of adhesion molecules, in particular E cadherines and alpha-2 integrins, which have been demonstrated to be associated with metastasis progression and development, and increased vascular endothelial growth factor secretion which supports new vascular formation.

[Slide]

What is the clinical relevance associated with HER2 overexpression?

[Slide]

Retrospective analyses of clinical data have demonstrated that HER2 overexpression is a negative prognostic indicator. Patients whose tumors overexpress HER2 have shorter disease-free interval and a shorter overall survival. HER2 has been seen as predictive of aggressive disease, regardless of disease stage or node

status. These tumors are more invasive. They have a higher incidence of metastasis, and they are more resistant to chemotherapy.

[Slide]

Finally, what is Herceptin and how does it work?

[Slide]

Herceptin is a recombinant humanized murine monoclonal antibody in which the complement-determining regions, derived from the 4D5 antibody, have been grafted into the human backbone of IgG1. It contains 6 percent of murine residues, and it binds with high affinity to the extracellular domain of the HER2 receptor. Herceptin is produced at large scale in CHO cells and is purified by standard chromatographic procedures.

[Slide]

In vitro studies have demonstrated that Herceptin exerts its effect mainly by two arms. This slide sows the biochemical effects and the next slide will show the immunological arm of the response.

The biochemical effects are pictured inside the circle, and are due to the antibody binding to the HER2 receptor. In vitro studies demonstrated that Herceptin mediates receptor down-modulation, and also heterodimerization blockade. Both of them lead to signal transduction blockade. In addition, Herceptin has a

cytostatic effect. In particular, it up-regulates CDK2 kinase, and also sensitized breast tumor cells to TNF alpha.

[Slide]

Immunological response is due to Fc binding to the Fc receptor gamma-3 of CD16. In vitro studies have shown that Herceptin mediates antibody dependence and cytotoxicity, and it is postulated that the in vivo effect would be the recruitment of CD16 bearing cells to the site of the tumor. Other in vitro assays and animal models have demonstrated enhancement of chemotherapy-induced cytotoxicity. In particular, Herceptin synergizes with cysplatinum and has an additive effect when administered in combination with doxorubicin, paclitaxel, methotrexate and vinblastine.

[Slide]

In summary, HER2 is expressed at low levels. It functions by forming heterodimers with the other ErbB proteins and, therefore, is involved in signal transduction. Overexpression leads to constitutive activation of the receptor. Analysis of clinical data has been associated with poor prognosis.

Herceptin regulates down-modulation of the HER2 receptor. It inhibits dimer formation. It has a cytostatic effect, and is able to mediate antibody dependence and cytotoxicity.

This concludes my presentation.

DR. DUTCHER: Thank you very much. We have now had an overview of the biology and we will now proceed to the sponsor's presentation.

Sponsor Presentation

Introduction and Regulatory History

[Slide]

MR. TRASS: Welcome to the afternoon session of the Oncology Drugs Advisory Committee meeting.

[Slide]

For the next hour, Genentech will present the results of the clinical program for Herceptin, trastuzumab, indicated for the treatment of patients with metastatic breast cancer who have tumors that overexpress HER2.

[Slide]

My name is Karl Trass, and I will provide a brief regulatory history of the molecule. Dr. Steve Shak will take us through the scientific rationale and clinical efficacy, and Dr. Virginia Paton will provide a comprehensive safety analysis. Finally, Dr. Shak will return to discuss the benefits and the risks of Herceptin treatment.

[Slide]

The human epidermal growth factor receptor 2 gene was cloned in 1985, and Genentech has been committed to the

molecule and to the HER2 program since that time. Based on the murine monoclonal antibody 4D5, we developed a recombinant humanized monoclonal antibody, and initiated Phase 1 clinical trials in 1992, and followed with Phase 2 the next year. Based on these encouraging results in which we demonstrated activity and safety, we met with the agency to discuss the clinical program and the manufacturing plans for Herceptin. At that time, we obtained agreement on the Phase 3 protocols and initiated the Phase 3 program the following year. They were only completed in 1997, and in 1998, in March of this year, Herceptin was designated a fast-track biologic. At the same time, we began a BLA submission with the agency and completed the application on May 1 of this year.

[Slide]

Genentech is seeking approval based on two pivotal studies. The first study, Herceptin in combination with chemotherapy in first-line metastatic disease, enrolled 469 women. This trial was originally designed as a placebo-controlled trial.

Accrual to the protocol was slow, and we amended the protocol to allow women who had received prior anthracyclines in the adjuvant setting to enroll and receive paclitaxel as a therapeutic option.

Early in 1996, accrual was still slow. We began

discussions with the agency to amend the protocol to an open-label, randomized, controlled study. However, the primary endpoint of time to disease progression did not change.

Amendment 2, discontinue for placebo, broaden the eligibility requirements, and simplify study procedure to include the discontinuation of cardiac monitoring. This amendment did facilitate enrollment. Early in 1997, we received 4 unexpected cases of cardiac dysfunction. At that time, we alerted investigators, agencies worldwide and, most importantly, the patients of these unexpected events. The third and final amendment reinstituted noninvasive cardiac monitoring.

[Slide]

The second pivotal study, Herceptin as a single agent in relapsed metastatic disease, enrolled 222 women. This protocol was amended twice. First at the suggestion of the FDA, we moved a co-primary endpoint of time to disease progression to a secondary endpoint, but the primary endpoint of response rate did not change.

The second amendment allowed women with one prior chemotherapy regimen to enroll, and also broadened the therapeutic options if patients progressed while on study.

[Slide]

That was a very brief regulatory history. For the

rest of the afternoon, Genentech scientists and advisors will be here to answer any questions you may have. At this time, I will turn it over to Dr. Shak and he will take us through the scientific rationale and the clinical efficacy.

Scientific Rationale and Clinical Efficacy

DR. SHAK: Hello, good afternoon.

[Slide]

My name is Steven Shak, and I appreciate the opportunity today to present the results of the Herceptin studies.

[Slide]

In the last decade, a number of exciting and important breakthroughs have occurred with regard to an increased understanding of the molecular mechanisms that cause cancer. Specific defined DNA alterations, some inherited and some acquired, have been elucidated. In addition, we have defined precise molecular mechanisms by which the growth of cells is regulated. The Herceptin program arose out of the discovery of a specific genetic alteration in breast cancer.

[Slide]

In 25-30 percent of women with breast cancer there is amplification of the HER2 oncogene which is associated with overexpression of the HER2 protein, here shown by immunohistochemistry. Most importantly, it was shown that

amplification and overexpression leads to poor prognosis and shortened survival. This is not just a marker of bad prognosis but, in fact, there is clear evidence that suggests that HER2 amplification overexpression is causally related to the cancer progression.

For example, studies have been performed where the rodent homolog of HER2 is introduced into a mouse, creating a transgenic mouse and, as shown here, the HER2 transgenic females developed breast tumors at a high incidence. It was, therefore, on the basis of this data that HER2 was specifically targeted.

[Slide]

Herceptin is a humanized anti-HER2 monoclonal antibody, highly specific and binding with high affinity to breast cancer cells that overexpress HER2. Genetic engineering created a molecule, as shown here in grey, which is 95 percent human. Murine residues are shown in yellow. It was intended by the humanization to decrease the potential for immunogenicity and to increase the potential for increasing the recruitment of immune effector mechanisms.

[Slide]

Since Dr. Goldstein did such a very nice job, I will briefly summarize the preclinical data. With regard to efficacy, Herceptin is active in cell culture. Most

importantly, it directly inhibits HER2 overexpressing breast cancer cells at a concentration of 1-10 mcg/ml.

[Slide]

As shown on this slide, in experiments performed in the murine xenograft model Herceptin inhibits tumor growth in a dose-dependent fashion, as shown here at 3, 10, 30 and 100 mg/kg doses compared to no effect of the control immunoglobulin. In these studies, serum assays identified that the target trough serum concentration for activity was 10-20 mcg/ml, concentrations that were readily achieved by the human clinical dose.

[Slide]

Finally, studies were performed with Herceptin in the murine xenograft model to evaluate its activity in combination with chemotherapy. Here are doxorubicin and paclitaxel. With both agents it was shown that the combination of Herceptin plus chemotherapy, shown in blue, had the greatest activity, more activity than the antibody alone or chemotherapy. It was on the basis of these studies that the pivotal clinical trials were designed.

[Slide]

Finally, with regard to safety, an extensive series of studies was performed. Studies were performed in animals, examining Herceptin doses at a concentration up to 12.5 times the human clinical dose. It was well tolerated

at all doses. There was no effect on heart rate or ECG. No anaphylaxis was observed. And, as expected, clearance from the serum was slow, with a half-life of 5-10 days. Tissue binding studies showed that Herceptin recognizes epithelial cells from a variety of tissues but no detectable binding was shown with cardiac or neural tissues.

[Slide]

In summary, the preclinical studies demonstrated activity and an excellent preclinical safety profile.

[Slide]

I would now like to turn to the clinical program and then to summarize the results with regard to clinical efficacy.

A series of 10 clinical trials were performed with Herceptin, 5 Phase 1 and Phase 2 studies were performed with Herceptin as a single agent and in combination with chemotherapy which identified that Herceptin was active, which defined that it was well tolerated, and which identified the dose and schedule that was used in the pivotal clinical trials.

The pivotal clinical trials are, first, the comparative study of Herceptin plus chemotherapy versus chemotherapy alone, a randomized, controlled study in women with no prior chemotherapy for metastatic disease. This study, H0648g, enrolled 469 women.

The second study, a study of single-agent Herceptin in more advanced disease, enrolled patients who had relapsed following 1 or 2 prior regimens of chemotherapy for metastatic disease. This study, H0649g, enrolled 222 women.

There are 3 other ongoing studies, first, an open-label extension study for women with disease progression in a comparative trial. Second, a single-agent study in women with no prior chemotherapy for metastatic disease. As described previously, we have had an expanded access program since the beginning of 1996.

At this time, I would very much like to acknowledge a number of key contributors: First, the investigators and their staff that participated and performed these trials; second, the breast cancer patient advocates that advised us, that served on our steering committee and that served on the data safety monitoring committee; and finally, and most importantly, the patients and women who volunteered for this clinical trial. In addition, we have had extensive and useful advice from the FDA, both the Division of Biologics as well as the Office of Women's Health and the Cancer Liaison.

[Slide]

There are two features of the pivotal trials which I would like to discuss specifically because they were key

and important to the conduct of the study. First, as Karl mentioned in the introduction, the comparative trial was amended to remove the placebo.

To maintain and have the highest rigor and objectivity with regard to assessment of the primary and secondary disease progression and tumor response endpoints in this study, we established an independent response evaluation committee which reviewed efficacy on an ongoing basis during the course of the clinical trial. Reading teams were composed of radiologists and oncologists. Only objective tumor data -- films, photographs and physical exam measurements -- were reviewed, and the response evaluation committee remained blinded. They had no knowledge as to whether the patient was on the comparative trial or on the single-agent study, and in all cases they remained blinded to treatment assignment.

Finally, disease progression determined by the response evaluation committee was required in order to get entry into the open-label extension so that no patients on the control arm could get access to Herceptin without documented disease.

[Slide]

The second key feature of this study that I would like to refer to relates to HER2 testing. At the time of the initiation of the pivotal studies there was no approved

diagnostic for measuring levels of HER2 overexpression. To provide rigor and standardization, therefore, we established a central core laboratory which used a standardized immunohistochemistry assay. And, 2+ or 3+ overexpression was required for study entry.

As described by Dr. Goldstein, subsequently we have collaborated with a diagnostics company to develop a commercial immunohistochemistry kit which was studied for its concordance with the clinical trial assay. This kit will be reviewed on Friday, at a diagnostics advisory committee meeting.

[Slide]

With regard to the single-agent study, H0649g, this was a single-arm, open-label study. Women were treated with Herceptin, with a 4 mg/kg loading dose and then 2 mg/kg IV weekly. Efficacy was assessed at regularly scheduled intervals and, as I mentioned previously, tumor response was determined by the response evaluation committee.

[Slide]

Shown here are the demographics of the women enrolled in this clinical trial. As might be expected for patients, all of whom had overexpression of HER2, there is evidence for aggressive disease and extensive prior treatment. More than half the patients, 55 percent, were ER negative. A third of patients, 36 percent, had disease at 3

or more metastatic sites, and 70 percent had disease in the liver or lung.

[Slide]

As required per protocol, all patients had at least 1 prior chemotherapy regimen for metastatic disease, and 32 percent had 1, and 68 percent had 2 prior regimens; 68 percent had prior adjuvant chemotherapy and 26 percent had prior transplant; 94 percent had been treated with anthracyclines and 67 percent had been treated with taxanes previously.

[Slide]

The prospectively defined endpoints of this clinical trial are listed here. The endpoints were assessed and the data will be presented today by an intent-to-treat approach. The primary endpoint of this study was overall response rate as determined by the REC. The secondary endpoints included duration of response, time to progression, survival and quality of life.

[Slide]

Shown here are the results for the primary prospectively defined endpoint of the study. The overall response rate as determined by the REC was 15 percent. There were 8 complete responses and 26 partial responses.

[Slide]

The duration of response is plotted here from

months or time from the initial response. It is notable that in the responders the median duration of response was 9.1 months.

[Slide]

Time to progression was assessed, as shown on this slide. The median time to progression was 3 months and 22 percent of patients were free of progression at 6 months.

[Slide]

Finally, shown here is survival from time of first treatment. The median survival in this patient population was 13 months.

[Slide]

In examining the efficacy in this study, we assessed subgroups in order to examine the consistency of clinical benefit. The confidence intervals for all subgroups examined overlapped the overall response rate of 15 percent.

[Slide]

In addition to the results of this clinical trial, H0649g, that we have just reviewed, we also have data from 2 other single-agent studies. The Phase 2 study, H0551g, showed a response rate of 11 percent. In a preliminary analysis of the results of the single-agent study in women with no prior chemotherapy for metastatic disease the response rate is 24 percent.

[Slide]

In summary, therefore, Herceptin as a single agent is active and induces objective, durable tumor responses. There is consistent evidence of tumor response in subgroups.

[Slide]

We will now turn to the comparative trial. This study enrolled 469 women. Women were eligible if they had metastatic breast cancer, HER2 overexpression, no prior chemotherapy for metastatic disease, and all women had to have measurable disease.

A key feature of this study is shown on this slide. Patients were stratified to chemotherapy based on their history of chemotherapy in the adjuvant setting. Women with no prior anthracyclines in the adjuvant setting were randomized to Herceptin plus anthracycline cyclophosphamide, or AC, or AC alone. Women who had prior anthracycline in the adjuvant setting were randomized to Herceptin plus paclitaxel or paclitaxel alone. We might expect, and in fact did see, that the AC stratum was a population different from the paclitaxel stratum.

[Slide]

Treatment in this study was protocol specified. Herceptin was administered at the same dose and schedule used in the previous study. Chemotherapy was also protocol specified. AC or doxorubicin or epirubicin plus

cyclophosphamide was administered at a standard dose and schedule. Paclitaxel was also administered at a standard dose and schedule. To provide data relevant to the real-world of oncology practice, chemotherapy could be continued for more than 6 cycles at the discretion of the investigator.

[Slide]

We will now examine the demographics of the patients enrolled in this clinical trial. The data is shown on the next 2 slides, and I am going to go through it slowly and focus on 3 major points. First, the population as a whole; second, the balance within chemotherapy stratum; and, third, the balance between chemotherapy stratum.

With regard to the patients enrolled in this study, as was the case with the single-agent study, in women who were all HER2 positive we saw evidence of aggressive disease. A third of the women had a Karnofsky performance status of 80 percent or less. Again, a third had metastatic disease at 3 or more sites. Half were ER negative and a high percentage of the women at primary diagnosis had 4 or more positive lymph nodes.

With regard to balance within chemotherapy strata, randomization was successful. In other words, the population of patients in the Herceptin plus AC stratum was comparable to that in the AC. The group of patients in the

Herceptin plus paclitaxel arm were, again, similar to those in the paclitaxel treatment arm. The only imbalance on this slide that achieves statistical significance is noted with the asterisk here. There was a higher percentage of women with a lower performance status in the paclitaxel alone group, an imbalance in favor of Herceptin.

[Slide]

On this slide is shown prior treatment in the patients enrolled in this study. There was, again, only one imbalance within chemotherapy strata, shown here. In this case, more patients in the Herceptin plus AC stratum received prior adjuvant chemotherapy, 57 percent versus 37 percent, in this case an imbalance in favor of the control group.

Finally, with regard to the demographics, we do, in fact, see that the paclitaxel patients are different than the AC patients. They had more adjuvant chemotherapy and they had a higher percentage of prior transplants. With regard to these imbalances, we incorporated a correction for these imbalances in the statistical analyses that were performed with regard to efficacy.

[Slide]

The endpoints of this study are shown here. The primary endpoint is time to disease progression as determined by the response evaluation committee. The

secondary endpoints included overall response rate, duration of response, time to treatment failure, 1-year survival and quality of life.

[Slide]

This is a Kaplan-Meier plot showing the results of the primary, prospectively defined endpoint of time to disease progression. The percentage of patients free of disease progression or death is plotted as a time from randomization. Shown in yellow are the results for the treatment group of Herceptin plus chemotherapy. Shown in green are the results with chemotherapy alone. Herceptin significantly increases the time to disease progression. The median time to disease progression with chemotherapy alone was 4.6 months versus 7.6 months with Herceptin plus chemotherapy.

As can be seen, at 12 months a greater percentage of women are free of progression when treated with Herceptin plus chemotherapy, 28 percent versus 9 percent with treatment with chemotherapy alone. The overall difference with regard to time to disease progression was statistically significantly different, with a p value of 0.0001.

[Slide]

The results of the analysis for time to disease progression broken out by chemotherapy strata are shown on this slide. For the AC strata we observed a significant

increase in time to disease progression. A median of 6.1 months increased to 8.1 months with Herceptin plus AC. The paclitaxel strata showed a median time to progression of 3 months with paclitaxel alone versus 6.9 months with Herceptin plus paclitaxel. As you can see, the magnitude of the treatment effect is greater with paclitaxel.

These results were done with data that was submitted in our BLA. As noted in the FDA briefing book, we have since, at their suggestion, performed 68 additional reviews of patients in this clinical trial. That additional information shows high concordance, actually, between the investigator and the REC. You have been handed a summary that outlines the updated data analysis for both time to progression as well as the other efficacy endpoints. Those results are consistent with the data which is being presented here.

[Slide]

The overall response rate was also significantly increased by Herceptin. The overall response rate was 32 percent with chemotherapy alone and 49 percent with Herceptin plus chemotherapy.

[Slide]

We saw also increases in overall response rate with AC and with paclitaxel. With AC alone, 43 percent; Herceptin plus AC, 52 percent; with paclitaxel alone, 16

percent; and with Herceptin plus paclitaxel, 42 percent.

[Slide]

We also examined the duration of response. The median duration of response was 6.5 months with AC alone compared to 9.1 months with Herceptin plus AC. The median duration of response was 4.4 months versus 11 months with Herceptin plus paclitaxel. Thus, not only did Herceptin increase the percentage of women who had a tumor response, but in those women who had a response it significantly increased the duration of response.

[Slide]

Time to treatment failure was prespecified and defined as time to disease progression, death, discontinuation of study or discontinuation of Herceptin for any reason, or the initiation of new anti-tumor therapy. Herceptin significantly increased the time to treatment failure when used both in combination with AC and in combination with paclitaxel.

[Slide]

Quality of life in this study was assessed using a validated EORTC questionnaire. Overall, there was no significant difference between groups.

[Slide]

However, trends for maintained quality of life as shown on this slide were seen in patients treated with

Herceptin plus chemotherapy. Shown here is the quality of life domain plotted as change from baseline at week 8, week 20 and week 32. At week 8, during chemotherapy in both groups there is a decline in quality of life. At week 20 and at week 32, there is a trend for maintained quality of life with Herceptin plus chemotherapy compared to a persistent decrease with chemotherapy alone.

[Slide]

Finally, 1-year survival was an important prespecified secondary endpoint. Survival data, as of March 1998, is available in 99 percent or more of the patients. The survival in the chemotherapy alone group at 1 year was 67 percent and was increased with Herceptin treatment to 78 percent, an increase which was statistically significant with a p of 0.008.

[Slide]

In addition, we examined the Kaplan-Meier curve of overall survival for the data available as of March, 1998. The Kaplan-Meier curve, shown here, probability alive plotted as time from randomization in months shows, in yellow, with Herceptin plus chemotherapy the early survival advantage. A difference in survival is observed as early as 6 months after randomization. We are cautious in interpreting this part of the Kaplan-Meier curve at this time.

[Slide]

On this slide is shown the percentage of patients with follow-up at each point in time following randomization. We have a lot of data with regard to the early time points of follow-up. As much as 81 percent of patients have reached a survival follow-up time of 15 months, but only about 40 percent have reached a survival follow-up time of 25-30 months. We clearly look forward to updating the survival data with continued follow-up in order to better define survival in this region.

[Slide]

In addition to the immaturity of the data at this point in time, we also need to note the crossover that was allowed per protocol. With REC documented disease progression, women could get Herceptin in the open-label extension study.

As you can see, even at some of the earlier time points, at 10 months for example, 25 percent of the patients in the chemotherapy alone group entered the open-label extension study and were receiving Herceptin. At later time points almost 60 percent of the control arm patients had received Herceptin. This crossover, therefore, confounds our ability to assess overall survival, and makes this early difference, I think, even more notable.

[Slide]

With regard to survival, we also examined survival at 1 year in both the AC stratum and in the paclitaxel stratum. With AC alone, survival at 1 year was 72 percent and increased to 83 percent with the addition of Herceptin. With paclitaxel alone, the survival at 1 year was 60 percent and increased to 72 percent with the addition of Herceptin.

[Slide]

Finally, as we did in the single-arm study, we also performed subgroup analysis in order to assess the overall benefit. I will take you through the subgroup analysis that we performed in the next 3 slides. Overall, as you will see, consistency was demonstrated. However, testing did indicate a significant interaction between treatment group and the level of HER2 overexpression.

[Slide]

Let me take you through this slide slowly, focusing first on this part of the slide. Plotted here for the primary endpoint of time to disease progression is the relative risk of disease progression where the solid white line at 1.0 would indicate equivalent risk of disease progression between the Herceptin plus chemotherapy group and the chemotherapy alone group. A risk reduction of less than 1, as shown here for the overall population, would indicate that the combination of Herceptin plus chemotherapy is better. A risk ratio of greater than 1 would indicate

that the combination of Herceptin plus chemotherapy is worse.

Shown here for the overall population and then for these patient subgroups that were examined was the point estimate of the risk ratio of time to disease progression, with the lines indicating the 95 percent confidence intervals. Finally, the size of the squares is proportional to number of patients in the subgroup.

The data here indicate that with regard to the subgroups of age, race, Karnofsky score, disease-free interval and number of metastatic sites at study entry, we see that the point estimates for the reduction in the risk of disease progression indicate that Herceptin plus chemotherapy is better. In all cases, the confidence intervals overlap the point estimate of the overall result.

[Slide]

On this slide are shown additional subgroups. We noted that testing indicated an interaction with the level of HER2 overexpression. This interaction can be seen right here. With HER2 overexpression at the 2+ level the risk of disease progression in patients treated with Herceptin plus chemotherapy is a risk ratio of 0.8 compared to 0.4 for those enrolled with 3+ overexpression. As you can see, fewer patients, as indicated by the size of the square, had a 2+ level of overexpression, and the confidence intervals

are broader. Note, however, although there is a lesser magnitude of benefit, these results do not indicate a lack of benefit or that these patients did worse.

[Slide]

Finally, with regard to the last group of subgroups, we again see a consistent evidence of treatment benefit with regard to time to disease progression for all these subgroups that were examined. In no case did the results indicate that Herceptin plus chemotherapy was worse.

[Slide]

In summary then with regard to the efficacy in this randomized, controlled trial, the addition of Herceptin to chemotherapy significantly increases the clinical benefit. Time to disease progression is increased. Response rate and duration is increased. Time to treatment failure is increased, and survival at 1 year is increased.

[Slide]

We will now turn to a discussion of clinical safety by Dr. Paton.

Clinical Safety

DR. PATON: Thank you, Dr. Shak. Good afternoon.

[Slide]

The safety of Herceptin will be described in two settings this afternoon, first as a single agent using data from the pivotal H0649g study and then, secondly, in

combination with chemotherapy using data for the pivotal H0648g study.

As Karl alluded to in his introduction, we identified a cardiac safety concern, and I will close my discussion of the safety of Herceptin this afternoon with a detailed analysis of patients who experienced cardiac adverse events.

[Slide]

In our safety analysis of Herceptin, all patients who received treatment on study were evaluable for safety. Safety was assessed in patients who received Herceptin plus chemotherapy or Herceptin alone on a weekly basis. Patients who received chemotherapy alone in the pivotal comparative study were evaluated every 3 weeks during the period of time of therapy administration and then every 2 weeks once chemotherapy was stopped. Patients were evaluated for safety until the documentation of disease progression. As Dr. Shak provided you with those details, patients who received Herceptin remained on study for a longer period of time. Therefore, patients who received Herceptin were evaluated more frequently and for a longer duration compared to the patients who received chemotherapy alone.

[Slide]

Safety was assessed using a 3-scale system, mild, moderate and severe. Mild adverse events were those events

arm are coded with "H" and are always the first bar in each graph.

Again, globally you can see that many of these adverse events were mild to moderate in severity, and severe events were infrequent. We did observe infusional-related symptoms of chills and fever, headache, and pain with the first dose of Herceptin. We also observed cardiovascular adverse events of congestive heart failure accompanied by cough, dyspnea in Herceptin-treated patients. We also observed some back pain.

[Slide]

We also observed gastrointestinal adverse events that were increased in Herceptin-treated patients, nausea, vomiting and diarrhea, with some metabolic complications of dehydration and hypokalemia. We also observed an increased rate of infection, leukopenia, pharyngitis and insomnia in the antrhacycline treatment group.

[Slide]

The serious adverse events that were observed in the anthracycline treatment arm included an increase in fever, 23 percent in the Herceptin plus anthracycline arm compared to 16 percent in the anthracycline alone arm. However, the rate of sepsis was roughly balanced across the treatment groups, and we also observed pneumonia. We did observe serious events of congestive heart failure, and

cardiomyopathy increased in the Herceptin plus treatment group compared to the control arm.

[Slide]

In patients who received Herceptin plus AC, we observed 111 discontinuations of the 143 patients who were enrolled and treated in this arm. The majority of patients discontinued for reasons related to disease progression, however, 20 patients discontinued Herceptin for an adverse event. The majority of these adverse events were cardiovascular in nature.

[Slide]

Turning now to the paclitaxel treatment group, these are the adverse events that were increased in the Herceptin plus paclitaxel treatment arm. We observed chills and fever and arthralgia that were common to the first dose of Herceptin, and insomnia. We also observed diarrhea, cough, tachycardia and accidental injury. Again, you see a similar pattern. The majority of these events were mild to moderate in severity and severe events were infrequent.

[Slide]

We observed some dermatologic adverse events of acne and rash, epistaxis, hypertonia, herpes simplex, and some infectious complications that were increased with Herceptin treatment.

[Slide]

We observed 2 serious adverse events that were increased with Herceptin. Fever was one but the rate of dehydration was balanced across the treatment groups.

[Slide]

Sixty-five of the 91 patients who were treated with Herceptin in the paclitaxel treatment group discontinued Herceptin. A majority of those, 50 patients, discontinuations were related to disease progression, and 6 patients discontinued for reasons due to an adverse event. Three of those adverse events were cardiac in origin.

[Slide]

We assessed 903 patients for immunogenicity to Herceptin using an ELISA assay. We observed only 1 positive result. This patient is a 49-year old woman who was treated in the open-label, single-agent H0649g study. She had received 9 doses of Herceptin and discontinued the trial on day 65 due to reasons related to disease progression. A serum sample was drawn and the titer was found to be positive. However, upon review of the adverse events at the time of discontinuation, there were no events that suggested an allergy to Herceptin.

[Slide]

Turning now to the cardiac adverse events, I would like to start the discussion by providing you with a background of the safety concern, followed by a discussion

of the procedures and methods used by our cardiac review and evaluation committee, and then close with a discussion of the results of their assessments by incidence severity, outcome and analysis of risk.

[Slide]

A cardiac safety concern was identified after 4 serious cases of cardiomyopathy were reported to Genentech as serious adverse events. The safety concern was unexpected given the prior anthracycline histories in all 4 cases, but was also unpredicted based on our preclinical safety program and our Phase 1 and 2 clinical trial data.

In response to the safety concern, we provided information to our independent data monitoring committee for review, and also alerted our investigators, patients and regulatory authorities, with amendments to our protocols, revisions to our informed consents and investigator brochure. Most importantly, we informed retrospectively an independent cardia review and evaluation committee to assist Genentech with assessment of the severity of this issue.

[Slide]

The cardiac review and evaluation committee was charged with defining the syndrome of cardiac dysfunction, to determine the incidence and assess the severity using the New York Heart Association functional classification scoring system at the time of presentation and following treatment.

The committee was independent of Genentech and not otherwise participating in the clinical trial, and were blinded to Herceptin treatment exposure. The committee was comprised of 2 oncologists who were specialists in breast cancer and 1 cardiologist.

[Slide]

The cardiac review and evaluation committee prospectively defined cardiac dysfunction to include any one of the following characteristics: signs and symptoms of congestive heart failure, a cardiomyopathy that was characterized by a fall in cardiac ejection fraction with hypokinesis that was either global or more severe in the septum, and criteria for decline in cardiac ejection fraction for both symptomatic and asymptomatic patients.

[Slide]

The CREC used the New York Heart Functional Association classification scale to measure the severity of cardiac dysfunction at initial presentation and following treatment. For those of you who are not familiar with this system, here are the key points. It is a 4-class system. Class I patients have no limitations of physical activity. Class II patients have slight limitations of physical activity, and ordinary activity can result in symptoms related to cardiac dysfunction. Class III patients have marked limitations of physical activity and less than

ordinary activity can result in symptoms. Class IV patients, the most severe class, are patients who have an inability to carry on any physical activity without symptoms. They very often are symptomatic at rest.

[Slide]

Here are the results of the CREC review. The review process was intended to be comprehensive and without bias. The committee provided Genentech with search criteria describing cardiac dysfunction. We then applied that search criteria to our safety databases, and provided the cardiac review and evaluation committee with patient profiles for review that contained adverse events, medications, and ejection fractions, and 1024 patients were in the database that was screened by this process.

Out of this initial screening, the cardiac review committee identified 153 patients for complete medical review. The committee was provided with copies of medical records and select data from the clinical trial database for review. From those 153 patients, 97 were diagnosed with cardiac dysfunction. Seven patients were determined to be not evaluable due to lack of complete data for review, and 49 patients were diagnosed with conditions other than cardiac dysfunction. Those conditions in many patients included arrhythmia, tamponade, etc.

[Slide]

Here is the summary of the cardiac review and evaluation committee results by treatment. Again, there were 97 patients diagnosed with cardiac dysfunction. The majority of those patients were participating in the comparative study, H0648g, and a smaller number of patients were receiving Herceptin as a single agent or in combination with other chemotherapies from 3 other smaller studies.

Because the H0658g study is a comparative trial and contains the majority of data in this data set, I would like to spend a couple of minutes discussing the results and analysis of patients in this trial.

[Slide]

This slide details the incidence by treatment group of cardiac dysfunction. The patient subgroup with the highest incidence was in the Herceptin plus anthracycline treatment arm and 27 percent of patients were diagnosed with cardiac dysfunction, which is increased over the 7 percent incidence in the anthracycline alone treatment group. We also saw an increase in Herceptin-treated patients in the paclitaxel cohort and 12 patients were diagnosed with cardiac dysfunction compared with 1 patient in the paclitaxel treatment group, although the magnitude of this increase is not as large as that seen in the anthracycline treatment arm.

The severity of cardiac dysfunction at the initial

event is listed here, and 9 percent of patients in the Herceptin plus AC treatment group had class IV; 7 percent had class III; and 3 percent had class II. All 3 classes were symptomatic at presentation. Six percent of patients were asymptomatic at initial presentation. We saw similar trends in the control arm. Conversely, in the paclitaxel treatment arm there were no patients at initial presentation with New York Heart grade 4 cardiac dysfunction. In fact, many of the patients were either symptomatic or mildly symptomatic at initial presentation. It suggests that the syndrome that we observed in the anthracycline treatment group compared to the paclitaxel group is somewhat different. The syndrome appears to be less frequent and less severe at initial presentation.

[Slide]

Here are the results of cardiac dysfunction following treatment. Again, many of the patients at initial presentation in the anthracycline treatment group were symptomatic, and many of those patients received therapy for cardiac dysfunction, most frequently multiple therapies. Cardiac dysfunction appears to be responsive to treatment, as seen by the shift in New York Heart Association scores.

Following treatment there was no case of class IV cardiac dysfunction; 6 percent of patients had class III, and the majority of patients in this group had class I and

II. However, we did observe 1 death related to cardiac dysfunction in the Herceptin plus AC treatment group. We saw a similar trend in response in the anthracycline alone treatment group, and again saw 1 death related to cardiac dysfunction.

[Slide]

Here are the results post treatment for the paclitaxel treatment arm. Again, many of the patients were moderate to mildly symptomatic at presentation, and we saw an improvement in those symptoms as seen by the shift in the New York Heart functional scores. Nine percent of patients had class I and 1 percent of patients had class II. Importantly, there were no deaths related to cardiac dysfunction in this treatment group. It is very difficult to compare the treated patients to the control patients due to the low percentage of patients with cardiac dysfunction in the paclitaxel alone treatment group.

[Slide]

Again, this safety concern was unexpected, and in order to try to identify patients who might be at greater risk for cardiac dysfunction we performed an exploratory analysis using these following baseline characteristics as possible risk factors for cardiac dysfunction. The only risk that we identified were patients who were treated with Herceptin plus AC. In those women increased age was

suggestive of risk.

[Slide]

We observed cardiac dysfunction in the 3 open-label studies, H0551g, which is the Phase 2 trial; the pivotal H0649g study; and the ongoing H0650g study. These are studies of relapsed metastatic breast cancer for these 2 trials.

The incidence of cardiac dysfunction was comparable in 2 studies, and much less in the ongoing H0650g study. All patients in these studies, with the exception of 1 in the pivotal H0649g study, have received prior anthracycline. Patients in the H0551g study have received either CAF therapy of CA therapy up to 6 cycles.

We did see persistent cardiac dysfunction in some patients who were diagnosed with the condition following therapy, however, again, these are women with metastatic relapse breast cancer who have received prior anthracycline treatment. Importantly, we did observe death secondary to cardiac dysfunction in these studies.

[Slide]

So, to summarize the cardiac adverse event profile, cardiac dysfunction was observed in 7 clinical studies during the Herceptin development program. The greater risk and probability appears to be with Herceptin as concurrently administered with AC chemotherapy. There is a

lower probability, and the condition appears to be less severe when Herceptin is administered with paclitaxel or given as a single agent. Cardiac dysfunction can be severe and life-threatening, however, it is responsive to therapy as seen by the relatively low incidence of persistent cardiac grade III dysfunction in 1 subgroup.

[Slide]

To summarize the overall safety profile of Herceptin, Herceptin appears to be generally well tolerated when administered as a single agent or in combination with chemotherapy.

Most of the adverse events that we observed were mild to moderate in severity, and severe adverse events were infrequent. This includes infusion-related adverse events, the majority being chills and fever with the first dose.

We did observe an increased incidence in cardiac dysfunction when Herceptin is administered in combination with anthracyclines.

We also observed an increased incidence in a variety of other adverse events, the majority of these adverse events being mild to moderate in severity.

Finally, discontinuations for adverse events were infrequent for single agents and for Herceptin plus paclitaxel. The higher incidence observed in patients treated with Herceptin plus AC appears to be related to the

syndrome of cardiac dysfunction.

[Slide]

I would like to turn the podium back to Dr. Shak who will discuss these risks in combination with the benefits.

Summary of Benefits and Risks

DR. SHAK: Thank you. I will conclude by briefly summarizing the benefits, summarizing the risks, and then addressing the net clinical benefit.

[Slide]

With regard to the benefits of Herceptin as a single agent, we have seen that Herceptin induces objective, durable tumor responses.

[Slide]

With regard to the benefits of Herceptin in combination with chemotherapy, the results of the analyses of the randomized, controlled trial indicate that with regard to the prospectively defined endpoint of median time to disease progression, a statistically significant and clinically important difference was observed, both with Herceptin plus chemotherapy compared to chemotherapy overall, as well as in the AC and in the paclitaxel stratum.

[Slide]

Significant benefits of Herceptin were also seen with regard to response rate;

[Slide]

with regard to the duration of response;

[Slide]

with regard to the time to treatment failure;

[Slide]

and, finally, with regard to survival at 1 year. In summary, in this randomized, controlled trial, we saw strong and consistent evidence of benefit.

[Slide]

With regard to safety, Herceptin is generally well tolerated. However, adverse events can be expected based on our analysis of the results of the controlled trials. Infusion-associated symptoms do occur in up to 40 percent of patients, usually fever and chills primarily with the first infusion.

In addition, we have identified an increased incidence of a number of other adverse events which can be expected. Most of those adverse events were mild to moderate in severity.

[Slide]

Importantly, we identified a risk of cardiac dysfunction. The risk was greatest and the incidence was highest in patients treated concurrently with Herceptin plus AC, 27 percent, and lower in patients treated with Herceptin plus paclitaxel treatment or treatment with single agent

Herceptin. It can be expected that with Herceptin plus AC 6 percent of patients would have persistent class III cardiac dysfunction. The incidence of persistent class III cardiac dysfunction is low, as shown, with Herceptin plus paclitaxel or paclitaxel alone.

[Slide]

As we think about addressing net clinical benefit, the benefits and the risks, we have found that 2 of our prespecified endpoints are useful in addressing this issue. First, time to treatment failure. Time to treatment failure balances the benefits of the delay in disease progression or death against the risks, as indicated by discontinuation of study or Herceptin due to adverse events. In both the Ac stratum and the paclitaxel stratum Herceptin significantly delayed the time to treatment failure.

[Slide]

Finally, the most important prespecified endpoint which integrates benefit and risk is survival. With regard to survival at 1 year, survival at 1 year was significantly increased, from 65 percent with chemotherapy alone to 78 percent with Herceptin plus chemotherapy, with maintained quality of life.

[Slide]

This survival difference was seen in both the AC strata and in the paclitaxel strata.

[Slide]

In summary, for women that have tumors that overexpress HER2 and metastatic breast cancer, a particularly aggressive form of this disease, an assessment of the benefits and risks supports the use of Herceptin as a single agent and in combination with chemotherapy. The benefits of Herceptin in combination with anthracycline regimens, however, should be carefully evaluated against the risk of increased cardiac dysfunction.

[Slide]

Finally, therefore, we would conclude on the basis of these data that Herceptin is safe and effective for the treatment of patients with metastatic breast cancer who have tumors that overexpress HER2.

Thank you, and we look forward to answering questions.

Questions from the Committee

DR. DUTCHER: Thank you very much. Are there questions for the sponsor from the committee? Dr. Schilsky?

DR. SCHILSKY: Well, it comes as something of a surprise to me that you said consistently that you had no expectation regarding cardiac events until they occurred. So, I am wondering about at least two types of information. One is what you observed in the Phase 1 trials. Was there any hint of cardiac toxicity? Was there any suggestion that

it might be dose related?

Secondly, I guess in the pivotal trials, at least early on, there was cardiac surveillance built in which was then removed and then reinstated.

DR. SHAK: Yes.

DR. SCHILSKY: But during the initial portion of the trial while there was cardiac surveillance ongoing, was there any suggestion that there was cardiac toxicity developing in those patients?

DR. SHAK: No. With regard to the questions, first of all, our experience in Phase 1 -- we didn't observe any cardiac adverse events. In Phase 2, there were 3 cardiac adverse events that were judged by the investigator and by us to be related to prior anthracycline use. We did assess initially cardiac ejection fractions.

In fact, our first DMC meeting occurred in September of 1996, after the first 50 or 60 patients had been entered into the trial. They reviewed the unblinded data, independent of us, and specifically answered the question did they see any increase in the toxicity of chemotherapy, and at that early point in time they did not report finding an increase.

We did actually identify this unexpected event through the appropriate and careful monitoring of serious adverse events that come in from investigators within 24

hours of their occurrence.

DR. DUTCHER: Go ahead, Dr. Weiss.

DR. WEISS: Dr. Shak, I have a few questions regarding the cardiac adverse event issues. Maybe if you could just clarify this, were there baseline ejection fractions obtained in a large number of the patients in the pivotal studies, pretreatment ejection fractions, by any chance at all?

DR. SHAK: Actually, Dr. Paton can summarize how much we know with regard to ejection fractions.

DR. WEISS: Okay. In the absence of baseline ejection fractions, I guess the follow-up question would be can one easily evaluate the effect of treatment on the presence or absence of any cardiac AEs as well as if you did have the ejection fractions?

You had some numbers for fall in ejection fractions, 55 percent minus 5 percent or 10 percent depending on symptoms. Is that an absolute fall or a fall from baseline? So, that is a very full question.

DR. PATON: So, your first question, to reiterate, is how many patients had baseline cardiac ejection fractions.

[Slide]

Here we have a slide that details that level of information by the 4 treatment groups. We have baseline

data on 13 patients on the Herceptin plus AC, and that is the second line on the graph: 23 patients on the AC alone; 11 patients on Herceptin plus paclitaxel; and 14 patients in the paclitaxel alone group.

DR. WEISS: So, would you comment on the fall from 55 percent or 5 percent or 10 percent? That was then an absolute decrement from 55 percent? Is that correct?

DR. PATON: I would like Dr. Deborah Keefe, who designed those criteria, to clarify that point for you.

DR. KEEFE: Debie Keefe, cardiology advisor to Genentech. That was when we had information available, and it was the actual percentage in primarily patients who were asymptomatic that we used that. In some cases there was data available that had been obtained for other reasons because many of these patients had received anthracyclines. In patients who were symptomatic we accepted a single number if it was low and correlated with symptoms, even though there was not a change.

DR. WEISS: May I ask another follow-up?

DR. DUTCHER: Sure.

DR. WEISS: Given that, I wonder if either of you or any of the three of you might comment on how one might accurately assess whether the cardiac adverse events are true adverse events, or perhaps a reflection of prior disease in some of the patients who didn't have baseline

echoes, or whether the AE is perhaps potentiated by prior disease. Can you sort that out just a bit?

DR. PATON: Dr. Keefe, would you like to comment?

DR. KEEFE: To sort it out as best we can, realizing that we have incomplete data since it was not prospectively collected completely, some of the cardiac events do appear to be real. Certainly, there were true clinical syndromes of congestive heart failure. It is not clear that this syndrome is entirely the same as anthracycline cardiotoxicity. In at least some of the patients there was much more improvement than you would expect from an anthracycline cardiomyopathy. However, there did seem to be an interaction, and the information that is actually most supportive of the fact that Herceptin may have had a role in this is not any of our preexisting information but the fact that it was a randomized trial and we did, in fact, see different numbers. In any given case, these were very sick patients who had multiple reasons to have dyspnea and symptoms of heart failure. As you heard, there was an overwhelming number who had lung involvement, and separating that out could be very difficult.

DR. WEISS: Any thoughts on the mechanism of possible interaction between Herceptin and the anthracycline, because the AE rate in that particular category was so dramatically higher than in patients on

anthracycline alone?

DR. SHAK: At the current time, we don't have any data that directly bears on the mechanism. That is obviously a subject of great interest to us, as well as our academic colleagues.

DR. DUTCHER: Dr. Lipschultz, do you have a question?

DR. LIPSCHULTZ: I also have some questions regarding the cardiac findings. You mentioned before that you had a core lab for your HER2 testing for rigor and standardization. Did you have anything similar for cardiac measurements, or were those just what was reported? Did you have any quality control for ejection fractions or things like that?

DR. SHAK: We asked for ejection fractions to be obtained either by MUGA or echo but, again, since this was unexpected, we did not institute the kind of procedures that you are talking about.

DR. LIPSCHULTZ: For the patients on the study -- we just saw the data for the numbers who had measurements of ejection fraction, did you have numbers for electrocardiograms or biopsy or autopsy findings relevant to the heart in the sense of trying to better understand this? Because at various points in here you speak of tachycardia; you speak of arrhythmias; and I am just wondering if you

have any additional cardiac data along those lines.

DR. SHAK: We actually don't have any additional data that would help with regard to that.

DR. LIPSCHULTZ: So, the electrocardiographic abnormalities were just those that were randomly reported, but it wasn't part of what was collected?

DR. SHAK: Correct.

DR. LIPSCHULTZ: At one point, and I think it was in the FDA supplied information, there was mention of at least histologic appearance of myocardium in one patient. Was there additional information in any other patient? I ask the question I was asking before about biopsy or autopsy.

DR. SHAK: Yes.

DR. LIPSCHULTZ: So, clearly, you have at least one. You don't have anything else?

DR. SHAK: It is just anecdotal, but there are studies that we performed in three cases for which we have data with regard to myocardial biopsy, and a fourth. Dr. Paton?

[Slide]

DR. PATON: We obtained the reports on 4 patients who had biopsies performed. One of these patients is from the single-agent trial and the remaining 3 patients are from the comparative study. In 3/4 patients there was evidence

of some damage. The first patient had received 426 mg of anthracycline and her biopsy was consistent with anthracycline toxicity. The second patient had also received significant anthracycline, however, her specimen was not of a good quality to make any assessment. So the only conclusion was that they could not evaluate it. They saw no evidence of toxicity. The third patient had received 2 cycles of AC on study and had a biopsy performed. There was no inflammation, necrosis or fibrosis, but occasional vacuoles seen in her specimen. In the fourth patient there was evidence for a grade 1 toxicity.

DR. LIPSCHULTZ: Grade 1 anthracycline toxicity?

DR. PATON: There was minimal evidence of anthracycline damage. This is directly out of the pathology reports that were supplied.

DR. DUTCHER: Why were these people biopsied?

DR. PATON: They were biopsied as part of the routine care and investigation of the symptoms that were reported. These patients were symptomatic.

DR. LIPSCHULTZ: Getting at some of these findings, we are focusing on anthracycline potentiation of toxicity, but in the same group they were receiving cyclophosphamide as well which could have an inflammatory pericarditis. I notice a couple of your patients were listed as having pericardial effusions or tamponade. I know

in some of the prior interleukin studies at high dose there was potentiation, and these also have effects. That is why I was wondering if you had any more information that you could potentially have available from patients to try to get a feel for the mechanism.

The other question I have is that in some of your data you speak of improvement in New York Heart Association with therapy. As a cardiomyopathy cardiologist, we usually don't find that to be a particularly useful prognostic scoring system, and certainly in the field of transplant and other things we rely on much more objective criteria.

One of the questions that I have for you is most patients will respond to therapy for congestive heart failure at least transiently. It was not clear to me from you presentation what the interval was between your assessment before and after anticongestive therapy? Because part of your conclusion is that most of these patients will respond that have congestive heart failure symptoms, and what sort of follow-up do you have of these patients?

DR. PATON; The duration of follow-up varied by the onset and length of participation in the trial. We initiated the cardiac review system in late 1997, and it continued through the second quarter of this year. As far as the quality of the response, I would like again to ask Dr. Keefe to comment on the quality of the responses that

she reviewed.

DR. LIPSCHULTZ: But the data that you showed for improvement on anticongestive therapy -- it looked like you had a cut-off on data of December 31. I am just wondering how long after starting anticongestive therapy did you make those slides?

DR. PATON: Actually, to clarify, the majority of the safety data that I presented today was data with the cut-off of December 31. Some of the cardiac data that we obtained was very current and does exceed that cut-off. So, to answer your question about the duration of those responses to anticongestive therapy, Dr. Keefe may want to comment.

DR. KEEFE: Just one additional comment, when we do talk about a longer-term response, we are allowing at least 2 visits, which would be a minimum of 2-4 weeks depending on the exact trial, after the acute event. In most cases, this was the latest information that was available and in several cases many months or years. However, the limitation in this trial was really that these patients had advanced metastatic breast cancer and that disease continued to progression. So, this is very different than our transplant populations where thy don't have another complicating factor. The ones that were not available, for example, couldn't be evaluated because they

developed brain metastases and couldn't walk or had other disastrous complications.

DR. DUTCHER: Dr. Weiss?

DR. WEISS: Yes, Dr. Lipschultz raises some very critical issues in his last set of questions. I just want to follow-up along similar lines. Many, many patients with severe cardiomyopathies and tremendous ejection fractions, as Dr. Lipschultz implied, respond dramatically to very straightforward anticongestive heart failure measures, and sometimes durably, and improvement in symptoms doesn't often equate with marked improvement structurally or even functionally by objective criteria.

I would just like to follow-up on the objective criteria question a little bit. Do you have any follow-up information, for example, on follow-up echocardiograms in those patients who did versus those patients who didn't improve? Was there improvement in ejection fraction by some objective means? And, finally, were there any particular agents that were particularly efficacious in making these patients better, any particular class of agents over other classes?

DR. SHAK: With regard to the cardiac ejection fraction data, again very simply, we did see in the data set some cases in which the ejection fractions did improve with therapy and in some cases they did not. With regard to

treatment, Dr. Paton can address that. The CREC also did document treatment in all of these cases.

DR. PATON: We observed combination therapies employed commonly for the patients in the Herceptin plus AC treatment group. The common combinations were digoxin plus a diuretic, most often Lasix, and an ACE inhibitor. That was a very common combination that we observed in the Herceptin plus AC treatment group. Only 2 patients required either dopamine dibutamine for control. In contrast, the patients who developed cardiac dysfunction in the Herceptin plus paclitaxel treatment group were treated with single agents for the majority, either diuretics or an ACE inhibitor. Digoxin was not a common agent in the Herceptin plus paclitaxel treatment group.

DR. WEISS: Just a final question, did many of these patients or any of them respond to prior pretreatment with dexrazoxane?

DR. PATON: Dexrazoxane was administered primarily to patients who were in the AC treatment cohort. It was administered after approximately 300 mg/m^2 which is consistent with the labeling with dexrazoxane. We could show the slide to see the distribution between the cardiac versus the non-cardiac patients. In patients with cardiac dysfunction, 5 patients received Zinecard. In patients without cardiac dysfunction, 7 in the Herceptin plus AC

group compared to 4 in the AC alone group. We did not control for Zinecard usage in our protocol.

DR. DUTCHER: Dr. Vose?

DR. VOSE: I have a couple of questions on a different topic, to change topics for a minute. In patients with breast cancer and bone disease it is sometimes very difficult to assess their response to therapy. Can you tell me the criteria that they used as far as assessment of complete response and partial response for those patients, and what percentage of the responders had bone disease alone or a major part of their disease as bone disease?

DR. SHAK: In the H0649g study, the single-agent study, patients with bone-only disease were enrolled.

DR. VOSE: In the other studies?

DR. SHAK: In the comparative trial we did allow bone-only disease, which is the case in about 8 percent of cases. So, it was very small. With regard to the assessment, which is the most important issue of progression or response in bone, there was a requirement in the response evaluation charter as well as a requirement for the investigators to document bone disease if it was to be an indicator lesion by objective criteria, most preferably an MRI or a CT scan. So, it was those studies then that were provided to the CREC for their assessments.

DR. VOSE: You were using MRI and CT scans --

DR. SHAK: Right.

DR. VOSE: -- the combination is somewhat difficult because you always have lesions that are left over and you don't quite know what they mean.

DR. SHAK: Right.

DR. VOSE: So, that is difficult criteria. So, you are saying for a complete response in bone-only disease you required that they had absolutely no evidence of abnormality?

DR. SHAK: Our definition of complete response was no evidence of disease. I think there was one case in which that might be questioned in the single-agent study.

DR. VOSE: And one other question with respect to patients. In some of the other similar antibody studies, patients that had failed transplant paradoxically actually had an improved response to the antibody studies, such as the C2B8 study and the B1 study. Did you look at that as prognostic criteria, in particular in the paclitaxel group? Did that account for some of the differences?

DR. SHAK: We actually looked at that in both studies, and that paradoxical effect actually was observed in a single-agent study. In that study, the overall response rate was 15 percent. But in 26 percent of the patients, almost a quarter that had a prior transplant the response rate was over 25 percent. With regard to the

comparative trial in prior transplants, we have it in terms of risk ratios of response, we will get that for you.

DR. DUTCHER: Could I ask you a little bit about the infections that seemed to be at a higher number in the group that received Herceptin? Did you explore that at all? Is it a function of some type of immunological interaction or pure chance, or whatever?

DR. SHAK: We have characterized the nature and severity of the infections.

[Slide]

DR. PATON: As I previously presented, we observed an increase in infection in Herceptin-treated patients. For those adverse events that were consolidated under the term "infection" we observed 2 primary types of infection. The first was upper respiratory tract, colds, viral type illnesses that were easily managed with over-the-counter cough and cold products. Those wee mild and moderate in severity. We also observed catheter-related infections that were probably related to the increased frequency of catheter manipulation for the antibody infusion. Again, many of these infections were easily managed with antibiotics and, in rare cases, removal of the indwelling catheter.

DR. DUTCHER: Dr. Miller?

DR. MILLER: Just getting back to the incidence of toxicities, you talked about that the cardiac events were

unexpected and I want to go back to your Phase 1 and Phase 2 study designs. Did you do dose-limiting toxicity in the Phase 1 study?

DR. PATON: No, we did not.

DR. MILLER: Then, your Phase 2 studies used a different drug, combination of cisplatin and Herceptin, than your pivotal studies. So, the cardiac finding was unexpected in a large trial, I think in some ways, because the Phase 1 studies didn't look at the same population. So, now we are left with trying to determine what chemotherapies we can and can't potentially use in combination with Herceptin. Do we need to do Phase 1 with this drug because we didn't pick this up?

Also, as Dr. Lipschultz said, this is not cytoxan, as you said, and as you dose escalate cytoxan potentially if you want to use these drugs potentially, it is the anthracycline in the AC, not the cytoxan, and how are we going to get that information? Can you just sort of give me an idea of the background about going into a Phase 3 with something that wasn't tested in Phase 2?

DR. PATON: I would like to ask Dr. Shak to explain the development and rationale.

DR. SHAK: A selection of the combination with cisplatin in the Phase 2 was based on very strong and compelling preclinical data. However, it was also clear

that in doing a randomized study it would be difficult to get patients in a control arm to randomize currently to that agent alone. Therefore, we did, in collaboration with our advisers and the FDA, design an appropriate trial that was relevant to answering the question of does the addition of Herceptin add benefit to available regimens that are commonly used.

With regard to the issue of how do we assure safety, that was again one of the reasons why we specifically had the data safety monitoring committee review safety after the first 60 patients. It was, in part, to be diligent about safety in that regard.

With regard to the question about safety with other chemotherapeutic agents, again the best way to evaluate safety is in controlled studies in which safety and ultimately efficacy is carefully established.

DR. MILLER: I have a follow-up question. In the randomized trial you changed your screening criteria with the second amendment and put it back in the third. Does screening for cardiac dysfunction affect the incidence of cardiac AEs? I mean, there was a time period where there was really no real screening. The patients could be as sick almost as they wanted to be as long as the investigator felt that he could -- I mean, the wording for when those patients could go on study was very vague, and I know that was

because you wanted to open enrollment. But is that the time period of the study that was at greatest risk, and when you actually then went back and added some more cardiac screening did your risk go down?

DR. SHAK: We did carefully look at the demographics of patients enrolled in the study, and with regard to eligibility, and although there was a handful of cases that might have been enrolled in the study, because of the change in the eligibility criteria when we looked at the incidence of cardiac dysfunction we saw no relationship to prior disease as being a predictor. So, in that regard, I don't think that there is a relationship. We did pick up this as an adverse event by doing appropriate and careful clinical monitoring both by our investigators and by us.

DR. MILLER: But I guess the question is what was the incidence early on when you were doing monitoring comparing to the incidence when you weren't doing monitoring?

DR. SHAK: Oh, we picked this up mainly related to the rate of enrollment in the study. As the rate of enrollment in the study increased, the number of patients on Herceptin plus AC increased. That was then precisely the point where it went from being just 1 or 2 cases, which is all we were aware of, to being I think at that point 8 at the time at which we decided that this was very much a

possible risk. So, it was the rate of enrollment that drove our recognition and not the change in eligibility per se.

DR. MILLER: Okay. So, we don't have any way we can sort of figure out which patients would be at greatest risk. So, a good screening for MUGA or ejection fraction going into a study, we don't think could be of any help?

DR. SHAK: We don't have data at this point. We have looked at whether we could predict this and, as Dr. Paton presented, when we looked at risk factors at this point, the only risk factor that was identified was in the subgroup of women who were treated with Herceptin plus AC and were of older age.

DR. DUTCHER: Miss Beaman?

MS. BEAMAN: I think I saw standard dosage. Was the dosage of Herceptin always standard or the same whether it was used alone or with chemotherapy, and would that have made a difference in varying that dosage in terms of toxicity?

DR. SHAK: The dosage that was used in both studies was the same. So, we have evidence that addresses the safety and efficacy at the recommended dose. We don't have data to address safety and efficacy at alternative doses.

DR. DUTCHER: Dr. Simon?

DR. SIMON: I have a couple of questions. One,

and maybe I missed it, what was the response rate in the comparative trial to the patients who crossed over to the Herceptin arm? And, what was the nature of their treatment?

DR. SHAK: The question is about the patients enrolled in the crossover study, H0659g. What was the nature of their treatment? We did, in fact, allow standard chemotherapy so a large number of regimens were employed in these patients.

DR. SIMON: I am talking about the patients who initially were randomized not to receive Herceptin and then they progressed --

DR. SHAK: Right, we will have a slide in a second that will show at least the most commonly used agents, and then there were many other regimens.

DR. SIMON: So, some of them received Herceptin at crossover.

DR. SHAK: Yes, they could receive Herceptin at crossover either alone or in combination with other regimens. With regard to your second question about the response rate in the crossover, the response rate overall --

DR. SIMON: Those who received Herceptin at crossover.

DR. SHAK: Yes, the response rate was 14 percent.

DR. SIMON: The other question I have had to do with survival data. It is very unusual in therapeutic

oncology studies to use 1-year survival as sort of the endpoint. Usually you use survival as the endpoint. In fact, a lot of times when people use 1-year survival it is actually very suspicious because people tend to pick the point where the curves are maximally separated post hoc. You indicated that this was defined as an endpoint in the protocol. Is that correct?

DR. SHAK: This was prespecified.

DR. SIMON: And what was the rationale?

DR. SHAK: The rationale was really two-fold. The first was that survival at 1 year is clinically important to patients who are HER2 positive with metastatic breast cancer. The second point did reflect the fact that we knew that there was a crossover and that might mitigate the interpretation of data with long-term follow-up.

DR. SIMON: Did you have patients on the study who were on study for less than one year, who at the time of analysis had entered the study within the previous 12 months?

DR. SHAK: I don't understand the question.

DR. SIMON: At the time of analysis, I guess it was April -- well, when did your accrual close?

DR. SHAK: The accrual closed in March of 1997, and we did our analysis in March of 1998. So we had good follow-up.

DR. DUTCHER: Dr. Doroshow?

DR. DOROSHOW: I have two questions. Could you tell us whether or not left chest wall irradiation was evaluated as a risk factor for cardiac toxicity?

DR. SHAK: Chest radiation was evaluated --

DR. DOROSHOW: Left chest wall irradiation, not irradiation therapy as a whole?

DR. PATON: The data that we collected included a history of radiation therapy, and when the questionnaire was answered "yes" and the patient had left breast disease, we evaluated that as being radiation therapy in the adjuvant setting to the left side. We also included mediastinal radiation in that assessment.

DR. DOROSHOW: In that assessment as separated from the totality of patients getting radiation therapy, was that a risk factor or was it not?

DR. PATON: It was not a risk factor in our analysis.

DR. DOROSHOW: Okay, and could you tell us whether you systematically evaluated whether or not the reinstitution or the continuation of single-agent antibody in patients who had had previous combination chemotherapy and antibody was itself a risk factor for the development of cardiac toxicity?

DR. PATON: Actually, the best setting to evaluate

that is in the roll-over study from the pivotal H0648g study. We do have data on the number of patients from the AC control arm. I think this is your question and please correct me -- no, it is not your question?

DR. DOROSHOW: The question is not whether or not there was reinstitution of antibody after patients had AC, it is whether patients continued. Some of those patients had had it before and continued antibody. The further exposure to additional antibody, was that itself a risk factor?

DR. PATON: No, by and large, that was not a risk factor. Many of the patients in the Herceptin plus AC treatment group discontinued for reasons of the cardiac event, and those patients who continued, their conditions did not appear to worsen either by physician assessment, changes in medication and so forth. So, the majority of patients appeared to do well with reinstitution of antibody.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: I have some questions that are all in some way or another related to HER2/neu expression on breast cancer. The first question is that I think somebody said that in the single-agent study there was an apparently higher response rate, although I don't know what the p value was for the small subgroup of patients who had undergone transplant, and I wonder if anybody went back and found that

that correlated with the high level of HER2/neu expression since those may be patients who presented with higher risk multiple node disease.

DR. SHAK: I don't think we have the ratio of 2+ to 3+ in the patients with prior transplant.

DR. MARGOLIN: Okay. The other related question is there has been a rumor around, and I don't know how far around it has gone, that there is a possibility that metastatic lesions are more likely to express HER2/neu than primary lesions. I think most of us screen only the primary blocks and I assume that is what was screened in this study. So, it is sort of a two-part question. I wonder if there is any validity to that. Then, the second part is that at some point I guess we are going to have to talk about the screening test for HER2/neu positivity that is going to be recommended for patient treatment selection, and the difference between the outcomes of patients who were 3+ positive and patients who were 2+ positive.

DR. SHAK: Dr. Slamon, could you address the issue of HER2 positivity?

DR. SLAMON: To my knowledge, there have been two large studies looking at metastatic and primary lesions, and there is no difference between metastatic lesions versus primary lesions. I have heard the same rumor, but when you look critically at the data that is published, as well as

some of the banks that people have, and we have a pretty extensive bank also, that doesn't appear to be the case. What is in the primary is in the metastasis. If it is a single copy, it remains a single copy. If it is multiple copy, it remains multiple copy at the same level.

DR. DUTCHER: Dr. O'Leary?

DR. O'LEARY: Yes, I would like to follow-up on some of these issues having to do with getting the patient into the study in the first place. I apologize if they seem not germane but they may be relevant to the meeting on Friday as well.

How many different sites -- not meaning body sites but clinical sites, did the initial biopsy materials come from for evaluation by the core laboratory?

DR. SHAK: For the vast majority of patients, the analysis at the core laboratory was done on the original tumor blocks from the primary diagnosis.

DR. O'LEARY: Right, but I am asking how many different hospitals or medical centers had these blocks been originally --

DR. SHAK: I don't know the exact number but I am sure very many.

DR. O'LEARY: One of the things that affects the ability to assess things immunohistochemically is differences in fixation protocols, time in which things

remain in fixative. Was there any evidence of heterogeneity from one site to another in the percentage of patients whose tumors appeared to be HER2 expressors?

DR. SHAK: Our pilot studies identified some of those same concerns with regard to slides. So, it was for that reason that with regard to this study we requested original tumor blocks and, therefore, at the core laboratory sectioned and stained them in a reproducible manner.

DR. O'LEARY: But that handles the determination after its gotten into the paraffin block, and immunohistochemistry is a total test system in which the treatment of the tumor prior to the time that it hits paraffin is also important in some cases in determining immunoreactivity. In particular, because the test system that you used in this study is different than the test system coming up on Friday, and because that won't be assessed against original patient response data it is really vital to understand, to the degree possible, whether any of these sort of pre-analytic factors can be discounted.

DR. SHAK: The pre-analytic factors, as I said, were not controlled but I guess the good news here is that we did, in fact, simulate what will likely be real-world testing as we go forward.

DR. O'LEARY: The second set of issues is that in real-world testing sometimes people will end up using

different tests than the ones that FDA may have approved to go into patient selection. I mean, we heard a letter, for example, from a FISH laboratory and this is popular in some places. There are a number of different antibodies against HER2/neu. Have you explored any of these in your investigations?

DR. SHAK: We have no data on the use of FISH or any of those other technologies.

DR. O'LEARY: Okay. And, the last question is sometimes in patients that present with metastatic disease assessments are being made on the basis of cytologic preparations, fine needle, and the question is has fine-needle aspiration as a source of material ever done in the course of any of these investigations?

DR. SHAK: I am sorry, could you repeat that?

DR. O'LEARY: Were fine-needle aspiration specimens used in the determination of immunoreactivity in any of these cases, or were they all regular biopsy tissue blocks?

DR. SHAK: In my recollection, the vast majority were tumor blocks. There were fine-needle aspirates but the core laboratory tested their procedure with regard to those fine-needle aspirate samples as well.

DR. O'LEARY: Thank you.

DR. DUTCHER: Last question, Dr. Schilsky?

DR. SCHILSKY: Maybe I can squeeze in two questions. First an efficacy question, in the randomized trial, and specifically in the paclitaxel portion of the randomized trial, it is somewhat striking that the response rate to paclitaxel alone in a group of patients getting essentially first-line chemotherapy for metastatic disease is 17 percent. It is also striking that when you add Herceptin which by itself has very little activity in metastatic disease, albeit in a more advanced patient population, the response rate zooms up to 41 percent. So, I am wondering if you could help us interpret those data, both with respect to why is the response rate so low to paclitaxel alone, and why is it so much better when Herceptin is added.

DR. SHAK: Dr. Norton, would you like to address this?

DR. NORTON: The answer is that these are the data. I mean, this is what happened. And, the nice thing is that it corroborates what was seen in preclinical systems. I mean, there was true synergy, not just an additive effect. The biochemical mechanisms for this still remain obscure but it is a major component of our program to try to figure that out. But, clearly, in the preclinical systems there was synergy between these agents, not just additivity. I think the clinical data that you see here

really substantiates that.

DR. SCHILSKY: The synergy may explain why it is better when you add Herceptin but why is it so bad with just paclitaxel?

DR. NORTON: Again, you know, this is why one does randomized trials, because you can't anticipate what the response rates are going to be. As Rich Simon told me many years ago, you can't argue with a p value. You know, the fact is that these were very poor prognosis patients, as you can see. Many of these patients really had extensive therapy in the adjuvant setting and very poor prognostic factors, and were quite sick with a lot of disease, and so a very low response rate to paclitaxel in that very sick patient population is not totally unexpected.

DR. SCHILSKY: If I can just ask one other question about the cardiac toxicity because I still don't have a real good sense of just how sick the patients were, particularly those who were on Herceptin with AC. You showed us data about the incidence of cardiac toxicity at the time it was diagnosed and at the time after treatment. But how bad did it get? In other words, after it was diagnosed it might have gotten worse before it got better. So, do you have any data on the worst case, the worst cardiac toxicity that was observed? And, for those patients who improved, they all improved pretty much to some extent,

but those patients who had persistent clinically symptomatic cardiac toxicity, how long did that last? Did it last for the rest of their lives? And, on average, how long was that?

DR. SHAK: Dr. Keefe, again, you reviewed the medical records for all of these patients.

DR. KEEFE: You will hear more information about the worst point coming up, but it was, in fact, very similar to the presentation. Most of the people were symptomatic at rest, not constantly necessarily. Some did transiently get worse and then got better. Overall, most of them did improve substantially, and it was the breast cancer that further interfered with the qualify of their life. There were, particularly in the Herceptin plus AC arm, some patients that had real significant heart failure despite therapy.

DR. DUTCHER: Thank you. What is your pleasure? Break or keep going? Break? Short break, five-minute break.

[Brief recess]

DR. DUTCHER: I think that we will begin.

FDA Presentation

DR. JERIAN: My name is Susan Jerian, and I am pleased to present the FDA perspective on the biologic license application for Herceptin, submitted by Genentech.

[Slide]

This BLA was filed May 4, 1998, and I just want to go through briefly the series in which we have received the data, which has been in a rolling fashion prior to that date and, in fact, after that date. The efficacy supplement was submitted May 22, 1998; safety update, July 7, 1998; another efficacy update which, in fact, was information that we requested on the additional patients that we asked the sponsor to go back and analyze, who had not been analyzed yet by the REC, was received just a week and a half ago. We have completed those analyses in a week and we will present those data here today. Additional information is being requested by the FDA and we are awaiting that in order to complete our review.

[Slide]

Genentech's proposed indication for Herceptin reads as follows: Herceptin is indicated for the treatment of patients with metastatic breast cancer who have tumors that overexpress HER2.

[Slide]

The clinical studies that I will be concentrating on and devoting 99 percent of my presentation to are 649, the Phase 2 study with Herceptin as a single agent enrolling 222 patients, and 648, the Phase 3 study which was a randomized, open-label study comparing chemotherapy with and

without Herceptin enrolling 469 patients.

[Slide]

There were additional reports from other studies submitted to the BLA. There wee 3 Phase 1 studies --

[Slide]

-- and 4 additional Phase 2 studies, 2 of which still remain open to enrollment: 650 is a study of patients receiving Herceptin as a single agent for first-line therapy and 693 is the expanded access trial which you have already heard about.

[Slide]

In my presentation, first I will provide you with our review of our design and efficacy results for the Phase 2 and then for the Phase 3 study. Following this, I am going to present an integrated summary of the immunohistochemistry data as it relates to the efficacy endpoints for the Phase 2 and Phase 3 study, and then an integrated safety summary, finishing with my conclusions.

[Slide]

As you have already heard, this Phase 2 study, submitted for consideration, is a single-arm study of Herceptin, conducted at 54 sites internationally with a target enrollment of 200 patients. Those patients enrolled had metastatic breast cancer with measurable disease, and had to have been positive on their tumor biopsies for

expression of HER2/neu protein by immunohistochemistry at the level of 2+ or 3+. Patients must have progressed after 1 or 2 prior chemotherapy regimens for their metastatic disease.

[Slide]

I will not go over this slide. You have already received this information on the dosing.

[Slide]

Once a patient progressed on the study, they had 3 choices. They could discontinue treatment; they could continue to receive Herceptin at the same dose with or without chemotherapy or hormonal therapy; or they could continue with Herceptin at double the dose with or without chemotherapy or hormonal therapy. The additional therapy was not given in a randomized fashion. It was simply left up to the patient and their physician.

[Slide]

The primary endpoint was overall response rate, which was defined as the sum of the complete and partial responses which had been sustained for at least 4 weeks as defined by the response evaluation committee. The secondary endpoints were duration of response, time to progression, time to treatment failure and survival.

[Slide]

You have already heard a great deal about the

response evaluation committee. I just want to point out a couple of factors. I think the committee functioned quite well and they stuck to their charter very consistently, and did a very good job in assessing tumor measurements or scans that were supplied to them and information that was supplied to them in a consistent fashion.

Their character was somewhat limited in that they could not call pleural effusions or ascites as malignant effusions unless they had pathologic evidence of disease. In addition, bone disease evaluations were somewhat limited in that physicians were not requiring all sites of bony disease unless patients were symptomatic at the sites. So, we don't always have follow-up information on bony sites of disease, except in the patients who have bone-only disease where there was good follow-up. Finally, the size of lesions was limited to 1 cm but there are many patients who have lesions right at that cut-off. As you know, with CT scans sometimes a 1 cm lesion can be missed on subsequent scans, and at times that makes tumor assessment difficult.

[Slide]

There were 222 patients enrolled, and 213 of these received treatment. If we look at reasons for treatment discontinuation, 7 percent stopped due to death; 5 percent by patient request; and 3 percent for adverse events; 1 patient was lost to follow-up.

[Slide]

Looking at the baseline demographics, you can see that this group had a fairly high incidence of poor prognostic factors. A third were ER/PR negative, had progressive disease less than a year from their primary, and two-thirds had positive lymph nodes at their initial diagnosis.

[Slide]

In terms of prior therapy, one-third had received 1 regimen of chemotherapy for their metastatic disease, and two-thirds had received 2 prior regimens. A quarter of patients had received transplant.

[Slide]

Now we have the efficacy results, the primary endpoint of overall response rate. This is the FDA analysis based on our review of all the case report forms, data submitted from the REC, in addition to adverse event reporting. Our numbers, as I will point out in a minute, differ slightly from the sponsor's and I will explain those differences.

The overall response rate was 14 percent with a median duration of response of 9 months. Of these, 3 percent of patients were complete responders, and we have not been able to give a point determination for median duration at this time due to immaturity of the data. The PR

rate was 11 percent.

[Slide]

The patients in whom there is a difference, and actually one of these patients we do agree on now -- 2 of the sponsor's patients whom they called CR, complete response, we called partial response.

The reason for 1 patient is that she had a persistent pleural effusion without evidence of congestive heart failure, without evidence of ongoing infection, no other etiology, and at her because evaluation it was deemed as a site of metastatic disease but the REC couldn't call it that because they didn't have the pathology.

One patient had bone metastases at enrollment but was never imaged after baseline. So, we could not call her a CR.

There were 3 patients that the sponsor called partial responses that we called non-responders or, in fact, were not evaluable for response. Some of that had to do with technical reasons. One person actually received 4 separate regimens of irradiation therapy to 4 different bony sites of disease over a 5-month period, and we felt that that may be clinical evidence of progression and so we didn't feel comfortable calling her a responder.

[Slide]

The median duration of response, as I mentioned,

was 9 months, and this gives you a little bit more of a feel for the distribution of the data. For the complete responders I have listed the individual durations, and for 4 of those patients, as you can see, we don't have complete follow-up. Those are the asterisk patients.

[Slide]

Median time to progression was a secondary endpoint, and was 3.1 months; time to treatment failure, 2.3 months; and median survival was 12.8 months.

[Slide]

This is a Kaplan-Meier plot of the survival for patients in the Phase 2 study. The aqua lines are the 95 percent confidence intervals and the yellow line is the survival curve. Basically, this is not a comparative study so we really can't say anything more than that this is simply the survival for this population.

[Slide]

So, in summary of the Phase 2 study, the overall response rate was 14 percent, with a median duration of response of 9 months, and a median survival of 12.8 months.

[Slide]

I am not going to go into too much of the study design for the Phase 3 study since you have heard a great deal about it. I will mention that patients were randomized by geographic region, metastatic site and prior

anthracycline therapy. Also, I will refer to Taxol as paclitaxel but I think Taxol is maybe known to more people than paclitaxel.

[Slide]

Patients enrolled in this study were to have metastatic breast cancer with measurable lesions. Again, they had to be 2+ or 3+ positive by immunohistochemistry, and have received no prior chemotherapy for metastatic disease. Patients could have brain metastases if they were stable and treated, and there was a general statement about eligibility where patients must be suitable candidates for receiving concomitant cytotoxic chemotherapy as evidenced by screening lab assessments of hematologic, renal, hepatic, and metabolic function.

[Slide]

I think you have already heard a great deal about treatment.

[Slide]

When a patient progressed on this study, they had 2 choices. They could discontinue or they could enroll into study 659, which was the extension study for 648. On 659 patients could receive Herceptin with or without chemotherapy or hormonal therapy, and this was up to the investigators, not in a randomized fashion.

[Slide]

The primary endpoint, as you have already heard, was median time to progression, and secondary endpoints were overall response rate, duration of response, time to treatment failure, survival and quality of life. I will not be commenting on the quality of life data at this point because our analysis is not complete.

[Slide]

I want to take a moment to discuss the differences that occurred in the trial as it proceeded in terms of study design. You have already heard some of these things mentioned in that the original protocol was modified in order to increase enrollment and make it more attractive to breast cancer patients to participate in the study. As you know, Taxol was added as an option for chemotherapy.

As far as immunohistochemistry staining, initially one antibody was used, the 4D5 antibody which is the parent antibody to Herceptin. Subsequently another antibody, CB11, was added and patients could be positive with either/or antibody.

Bone-only disease was initially not included, and subsequently allowed provided lesions were lytic and measurable in 2 dimensions. Brain metastases were not initially allowed and subsequently included if patients had received treatment and had stable metastases in the brain.

[Slide]

Cardiac assessment, as you heard, was required at baseline but not subsequently, and then further amended, as you heard, after that. Laboratory cut-offs were defined clearly in the beginning and subsequently eliminated. The statement that I read to you earlier was put in its place. Tumor assessment time points were increased by a few weeks and that is somewhat relevant to time to progression determinations. Initially there was no crossover study, the 659 study. That was added to allow breast cancer patients who wished to receive Herceptin the opportunity to do so after they had progressed if they were on the control arm. Subsequently that was put in effect.

[Slide]

I want to point out that some of these changes lead to issues that are relevant to the analysis of the data. First, the patients treated with paclitaxel had very different prognostic factors and, as you have already seen, were a different population. Therefore, we had to rely heavily on subgroup analyses.

Eligibility criteria were broadened considerably. There was a lack of baseline cardiac data for all patients. For some patients we did have it, but that made assessment of risk factors for cardiotoxicity very difficult.

The survival analysis is limited by the fact that patients did cross over and received Herceptin. So, we

can't say after the crossover that the effect was solely due or not due to Herceptin.

[Slide]

There were 469 patients enrolled in 118 sites. Most sites had less than 5 patients enrolled. Five patients were not treated, 2 on the Herceptin arm and 3 on the control arm.

[Slide]

These are the figures for enrollment. The first 2 rows are Herceptin plus chemotherapy and chemotherapy alone. You can see equivalent enrollment basically. Then, for the subgroups, AC-Herceptin, AC alone, paclitaxel-Herceptin and paclitaxel alone. As you can see, about 40 percent of the patients received Taxol and 60 percent AC.

[Slide]

The data that we have received, which has an earlier cut-off, shows that 33 percent of patients had enrolled into this extension study. Most of those are from the control arm. We haven't received the updated data. There are additional patients who have been enrolled since that time.

[Slide]

There were 11 patients whom we categorized as early deaths in that they died within the first 30 days of the study. In our analysis of cause of death not due to

Herceptin, 7 were in the Herceptin arm and 4 in the control arm. These patients in general were extremely ill at entry and, in many cases, did not meet the "spirit" of the patient selection criteria.

[Slide]

You have seen this data already on the baseline demographics for the randomized groups -- Herceptin plus chemotherapy versus chemotherapy alone, so I am going to go on to the next slide.

[Slide]

It is quite balanced between the 2 groups. This is prior therapy.

[Slide]

The main difference I want to point out is when you compare those patients who received AC therapy versus those who received paclitaxel. There are marked differences in prognostic factors and prior therapy. The number of patients who had positive lymph nodes is nearly doubled. More patients had mastectomy. This is all increased in the paclitaxel group. Nearly double the number of patients who received prior adjuvant chemotherapy, and no patients in the AC group received transplant, whereas 18 percent of the paclitaxel patients had.

[Slide]

Sites of metastatic disease was a stratification

factor, however, the definition that the sponsor used differed somewhat from what we interpret as standard practice in clinical trials in oncology in that lymph node disease, distal lymph node, supraclavicular nodes were classified by the sponsor as visceral disease. We classify that as soft tissue or superficial disease. So, we repeated the analysis just to ensure that those factors were comparable throughout and, in fact, they were on our reassessment.

[Slide]

Non-protocol defined chemotherapy or hormonal therapy was considered a protocol violation on this study. There was a slight imbalance in that more patients on the control arm received such therapy, primarily cytotoxic chemotherapy, and this was a variety of regimens that the investigator chose to give to the patient.

[Slide]

We also looked at possible differences in cumulative dose, and the most striking data was for the paclitaxel groups where the median number of cycles was greater by 1 in the paclitaxel-Herceptin subgroup compared to Taxol alone, and the number of patients who received more than 6 cycles of chemotherapy was increased by 9 percent.

[Slide]

I just want to comment here briefly that there is

some evidence that there is a paclitaxel-Herceptin drug interaction in that the serum concentration of Herceptin is increased in patients who received paclitaxel compared to Herceptin patients from alternate studies who received Herceptin alone. This is associated with decreased clearance. This was seen in the preclinical studies in monkeys and seen in humans in the clinical study.

[Slide]

We also looked at the data in terms of why patients chose to stop therapy, and one element that stood out was adverse event as a reason in patients in the AC-Herceptin arm, 17 percent compared to 1 percent of patients in the AC arm, and also slightly increased in the paclitaxel-Herceptin arm versus Taxol. Discontinuation of therapy on this slide refers to discontinuation of Herceptin, discontinuation of Herceptin and the chemotherapy, or discontinuation of the chemotherapy.

[Slide]

On this slide we looked at discontinuation of Herceptin independent of chemotherapy, which is why we don't have the 2 control arms here. We see that adverse events still stand out as an imbalance between the AC-Herceptin compared to the paclitaxel-Herceptin group.

[Slide]

The FDA analysis of the efficacy endpoints

consisted of a review of every case report form, the adverse events, and incorporating standard oncology practice.

[Slide]

This is basically the curve that you already saw, and it is the Kaplan-Meier estimate of time to progression in all patients. The yellow line -- and, actually, the color choice was independent of the sponsor; we both think the same on this -- the yellow line is the Herceptin patients and the green line is the chemotherapy alone patients. What you see is that the curves separate early and continue to stay separate throughout, and that there is fairly complete data in that the curves go almost to because, particularly the control curve.

[Slide]

And, pulling out the AC patients, we still see significance with a p value of less than 0.001.

[Slide]

Pulling out the paclitaxel patients, the effect is more impressive.

[Slide]

The specific numbers for median time to progression for the Herceptin plus chemotherapy group, we determined at 7.3 months compared to chemotherapy alone at 4.5 months.

[Slide]

Looking at the subgroups, there was an improvement in the AC arms by 2.1 months and for the paclitaxel arms 4.2 months improvement in median time to progression.

[Slide]

The secondary efficacy points that I will discuss are overall response rate, duration of response, and survival.

[Slide]

Again, in determining response rate we looked at all the case report forms and additional data that the sponsor submitted on their analysis of 69 patients who hadn't been seen by the REC. We found that in the Herceptin-chemotherapy arm the response rate was 43 percent, and in the chemotherapy alone arm 29 percent, with a p value of 0.001.

[Slide]

Looking at the subgroups, the difference was more striking for the Taxol-Herceptin compared to Herceptin alone subgroup.

[Slide]

Median duration of response for the Herceptin plus chemotherapy group was 9.3 months, and for chemotherapy alone 5.9 months, so improvement there as well.

[Slide]

Here we see that the improvement is carried

through within the subgroups.

[Slide]

Looking at the survival of all patients treated in the pivotal study, we have to keep in mind that the data after a year are immature and it is difficult to come to conclusions about median overall survival. If we look at this curve, we would determine that it is the same because the curves come together. If you look at 1-year estimates, they are separate for a period of time prior to coming together but, again, it is very difficult to come to any conclusions because of the immaturity of the data.

[Slide]

This is what the curves look like for the AC patients.

[Slide]

And, for the paclitaxel patients actually the curves do remain separate.

[Slide]

So, in summary for the Phase 3 study, there is an improvement in time to progression for patients on the Herceptin arm, both overall, 2.8 months, and in the subgroups, 2.1 months for AC-Herceptin and 4.2 months for Taxol-Herceptin.

[Slide]

The response rate of patients treated with

paclitaxel was significantly improved by the addition of Herceptin. The response rate of patients treated with AC was not significantly improved by the addition to AC. However, the absolute difference trended in favor of the Herceptin arm.

[Slide]

The ability to make conclusions about the median overall survival is limited because the data are not mature at this time. The 1-year overall survival is improved in the Herceptin arm, both overall and in the subgroups.

[Slide]

The treatment effect was greater in patients enrolled and treated in the paclitaxel subgroups than in the AC subgroups.

[Slide]

Now I want to go on and look at the efficacy endpoints in light of patients baseline assessment for level of HER2/neu protein overexpression, 2+ and 3+.

[Slide]

As I mentioned already, the initial antibody used for screening was 4D5 which is the parent antibody to Herceptin. It binds to the extracellular domain of the HER2 receptor. They subsequently added the use of antibody CB11 which binds to the intracellular domain of the receptor. The PMA filed for test kit is a polyclonal antibody. It is

neither of these antibodies, and it binds to the intracellular domain.

The indication that they are seeking for the test kit is for the selection of patients to treat with Herceptin. The assessment of the immunohistochemistry is semi-qualitative on a scale of 0-3, where patients who are 2+ and 3+ are determined as positives. In the test kit filed with the Center for Devices for licensing -- I just want to mention briefly that there are patients with that kit who tested as 2+ who would have tested negative by the concordance study in the pivotal study. That is a point I just want you to keep in mind.

[Slide]

This is the distribution of HER2 positivity by level of expression and, as you can see, it is very consistent. A quarter of patients were 2+, three-quarters of patients were 3+.

[Slide]

We looked at response rate by level of expression, and what we found in the Phase 2 study with Herceptin as a single agent is that there were more responders percentage-wise in the 3+ group than in the 2+ group, 17 percent versus 4 percent.

[Slide]

We then looked at response rates in the Phase 3

pivotal study, and we saw a similar effect where the patients on the Herceptin-chemotherapy arm who were 2+ overexpressors had a response rate of 32 percent, which was the same as the response rate on the chemotherapy alone arm of 33 percent. But when we look at 3+ overexpressors, there is a significant increase, 47 percent versus 27 percent.

[Slide]

We then looked at the data of the pivotal study in terms of median time to progression, and we looked at 2+ patients versus 3+ patients. I think you can see here that for the 2+ patients, whose data are shown on this slide, the curves overlap, with a p value of 0.56.

[Slide]

On this slide are the 3+ patients, and this curve is more reminiscent of the treatment effect that you saw earlier in the slides that I showed for the pivotal study, not separated out by 2+ and 3+, such that the curves separate early and remain separate throughout.

[Slide]

If we can go back to the previous slide, if we take the difference between these 2 curves --

[Slide]

-- and we compare it to the difference in these curves, there is an interaction, and that is significant as well, with a p value of less than 0.05.

[Slide]

Again, we did the same thing with survival. This is the survival plot for the 2+ patients.

[Slide]

And, this is the survival plot for the 3+ patients.

[Slide]

So, in summary of the immunohistochemistry data, there is a higher response rate among 3+ patients as compared to 2+ patients treated with Herceptin alone as second- or third-line therapy. Patients with tumor scored as 3+ had higher response rates when Herceptin added to chemotherapy compared to patients with tumors scored as 2+.

[Slide]

The addition of Herceptin to chemotherapy improved the median time to progression by 4.1 months, and improved survival among 3+ patients. The addition of Herceptin to chemotherapy did not improve median time to progression or survival for 2+ patients. There is a significant interaction between the level of overexpression and the effect of Herceptin on time to progression.

[Slide]

Now I want to turn to the safety data, and I will be dealing with the Phase 2 and Phase 3 studies together.

[Slide]

We will look at Herceptin as a single agent, Herceptin in combination with paclitaxel, and Herceptin in combination with anthracycline plus cyclophosphamide.

[Slide]

You have already heard a considerable amount about the infusional toxicity. We are in complete agreement with the sponsor's assessment. Nearly half the patients experienced one form or another of this toxicity. It primarily occurs with the first infusion. Patients experienced chills, fever, pain, sometimes pain at the site of the tumor, asthenia, nausea, vomiting and headache. Rarely hypotension occurred. These symptoms are self-limited and easily treated with standard medications.

[Slide]

Now I want to turn to the cardiotoxicity issue. We analyzed the data basically the same way that the sponsor's cardiac response evaluation committee did, using the same criteria of New York Heart Association classification and ejection fraction. However, we looked at the patient's worst status in our analysis.

[Slide]

This is a summary of the incidence of cardiotoxicity in the subgroups of the pivotal study, and the last column is the Phase 2 study of Herceptin alone. The black shaded area is patients who experienced class III

or class IV events, and the red shaded area is patients with less severe events, class I and class II. The sum of the 2 is the total percentage in each group.

For the AC-Herceptin group, the percentage is 28 percent; for AC alone, 7 percent; for Taxol-Herceptin, 11 percent; for Taxol alone, 1 percent. The Taxol alone patient, I just want to note, actually had staphylococcal endocarditis, and her ejection fraction was 71 percent, but we did include her because she did have a severe cardiac event.

The events that occurred in the AC-Herceptin arm in general were more severe than those that occurred in the AC arm. As you have already heard, some patients did require dopamine, dibutamine. One patient actually developed left ventricular dilatation, developed a thrombus to her brain, and was left aphasic and, I believe, hemiplegic.

6:00 pm [Slide]

The paclitaxel-Herceptin arm, if you compare it to paclitaxel alone, also has a considerable increase in the number of cardiac events though, as far as severity, they tended not to be as severe as those in the AC-Herceptin arm. We did see cardiotoxicity when Herceptin was administered alone, although this was in a group of much sicker patients. All but 2 of them had received prior anthracycline therapy

but those 2 patients had significant cardiac disease at enrollment. So, it is difficult to sort out that data.

[Slide]

We were trying to look at the events in terms of cumulative anthracycline dose received by the patients, and we divided it into those who had received less than 300 mg/m^2 and those who had received 300-450 mg/m^2, which actually would be the majority of patients, and those who received higher doses, above 450 mg/m^2. At the lowest dose group we saw 12 percent incidence overall of class III and IV events compared to AC alone where we saw none. In the mid range we saw 25 percent when Herceptin wa added to AC compared to 3 percent with AC alone. In the higher dose levels there was a smaller difference, 27 percent versus 20 percent.

[Slide]

Actually, the sponsor did this analysis too in their submission, and we also did the same analysis. This is comparing the cumulative anthracycline dose to the proportion of cardiac events in the population overall. I think most oncologists are used to seeing these curves. The yellow is the Herceptin group and the green is the control. These are only the AC patients. These do not include Taxol patients.

As you can see, if you look in the vertical

dimension, there are marked differences even at the lower doses. At the doses at which you would see most patients treated, the minimum number of cycles of this barring toxicity was 6 cycles, which was 360 mg/m^2, which falls right about here. Some patients continued to receive more than that. So, do see this sharp increase.

Now, the data further out -- these are much fewer patients who received higher doses, but the point of this is that the curve is shifted to the left for the Herceptin group.

[Slide]

We assessed death due to cardiotoxicity as 2 occurring in the AC-Herceptin arm and 2 in the AC alone arm; none in the Taxol subgroups. This could have been death due to cardiotoxicity and breast cancer but, as was mentioned already, it is sometimes difficult to differentiate the two and sort it out, but we certainly felt that the cardiotoxicity contributed significantly to the death of those patients. One of the AC patients died after she crossed over to the extension study and received Herceptin.

[Slide]

We also looked at past medical history for cardiac disease, prior radiation therapy to the chest, age and we really found no factor that was significantly associated but certainly all could play a contributory role. It is simply

difficult to tell because we don't have enough data to say. Dexrazoxane, as you know, was administered to some patients but did not appear to prevent cardiotoxicity.

[Slide]

Now I want to move on to hematologic toxicity. In evaluating the data that was submitted, the adverse event listings do list leukopenia, neutropenia, and anemia as events. However, some patients, if you looked on their medication listing, may have received blood transfusions but not have been recorded as being anemic, or required G-CSF or GM-CSF but not necessarily listed as neutropenic.

So, when we analyzed the data we did a composite, such that we looked at leukopenia related events and anemia related events. For the leukopenia related events we looked at leukopenia or neutropenia, making sure not to count patients double if they had both recorded; use of G-CSF or GM-CSF; and incidence of febrile neutropenia or neutropenic sepsis.

For the anemia related events we looked at any recordings of anemia, use of erythropoietin and any blood transfusions that were administered. A blood transfusion event was counted as one event no matter how many units were administered.

[Slide]

What we see here is that in the AC-Herceptin group

the incidence of leukopenia related events was 67 percent compared to 46 percent in the AC group. It was also increased with the Taxol subgroups, 32 percent in Taxol-Herceptin versus 24 percent.

For anemia related events there were also increases, not so great but still present in the AC-Herceptin compared to AC and Taxol-Herceptin compared to Taxol alone.

[Slide]

We also noticed that gastrointestinal toxicity was increased in the patients who received Herceptin and chemotherapy compared to chemotherapy alone. Here you can see that diarrhea is almost doubled in the AC patients and in the Taxol patients. If you look at patients who received Herceptin alone prior to crossing over within that study after the progressed, the incidence was 27 percent. Similarly, with abdominal pain we see increases in the Herceptin groups.

[Slide]

There were increases in the incidence of infection, 46 percent in the Herceptin plus chemotherapy group versus 30 percent in the chemotherapy alone group. The incidence in the single-agent study was 20 percent.

Neurotoxicity incidence was increased in the Taxol-Herceptin group but our analysis reveals that this is

most likely related to the fact that these patients received considerably more Taxol, but there was an increased incidence of paresthsias, peripheral neuritis and neuropathy. We can't necessarily attribute that to the Herceptin.

[Slide]

So, in summary of the safety data, Herceptin alone produces an infusional toxicity, cardiac toxicity and GI toxicity. Herceptin plus chemotherapy also results in infusional toxicity and increases of cardiac, gastrointestinal, hematologic and infectious toxicities.

[Slide]

Now I am going to present my conclusions overall.

[Slide]

Conclusion number one, Herceptin is active as a single agent in patients with metastatic breast cancer who have progressed following one or more prior chemotherapy regimens for metastatic disease.

[Slide]

Tumor responses can be durable, with a median duration of 9 months, and are seen in visceral, soft tissue and bone metastases.

[Slide]

Patients with tumors scored as 3+ in the Phase 3 study have a higher tumor response rate than those scored as

2+.

[Slide]

When administered as first-line therapy in combination with AC or paclitaxel chemotherapy regimens, Herceptin improves median time to progression by 2.8 months overall compared to patients receiving chemotherapy alone.

[Slide]

A greater clinical benefit is observed by the addition of Herceptin to paclitaxel than is observed by the addition of Herceptin to AC chemotherapy.

[Slide]

In an exploratory analysis, clinical benefit from the addition of Herceptin to chemotherapy was limited to patients with tumors scored as 3+, as opposed to 2+, for overexpression of HER2/neu protein by immunohistochemistry. Patients who were 3+ had improved time to progression, improved response rates and improved survival.

[Slide]

The 1-year overall survival is improved in the Herceptin plus chemotherapy arm, however, the data are not mature enough to assess the median survival at this time.

[Slide]

Moving on to safety conclusions, Herceptin commonly produces an infusional toxicity which is self-limited.

[Slide]

The addition of Herceptin to AC or to paclitaxel chemotherapy results in a marked increase in the incidence of cardiotoxicity.

[Slide]

Cardiotoxicity is frequent and severe in patients receiving AC plus Herceptin.

[Slide]

The incidence of hematologic and infectious toxicity is increased when Herceptin is added to AC or paclitaxel.

[Slide]

Herceptin produces gastrointestinal toxicity whether administered alone or in combination with AC or paclitaxel.

[Slide]

For the last few conclusions, these address some limitations of the development program. Only one schedule of Herceptin administration has been studied. It is not known if a shorter duration of therapy is equally beneficial or provides an improved safety profile. Basically, on both studies patients received Herceptin from the time of enrollment until progressive disease. No other schedules have been studied.

[Slide]

The combination of Herceptin with antineoplastic agents other than AC and paclitaxel is primarily anecdotal. It is not possible to make conclusions regarding the efficacy or safety of such combinations at this time.

[Slide]

Because the baseline demographics of the patients treated with paclitaxel are markedly different from those treated with AC in the pivotal study, it is impossible to make conclusions regarding the use of Taxol-Herceptin compared to AC alone as first-line therapy for metastatic breast cancer.

[Slide]

To pull together the limitations, only one dosing schedule has been tested. These are not studies to determine what is optimal first-line therapy for metastatic breast cancer, other than in those subgroups studied within the context of the protocols presented today. Selection characteristics of patients who will benefit from Herceptin, comparing 2+ to 3+ patients, is limited by the fact that this wasn't prospectively designed into the study, but certainly exploratory analyses are significant. Finally, the assessment of cardiotoxicity is limited by the manner in which the data was collected.

That completes my presentation.

DR. DUTCHER: Thank you. Before we entertain

questions, could you and perhaps Dr. O'Leary just comment on what the issues are with the test kit, because I don't think the members of the committee are really aware of the issues in terms of who got tested with what.

DR. JERIAN: The PMA for the test kit -- first of all, let me just say that the antibody used in the test kit, as I mentioned, is a different antibody but because there are not samples available from the clinical study to test that antibody a concordance study was done with the polyclonal antibody. The tissues obtained for that concordance study were from a registry, NCI registry I believe, tissue bank. Without getting into too much of the detail of the PMA because that will be dealt with on Friday, the concordance study showed fairly good concordance, although there were these differences in patients who were scored as 2+ by the polyclonal kit, the DAKO kit. Many of those were not scored as positive by the studies used to identify patients for this study.

DR. O'LEARY: So, basically, then the PMA that we will be looking at on Friday does not bear a direct relationship to the survival information being presented today, but that this is an extrapolation use of sort of a surrogate so that a question that is relevant to that and to this -- you said that there were two antibodies used in the study 4D5 and CB11. One of these two antibodies would

appear likely possibly to be more closely related in terms of the epitope target than the other to the test kit antibody. Is there a matrix that could be put up to show in any of these tumors that might have been assessed using both antibodies, both 4D5 and CB11, a concordance between those two antibodies in the same laboratory?

DR. JERIAN: We attempted to look at that actually, and one limitation we have in doing that analysis is that there are far fewer patients who had the CB11 antibody test done. I hesitate putting that data up at this point.

DR. O'LEARY: Can you give us some idea of what the proportion was, what fraction used the 4D5 and how many used the CB11, and how many had both?

DR. JERIAN: I am sorry, I don't have the numbers with me right now.

Questions from the Committee

DR. DUTCHER: Questions for FDA from the committee? Dr. Margolin?

DR. MARGOLIN: Just a very tiny question. When you looked at the potential for imbalance in terms of the randomization in the two groups, there were usual factors, but did you look at the use of eridia? In bone-only patients use of eridia might potentially alter the time to detection of progression since that was one of the primary

endpoints?

DR. JERIAN: No, we didn't do that evaluation, but I think that is a good point.

DR. DUTCHER: Dr. Schilsky?

DR. SCHILSKY: A couple of questions. I think the points you bring out about the differences in response with respect to intensity of staining are critical in helping to frame a risk-benefit assessment, and I wonder if there is any data from this study that helps to provide some ability, just to have a sense of what the concordance rates are among people who look at these slides. I don't do this but I don't have any idea, for example, how difficult or easy it is to discriminate 3+ from 2+ staining. You know, all of this was done in a central reference laboratory but one might ask if you took, you know, five pathologists and had them look at all of the same material what would be the agreement with respect to what is 3+ and what is 2+, just using the antibody that was used in the study.

DR. JERIAN: Understood. As you know, with immunohistochemistry staining, it can be very subjective and, in fact, for the PMA kit there are standards submitted for the 3+, the 1+ and the 0, but none for the 2+, and 2+ patients are difficult to determine; 1+ are difficult to determine; 3+ are quite apparent and 0 is quite apparent. But it is very difficult to know what to do with the 2+ and

what to do with the 1+, and who actually is falling into which group.

DR. SCHILSKY: That strikes me as being particularly important for a patient who might, you know, be appropriate for AC with Herceptin and who has a 2+ tumor. She would be exposed to lots of risk for toxicity and not much benefit.

I have one other question for you about the toxicity. You mentioned that in the Phase 2 study patients who progressed had several options, one of which was to continue to receive Herceptin at twice the dose that they had been receiving previously. I am wondering how many patients actually did that, and whether that sheds any light about dose-response relationships and risk of cardiac toxicity.

DR. JERIAN: A lot of those data are, you know, anecdotal. Patients could receive a variety of regimens. They may have received tamoxifen and Herceptin, 5FU and Herceptin, CMF and Herceptin. It is very difficult to come to any conclusion from that data regarding efficacy.

DR. DUTCHER: Dr. Simon?

DR. SIMON: Am I correct in saying we don't really have information about whether Herceptin alters the pharmacokinetics of Taxol or Adriamycin or cyclophosphamide?

DR. JERIAN: I am sorry, I didn't hear the last

part.

DR. SIMON: We know about the effect of Herceptin on the pharmacokinetics of the chemotherapy drugs used?

DR. JERIAN: Well, as I mentioned, we may know something about what it does to the Herceptin concentration. It doesn't affect Taxol levels in the preclinical studies, but those were not assessed in the pivotal study, and AC levels were not assessed in the pivotal study. So, we don't know what it does --

DR. SIMON: But preclinically there was no indication?

DR. JERIAN: Preclinically there was no indication of an effect on the chemotherapy agents.

DR. DUTCHER: Yes, Dr. Weiss?

DR. WEISS: Based on your look at the cardiotoxicity data, do you have any thoughts as to when, how or whether patients who were candidates for this agent should be screened in any way prior to therapy, particularly if the indication ever broadens to people without metastatic disease? Is there something that a physician should be doing before --

DR. JERIAN: That is one of the questions we have for you!

[Laughter]

DR. WEISS: I was hoping you would answer it.

DR. JERIAN: You know, it is very difficult to say. Actually, I will commend the sponsor for going back and trying to get the because information on these patients, and without that comparison it is difficult to say. Certainly, monitoring needs to be in place on some level.

DR. DUTCHER: Was it being done in the open label?

DR. JERIAN: It is being done now.

DR. DUTCHER: Dr. Simon?

DR. SIMON: I just wanted to clarify whether I heard your answer to Dr. Schilsky's question before. Did you say with the kit that is coming up for review on Friday the determination of who is 3+ is straightforward?

DR. JERIAN: It is rather straightforward, yes.

DR. SEIGEL: We probably have a concordance table. I think what you are trying to point out is that there is pretty high concordance at the 3+ level, and when you get to the 2+ a significantly large number of them are 0 or 1+. Some are 3+; some are 2+. Do you have that?

[Slide]

DR. JERIAN: This is actually going to be presented by the FDA at the CDRH meeting. This is a concordance table, and 3, 2, 1 0 refer to the immunohistochemistry score. At the top you have the assay used and the clinical study. A slide could either be positive with CB11 or 4D5. On the other axis you have the

DAKO assay. If you look at the two italics numbers, those are patients whose scores are 2+ by the DAKO assay but were negative by the core laboratory clinical trial assay.

DR. SEIGEL: The reason that we emphasize that second line in a couple of comments as developed in one of the questions that we might ultimately get to tonight, is that we can present the clinical data, of course, regarding the first two columns -- response rates, if you were 3+ or 2+, and the relatively weaker evidence of benefit in 2+ patients, but we will not be able to write an indication for those columns because that test is not developed throughout. We can only write indications for the patients in the row, and if one were to look at that 2+ row, you would have to recognize that that includes a lot of patients who would have been in the trial, but also a lot who would not have been in the trial.

DR. JERIAN: I just also want to point out that one of the reasons they brought forth the polyclonal kit is that the other immunohistochemistry stains required multiple, multiple steps and were very cumbersome to employ, and the polyclonal kit apparently is less cumbersome in methodology.

DR. SIMON: Do I understand the other part to Dr. Schilsky's question, that you don't really have inter-lab reproducibility data?

DR. JERIAN: I am sorry?

DR. SIMON: You don't have inter-lab reproducibility data?

DR. JERIAN: They looked at inter-reader variability. They they did assess all those points but I don't have those data for you.

DR. DUTCHER: Yes?

MS. ZOOK-FISCHLER: As a patient rep, I am very excited about the potential that Herceptin appears to present, but it seems to me that the patient population was a very sick population whose quality of life is already quite compromised. Then I am hearing all of the potential toxicities in addition to the cardiotoxicities. I wonder whether there has been consideration of studying Herceptin on women who are not quite so sick, or to limit it only to women if they are that sick if they are overexpressing 3+.

DR. JERIAN: Yes, understood. I think the sponsor certainly is planning on pursuing other studies. I think that is quite an active area of consideration but we haven't received any other, you know, complete studies, other than what I have shown you today.

DR. LIPSCHULTZ: I just have a couple of questions. One of your slides -- I just want to see if I understand it correctly. We were looking at the incidence of grade III and IV cardiac disease, in other words,

symptomatic left ventricular dysfunction, presumably. I think I saw there that in the 301-450 group it was 25 percent in the Herceptin and AC group. Am I understanding that correctly, that 25 percent of patients on that regimen in the 301-450 cumulative anthracycline dose had symptomatic left ventricular dysfunction or congestive heart failure?

DR. JERIAN: Right. That is of the total patients treated at that dose.

DR. LIPSCHULTZ: Right, okay. I saw in the original protocol that ejection fractions of 45 percent or above were acceptable for inclusion in the study. Oftentimes people think 45-55 as being somewhat depressed. Do you have a feel for that, those that had baseline, were any in that range when you reviewed the data?

DR. JERIAN: When we looked at the baseline ejection fraction data that was provided for the patients who had cardiotoxicity, again, a lot of that was missing for the patients who didn't experience cardiotoxicity, and I don't see any major differences between the subgroups of patients who had cardiotoxicity. I think the mean was around 60 percent, or something like that.

DR. LIPSCHULTZ: When you reviewed the data, in the last 20 months or so, whatever, since cardiac problems became apparent, was there an increased number that had ejection fractions or other cardiac parameters -- I am just

trying to get a feel for this. You know, when I look at that and see that for the Herceptin-AC patients only 50/143 had baseline, I am trying to get a feel for who these patients are. Are these only the ones that had heart failure? I guess the thing is that when I look at a rate of 25 percent and I know that in the AC group you have 3 percent, and in FAC regimens this is a factor of 10 higher, you know, this is an enormous amount of symptomatic heart disease. I am just trying to get a feel for it. It seems that this may be a minimum for combined asymptomatic-symptomatic LV dysfunction. I am trying to get a feel for who these patients are that you actually have data on, or they have data on.

DR. JERIAN: Not all patients were symptomatic. Well, if they were III or IV they were symptomatic, but there were some class I patients who were monitored by their investigator, I assume, because they had a cumulative anthracycline dose so that that investigator typically would check the ejection fraction at that time point, and they were evaluated and found to have a decreased ejection fraction. That would be the practice of many oncologists. But that practice did vary depending on the investigator and the geographic region. There was one site in Germany where they looked at fractional shortening instead of ejection fraction. So, that is another factor that makes this

analysis difficult. It was very investigator dependent, and you had to look at each individual patient as a unit of one because one investigator would be more aggressive and the next one may not be more aggressive in checking ejection fractions in the absence of symptoms.

DR. SCHILSKY: As I understand it, this was a set of samples from a registry, not from the patients in this trial. Right? And the clinical trial assay was performed and the DAKO assay, which is the one that is proposed to be used in the future, was performed. So, there are 126 specimens that were 2+ by the DAKO assay and, of those, 16 would have been 3+ by the clinical trial assay. Right?

DR. JERIAN: That is right.

DR. SCHILSKY: So if, for example, a decision were made to exclude from therapy with Herceptin all patients who score 2+, then potentially 16/126 patients might be excluded who might otherwise have benefitted because they were actually 3+ using the assay done in the study.

DR. JERIAN: That is right. It is very difficult to know what to do. I will comment on this data. The ratio of 2+ and 3+ slides was 50-50, and then they extrapolated that to what a normal population would be, which is 25-75.

DR. SEIGEL: Yes, let me just pursue that point. If you are looking at fractions of that 126, you should recognize that these were not all specimens from all

patients in the registry that would have been eligible for the trial. They specifically selected for having a higher proportion of samples that were positive to give this 50-50 ratio.

DR. SCHILSKY: What I am struggling with I think is that, you know, since the assay isn't perfect, and if the data are true that the only patients who benefit are those who are 3+ in their staining, and since the toxicity risk, at least with AC, is substantial, if one arbitrarily decided to only offer this therapy to patients with specimens with 3+, then who might be left out who could potentially benefit just based upon variability in the assay? That is the hard part.

DR. DUTCHER: Dr. O'Leary?

DR. O'LEARY: Yes, I wanted to get back to that. Can one renormalize this in some way to what the proportion would have been in the trial population? Because the piece of this that doesn't come out clearly, at least to me, is if you make a cut-off at 3+ on the DAKO assay, and we assume that the DAKO assay is perfect, then what proportion of folks that would have benefitted or would have potentially benefited would we miss? Alternatively, if the cut point were made at 2+, what percentage are potentially included that should not have been included when one looks at this in terms of the distribution of staining in the real population

as opposed to something skewed to look at the concordance with a higher proportion of positive tumors?

DR. JERIAN: I am sorry --

DR. O'LEARY: Well, the initial look is if you were to assume -- it would appear that around -- if you use the 2+ cut-off, about 40 percent of the folks that would be included as eligible for therapy would be folks that would be negative, 0 or 1+ by the lab core assay. Alternatively, if you just include 3+ it looks like you lose about a third of the patients that would have been eligible for the lab core assay. I think that is actually probably preserved in the sense that the 0s and 1s isolate pretty well.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: My questions are biological and may be best directed at Dr. Slamon. We have to decide whether to approve this, with all sorts of caveats about the safety of combining the drug. But, we learned that there seems to be some interaction between expression or amplification of HER2 and response to Adriamycin without Herceptin. We also learned from this month in JCO that there might be some important interactions with cisplatinum and HER2/neu in the antibody.

So, I guess the question is would the scenario be that in patients who are overexpressors when one gives some Adriamycin as part of their therapy and then, as soon as

they fail, you give them either Taxol plus Herceptin, or platinum plus Herceptin, or Taxol plus platinum and Herceptin and at that point avoid the Adriamycin even if the time to relapse is long?

DR. SLAMON: I think that you are right on the money with some of the questions you are asking. The Adriamycin interaction is real, I think, based on the data that everybody has been showing, and the company was very, very up front with the investigators and was on top of it all along when it first started to happen. But I don't think anyone has been saying that it can't be used absolutely with anthracycline, it just needs to be used with caution. I mean, the only thing I wanted to get out into this discussion is, remember, I mean, those cardiac events are real but HER2 overexpressing breast cancer in the metastatic setting is a very deadly disease and it needs to be weighed in that context.

Now, can you use Adriamycin with the antibody? I think the answer is yes. I think it should be used cautiously, as the recommendation, as I understood it, was alluding. Are there better combinations? I think the answer is very possibly yes, and that is something that the sponsor is beginning to evaluate now. Should you use Adriamycin? Do we always have to use Adriamycin? I think that is something that we are not going to get out of this

trial. Why is it the eleventh commandment that everyone with breast cancer has to be treated with Adriamycin?

DR. MARGOLIN: Well, maybe also you don't need the Herceptin with Adriamycin. Maybe you need it with the other drugs to get the interaction but with Adriamycin you already have that interaction.

DR. SLAMON: While I absolutely agree with that, I would still be somewhat concerned about the toxicity we are seeing, even delayed, in patients who have had prior anthracyclines. So, I think the phenomena are real. I think the drug can be used with anthracycline but with caution. I also think, without any hard data yet except for the sort of interesting data in JCL, that there may be better combinations, and better combinations up front.

Open Public Hearing

DR. DUTCHER: If there are no further questions for FDA, I think we should move along. We do still have five more minutes of open public hearing. Is Mr. Erwin here? Could you please identify yourself and your associations, as well as your financial support?

MR. ERWIN: Sure.

I am Robert Erwin. Thank you for agreeing to my request to speak after the data was presented. I have no financial interest in Genentech. I am Chairman of the State of California Breast Cancer Research Council, which spends

about 10-15 million a year in cigarette tax money on breast cancer research. I work for a small private biotech company which neither collaborates with nor competes with Genentech.

I am here today, representing the Marti Nelson Cancer Research Foundation, and the cancer patients that we assist to enroll in clinical trials to obtain access to experimental medicine to evaluate off-label uses of drugs approved for other indications, and to assess the potential value of treatments unavailable in the United States.

My wife, Marti, died of breast cancer in 1994 after unsuccessfully attempting to gain access to the drug now known as Herceptin. Since that time, Genentech has demonstrated its moral leadership in the biotechnology industry, and its compassion, by establishing an expanded access protocol for Herceptin, whereby as of now over 400 women with advanced, HER2 overexpressing metastatic breast cancer have been able to obtain this drug in the realistic hope of extending life, or at least improving its quality.

Although a scientist might not call these cases significant and refer to them as anecdotal, the benefit experienced by each individual who was helped by this protocol was as clinically real as the benefit experienced by any individual in the pivotal studies.

The data presented today, in my opinion, speak clearly, and there is no doubt that this drug should not

only be approved, but should become a part of the standard of care for HER2-overexpressing metastatic cancer. The patient groups that we work with tend to be quite aggressive and we extrapolate aggressively from early stage data. We would be very likely to recommend Herceptin plus Taxol over AC as first-line therapy for HER2-expressing metastatic breast cancer.

Two very important questions remain, however. One, why has it taken so long to get to this point when it was so clear to so many people in 1994 that this drug could extend life?

I believe that something is wrong with our institutional approach to providing effective treatment for cancer. We are not talking about a healthy population in this regard but about people who are dying. When every day counts we are losing years, as was illustrated in the early slide showing the regulatory time line going back to the completion of the Phase 2 study. The fast track is not fast enough. The sacred cows of the research funding process and the drug development and approval process are clogging up the road and, in the absence of data suggesting actual divinity, I think they need to be put back to pasture to enable innovative researchers and companies like Genentech to move more quickly, and move significant discoveries into general use.

Those of you in the FDA know which experimental drugs are working and which are not early enough to pull the promising candidates to the process proactively and rapidly, perhaps into pivotal Phase 2 studies. You also know which combinations of as yet unapproved biologics have rational medical promise but are unlikely to be tested in combination for years to come.

How long do we have to wait to find out whether or not Herceptin in combination with Theratope, or some other proprietary biologic, can extend life beyond either alone? Under the current system, it will be well into the new millennium. Why? Disclosure of risk is essential, as is monitoring for unexpected toxicity. Delays in access are fatal.

The second question is why is Genentech the only company to have an established practice of providing expanded access to promising cancer therapeutics? Where are Chiron and Biomira and Janssen and Bristol-Myers and ImClone and Medarex, and all the other companies who plan to profit from cancer? Those of you out there from the corporate world who sell Taxol and Adriamycin, and other chemotherapeutics, are selling products that usually benefit less than a third and harm 100 percent of your customers. People buy your products not because most of them benefit, but because all of them hope for benefit, and your profit is

the same whether your customer lives or dies.

I believe that this truth carries with it a moral and ethical mandate to rethink the status quo and factor compassion into your operating practices, as Genentech has done. And, it is not just the corporations who develop and sell oncologic drugs that share this obligation. It doesn't really matter whether your currency of choice is the profit you might derive from the sale of marginally beneficial products or the tenure that you have derived from the tragically disappointing war on cancer. Everyone whose profession exists because of the suffering of cancer patients has a moral obligation to step up to the line and deliver the best that science has to offer to people who need it the most as rapidly as possible. This includes insurance companies, managed care organizations, and the FDA itself.

Herceptin may be the first drug for the treatment of metastatic breast cancer that actually helps more people than it harms, but I hope it won't be the last. With this new generation of cancer drugs, expanded access is not only a matter of altruism. Genentech has demonstrated that everyone can win from expanded access and from a close and constructive relationship between a company and the community of people most affected by cancer. Genentech has also shown that expanded access is compatible with good

science and good medicine.

I urge you to accept the challenge of Genentech's leadership and remember that each individual is more than an anecdote. Each person is a valuable, loving, loved and irreplaceable individual. Expanded access for all of the new generation of cancer therapeutics is what we need. And, don't wait around until organizations like ours and the broader coalitions of cancer activists engage you in this issue. Do it now because it is the right thing to do.

As Marti was dying, I promised her that her death would not be in vain. I intend to keep that promise. We have only made a very small start. We are going to continue because it is the right thing to do.

Thank you.

Committee Discussion and Vote

DR. DUTCHER: Thank you very much.

We are now going to consider questions regarding this agent. We have heard a lot of information.

First, we will try to go through in order, but I know that Dr. Weiss has to leave quickly and I want him here when we talk about the cardiotoxicity issues. We will start with the first question and then we will see where we go.

The first question is -- you can't hear me? Now you can hear me? Okay.

We are going to be going through the questions, as

I said, except that if we get close to a certain time limit we want the cardiologists here to discuss it. So we will jump ahead. You have to leave at 7:30? We will be done. We will be fine.

As a single agent, Herceptin produced objective tumor responses in 14 percent of patients studied in clinical trial H0649, with a median duration of 9.1 months. The patients in this study had all received one or more prior chemotherapy regimens with or without hormonal therapy for metastatic disease. Responses were seen in a variety of metastatic sites including visceral, soft tissue and bone lesions. Herceptin, when administered as a single agent, was associated with infusional toxicity commonly seen with other monoclonal antibody therapies: fever, chills, myalgias, back pain, tumor site pain, nausea, and flu-like symptoms. This toxicity appeared to be self-limited and controlled with medications and/or with adjustments in the rate of the infusion. Diarrhea (32 percent), abdominal pain, (27 percent), and stomatitis (10 percent) were commonly seen and may be related to the known binding characteristics of parent antibody of Herceptin, 4D5, to normal gut tissues. Cardiotoxicity (7 percent) when observed was most commonly manifested as heart failure, with a decrease in the cardiac ejection fraction. It was more often severe in nature and occurred in patients with and

without prior anthracycline exposure; although, those without anthracycline exposure did have preexisting cardiac disease. Anemia (10 percent) and leukopenia (8 percent) were noted in this heavily pretreated population.

So the questions are three.

(a) Do the objective response data demonstrate efficacy of Herceptin as second- or third-line single-agent therapy of metastatic breast cancer?

(b) Is the toxicity profile of Herceptin acceptable for use as a single agent in second- or third-line therapy of metastatic breast cancer?

(c) Does therapy with Herceptin as a single agent provide net clinical benefit for patients with metastatic breast cancer when used as second- or third-line therapy?

So, who would like to take a stab at (a)?

DR. MILLER: I think the trial did show objective evidence of efficacy in the Phase 2 trials. So, they met the criteria put out by the trial.

DR. DUTCHER: Any other comments? And, in terms of the toxicity profile for use as a single agent in second or third line? Any comments? Dr. Doroshow?

DR. DOROSHOW: Let me take a stab. I think that while the toxicity profile is acceptable, it is very important, I think, to point out to everyone here that the level of III and IV cardiac toxicity for Herceptin alone was

greater than for AC.

And, while we may very much want to have this therapy available to us, it is really quite extraordinary, and I believe that there is probably a lot about the biology of this protein that we can learn with respect to this novel toxicity that the antibody alone produces and, hopefully, there will be a lot more study to make us understand that.

In essence, we are saying that this protein produces a level of heart damage that is equivalent to Adriamycin alone, which is a pretty remarkable thing in and of itself, and the question really is the risk-benefit analysis.

DR. WEISS: I would agree with that and I would add, as to question (b), that I would give an answer of yes, with the qualification that the committee consider recommending some pretreatment evaluation, cardiac evaluation of patients noninvasively in some way or other to help avoid a catastrophic cardiac complication whenever possible.

DR. DUTCHER: For use of the antibody alone?

DR. WEISS: Yes.

DR. DUTCHER: Okay. You know, we usually vote on each question, Jay. So, I think what we will do is vote on each of these parts. Is that what you want us to do?

DR. SEIGEL: I think if you discuss them all and

vote on (c), I think that will work.

DR. DUTCHER: Okay. Any other comment on (b)?

[No response]

On (c)? Does therapy with Herceptin as a single agent provide net clinical benefit for patients with metastatic breast cancer when used as second- or third-line therapy? Dr. Vose?

DR. VOSE: I think we have all heard today what a bad disease overexpression of HER2 breast cancer can be as far as the overall outlook, and I think relative to what the other options are for these patients, this is actually an excellent choice as long as we do make sure that we know that the baseline cardiac evaluation is done and that the physicians are aware of these possible toxicities, and that overall it does provide an excellent risk benefit.

DR. DUTCHER: Any other comments?

[No response]

All those who would vote yes on 1 (c), please raise your hand.

[Show of hands]

Eleven, yes. We have 12 votes, so it is 11 voting. So zero, no.

The next question is with respect to Herceptin in combination with chemotherapy, and particularly with paclitaxel.

Protocol H0648 tested the use of Herceptin with chemotherapy compared to chemotherapy alone as first-line therapy in patients with metastatic breast cancer. Chemotherapy consisted of an anthracycline, doxorubicin or epirubicin, plus cyclophosphamide or, in patients who had previously been treated with an anthracycline, paclitaxel. The groups receiving the two different chemotherapy regimens differed not only in prior therapy and study treatment but also in response rate, survival, and toxicity profile. Therefore, they are considered separately in questions 2 and 3.

Question two, when compared to paclitaxel alone, Herceptin used in combination with paclitaxel chemotherapy, at 175 mg/m^2 infused over 3 hours, was associated with a greater median time to progression by 4.2 months, and a higher 1-year survival rate, 61 percent versus 73 percent, but no significant difference in median survival. The patients studied had not received chemotherapy for their metastatic disease, though they may have received hormonal therapy, and they had received prior anthracycline therapy in the adjuvant setting. In addition, a few patients had received dose-intensive chemotherapy. Herceptin in combination with paclitaxel was associated with infusional toxicity as noted above. In patients receiving TH there was an observed 11 percent incidence of cardiotoxicity as

compared with the 1 percent incidence in patients treated with Taxol alone. The incidence of severe cardiotoxicity, class III or IV, was 4 percent for patients treated with Herceptin plus Taxol compared to 1 percent for patients receiving Taxol alone. Other toxicities which appear to be increased when compared to patients receiving paclitaxel alone included: anemia, leukopenia, abdominal pain, diarrhea, vomiting, and infections.

(a) Do the data regarding time to progression and survival provide evidence of improved efficacy of the combination of Taxol-Herceptin over Taxol alone for the first-line treatment for metastatic breast cancer?

Who would like to comment? Dr. Schilsky?

DR. SCHILSKY: I would have to say unequivocally yes. In fact, I think the data are quite striking and perhaps the greatest demonstration of clinical synergy that I have seen in any solid tumor therapy. It is quite remarkable.

DR. DUTCHER: (b) Given that only patients who had received prior anthracycline therapy were studied in these regimens, if approved, should the indication be limited to patients who have received prior anthracycline therapy? Dr. Miller?

DR. MILLER: I don't think so. I mean, we are concerned about the cardiotoxicity, and I don't think we

should mandate that. I mean, clearly this shows efficacy even in patients who have previously been treated with a very active drug. So, I do not think it should be limited to patients who received prior anthracycline.

DR. VOSE: I would have to agree with that. I think we can only actually get better results. So, I don't think we should mandate that.

DR. DUTCHER: Okay. I agree.

(c) When compared to Taxol alone, does the efficacy profile for Taxol-Herceptin provide sufficient additional clinical benefit to outweigh the increased incidence of toxicities, particularly infusional toxicity and increases in cardiac, hematologic, GI, infectious and neurologic toxicities?

I think the answer to this is yes. This profile is certainly in favor of the combination.

DR. VOSE: I agree.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: The times to treatment failure are integral of that and progression is still strongly favorable for that combination.

DR. DUTCHER: So we should vote on (c). All those who would vote yes for (c)?

[Show of hands]

Eleven yes and zero no.

Question three, when compared to doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2 plus cyclophosphamide 600 mg/m^2 AC chemotherapy, Herceptin used in combination with AC was associated with a greater median time to progression by 2.1 months, and a higher 1-year survival rate, 73 percent versus 83 percent, but no significant difference in median survival. The patients studied had not received chemotherapy for metastatic disease, although they may have received hormonal therapy. Herceptin in combination with AC therapy was associated with infusional toxicity. The observed incidence of cardiotoxicity in patients receiving AC plus Herceptin was 28 percent as compared to an incidence of 7 percent in the AC alone arm. The incidence of severe cardiotoxicity, class III or IV, was 19 percent in patients receiving Herceptin plus AC compared with 2 percent in patients treated with AC alone. Other toxicities which appeared to be increased in incidence and severity when compared to patients receiving AC alone include anemia, leukopenia, abdominal pain, diarrhea, dyspnea, and infections.

(a) Do the data regarding time to progression and survival provide evidence of improved efficacy for the combination of AC plus Herceptin over AC alone used as first-line treatment for metastatic breast cancer? Dr. Miller?

DR. MILLER: Similar to the previous discussion, you know, it seems pretty clear that it does have benefit over AC alone in the efficacy.

DR. DUTCHER: Any other comments? We agree?

(b) When compared to AC alone, does the efficacy profile of AC plus Herceptin provide sufficient additional clinical benefit to outweigh the increased incidence and severity of cardiotoxicity, 28 percent versus 7 percent, the increased incidence of hematologic, gastrointestinal, and infectious toxicities and infusion toxicity? Go ahead.

DR. WEISS: Again, as with the agent alone, I would say yes, but I think given the 4-fold cardiotoxicity incidence with ACH versus AC, again, I think we might insert a caveat about a noninvasive cardiac evaluation prior to institution of therapy, if everyone agrees.

DR. DOROSHOW: I would like to present a different view. I think that, in fact, Herceptin produces synergistic cardiotoxicity with Adriamycin, and I am not at all sure that the very modest clinical benefit, though real -- certainly the time to progression is real, if not for survival, is really worth this synergistic cardiac toxicity, in my view.

DR. WEISS: In saying what I said I was hoping to avoid causing more damage to already seriously injured hearts basically. I don't disagree with what you say but if

we do decide to say yes to the question, I think a higher cardiac evaluation is important.

DR. SEIGEL: I would like some clarification on that because, although there wasn't a vote and not necessarily everyone spoke, I got the impression that there was a general consensus that even patients getting single-agent Herceptin or Herceptin with paclitaxel ought to have prior cardiac evaluation. So, we could give additional warning about the higher risk level.

DR. DUTCHER: I think the issues are that there is something going on with the heart with the molecule by itself, and the dosing of the Adriamycin in these regimens is right on the cusp of when it starts to interact. So, those are the issues. Dr. Schilsky?

DR. SCHILSKY: Well, I guess I share many of Jim's concerns. In my mind, you know, in this patient population there is only a 2-month improvement in median time to progression, and you have to weigh that against the risk of better than 1 chance or more that the patient will develop significant cardiac failure.

I am also thinking of this in terms of the fact that, sort of in contemporary times, relatively few women would actually be getting an anthracycline-based chemotherapy regimen for metastatic disease because the vast majority would have already had an anthracycline as part of

their adjuvant therapy. So, in fact, if Herceptin were not approved for use in combination with AC, I think relatively few patients would be disadvantaged by that.

Then, there is the whole issue of the fact that a proportion of patients probably don't benefit from the addition of Herceptin at all to their chemotherapy. That has to do with the whole issue of intensity of staining and the variability of those data.

But, clearly, you know, one might be putting a lot of patients at risk for cardiotoxicity with this regimen, recognizing that the potential benefit is going to be confined to a relatively small subpopulation of the total group of patients who are, quote, HER2 positive. So, I have a lot of concerns about this.

DR. DUTCHER: Dr. Lipschultz?

DR. LIPSCHULTZ: I have some similar concerns about the issue of monitoring before therapy. I think in spite the best efforts of everyone involved with these studies, it is completely unclear to me what the real incidence and extent of cardiac involvement is, and even more so than that, really whether anything is effective as a predictor of an adverse cardiac outcome, whether it be a baseline ejection fraction, serial monitoring, other sorts of things, we have no idea from this data whether any particular type of screening would be worthwhile.

But I share the same concerns with this group as to whether the quality of life balance is really clear in terms of heart failure, for instance.

DR. DUTCHER: Dr. Weiss?

DR. WEISS: Yes, I do agree with what you said. I think what I am trying to emphasize is that we would be very hesitant to give this agent to someone with an ejection fraction of 15 percent, or something. I think it is important that we know what we are in for before we give this potentially very dangerous combination. That is my only point.

DR. LIPSCHULTZ: Oh, I agree. But usually what happens in these sorts of situations is it is clear-cut when someone has an ejection fraction of 15 percent, but when that patient has an ejection fraction of 43 percent and seems healthy otherwise, then you are in a dilemma in terms of what you do with a magic number like that. And, it is not clear from anything I have heard today that we are at all able to deal with that.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: I am curious, from Dr. Seigel and his colleagues, exactly what the vote to number 3 (b) -- how that would influence -- you know, the drug presumably would be approved but this would affect the package insert? Are you really going to say this is not approved for use with

Adriamycin? What exactly are you going to do with the information?

DR. SEIGEL: Well, I think the questions obviously don't get too highly specific about the labeling because what we would like to do is integrate your expert opinion into what makes sense. It is unlikely, unless we heard something that would say that, that we would write a contraindication to use with Adriamycin. It may be that, rather than have that in the listing of how to administer regimens, that that regimen and its outcomes will almost surely be described in the clinical pharmacology but may not be listed as the others as a so-called recommended dosage or administration. There are a lot of ways to go and, depending on what we hear and if you have specific ideas about it, we would like to know.

DR. MARGOLIN: It influences how we vote.

DR. SEIGEL: Pardon?

DR. MARGOLIN: It influences how we vote.

DR. SEIGEL: Yes.

DR. MILLER: And we have to sort of figure out whether we are lumping or splitting. Whether or not we are going to require that each different drug be looked at separately and how it interacts, or whether we are going to say that this drug is an effective drug and then let the clinical scientists figure out how best to use it as long as

we document the toxicity and the risk-benefit ratio.

Abbie Meyers is not here so I will say what she normally says. You know, the question if we write the label too limited, it does, in fact, affect the potential patient reimbursement issues. Also, the risks and benefits for one person may be different for the other person.

So, I am sort of on the other end. I think that we should request that further studies be done looking at that, but that we shouldn't split and say you can use it with this but you can't use it with different drugs.

DR. SEIGEL: So, if the labeling were to say, for example, that Herceptin is indicated for use in second or third line in metastatic, and then it is indicated for use in combination chemotherapy -- now, typically chemotherapy drugs labeling, as I understand it, although I am not an oncologist and deal less with them, indicates the approved regimens. But you are suggesting -- it sounds like you are suggesting in this case you would simply say it is indicated in combination with chemotherapy for first-line treatment of adjuvant, in which case we wouldn't be restricting it, and that would also open it up to all sorts of other chemotherapies that haven't been studied. Or, we could say it would be indicated in combination with paclitaxel, or we could say it would be indicated in combination with paclitaxel or --

DR. DUTCHER: Let's go back to where we were. Okay? We are going far beyond -- let's just talk about anthracyclines because some of us are old enough to have taken care of patients with Adriamycin cardiotoxicity where we couldn't do anything about it.

So, I think that the question is, you know, how much of a problem is this? What do we need to decide to do about either approving it for that use and/or building in monitoring and/or trying to decide what this molecule is doing to the heart. That I think is what we have to do right now. Yes, Dr. Vose?

DR. VOSE: No, I think in this type of patient population it really comes down to trying to look at the risk-benefit ratio and the patients quality of life, and does a 2-month improvement in time to treatment failure go against a 28 percent cardiotoxicity rate that in some patients was not reversible with medication, and their last 2 months or 3 months are going to be very bad?

So, I think that we should definitely have this information highly available to the physicians so that they can read that; so that they know what the risk-benefit ratio is. Personally, I would say that no, it is not a good risk-benefit ratio with this particular regimen in that population.

DR. DUTCHER: Miss Fischler?

MS. ZOOK-FISCHLER: Well, that was pretty much what I was going to say, but I would personally like to vote yes, but I would somewhere like to see a caveat that the oncologist prescribing it just keep in mind who the patient is. If the patient is very ill and she will only have a 2-month benefit, I would not like to see her quality of life be diminished any further. But I wouldn't want to preclude voting for it.

DR. DUTCHER: I guess the other question is, is there a dose of anthracycline that is less than 350 mg/m^2 in which we wouldn't see the same effect?

DR. DOROSHOW: Well, I think it is unlikely with a compound that has a half-life of a week used in combination with a therapeutic chemotherapeutic agent that has a half-life of several days that it is ever going to be possible to find a dosing schedule, unless these agents are very disparately administered in which there is a potential for interaction, whatever the molecular interaction is. In the same way, I think it is going to be very difficult to define a cumulative dose, either cumulative dose or schedule, where that is going to be possible.

DR. SEIGEL: Well, it is certainly possible that if one were to look at restricting the dose of one or the other one might find that one could preserve efficacy and decrease toxicity. That has not been looked at. For

example, the Taxol is given, as is discussed in a later question, basically until progression of disease. The lowest rate of toxicity for Taxol was noted in the single-agent study -- I am sorry, I am talking about Herceptin here -- and that may reflect the fact that it is least toxic in that, but it also could reflect, in part, that those patients had the shortest time to progression. They only had a 2- or 3-month time to progression on average so they only got Herceptin for a very limited period of time.

You know, there are a lot of questions still to be answered. I hear what you are saying about not being able to answer interaction questions, but it would be less obvious to me that you couldn't answer whether there are other less toxic but effective regimens.

DR. MILLER: Jay, can you remind us how we dealt with this on the biologic committee on the other monoclonal antibody that was approved, looking at it as approving it in general or whether we looked at it combined with other chemotherapy agents?

DR. VOSE: It was just by itself, Carole.

DR. DUTCHER: Well, we have had sufficient discussion for that. We can vote on that. I mean, assuming that there will be pretreatment cardiac monitoring, when compared to AC alone does the efficacy profile of AC plus Herceptin provide sufficient additional clinical benefit to

outweigh the increased incidence and severity of cardiotoxicity and the increased incidence of other toxicities?

All those that would vote yes?

[Show of hands]

Two. Two, yes.

All those that would vote no?

[Show of hands]

Eight, no.

Abstain? Ms. Beaman, did you vote? You voted no?

Nine, no; two, yes.

DR. DUTCHER: Number four, cardiotoxicity is a serious adverse event which was increased in the Herceptin-treated patients. Preclinical studies in monkeys given AC plus Herceptin and Taxol plus Herceptin, or Herceptin alone did not predict such events. Clinical studies, 648 and 649, as well as all other studies conducted with Herceptin have not been designed to adequately measure the rate of cardiotoxicity, the risk factors for developing cardiotoxicity, or the mechanism of cardiac damage. There is insufficient information upon which to base conclusions regarding the identification of patients who are most at risk, the specific role that anthracycline therapy may or may not have in the development of toxicity, and the rate of toxicity in anthracycline-naive patients who do not have

preexisting cardia disease.

(a) Please discuss what limitations, e.g. baseline characteristics of patients, dose, schedule of administration, monitoring, discontinuation recommendations, should be included in a label if Herceptin is approved for use with anthracyclines.

Let's go to (b). Please discuss elements which should be included in future studies designed to evaluate cardiotoxicity.

Maybe the modification of (a) would be that it should be able to show safety with anthracyclines. But I think the real issue here is how are we going to get at more information about the mechanism and the safe use of this agent in terms of the heart. Dr. Lipschultz?

DR. LIPSCHULTZ: My suggestion would be that in future studies that there be a centralized core lab to improve the reliability of whatever cardiac parameters you obtain, whether it be an ejection fraction -- there tends to be tremendous variability in that when one looks at 100-plus sites.

One should also consider several different types of cardiac testing that help give a feel for mechanism of injury, and definitions of what defines cardiotoxicity should be part of it as well.

Then, you know, on the other part of this

question, it seems from what I have heard today that it is still not clear what the mechanism is but if it is anthracycline related, it is still unclear to me whether patients who were treated with continuous bolus -- a few had Zinecard -- but those are some things that may be worth considering in subsequent studies.

DR. DUTCHER: Dr. Weiss?

DR. WEISS: I basically agree with that. I would personally advocate some standard procedure for quantifying LV function. Whatever is chosen; none are perfect. But, certainly, one of the accepted model systems for 2D ejection fraction is probably the most practical if you are going to look at a lot of sites.

I agree with the notion of a central core lab. If further investigations are going to be done, not clinical use but investigations, a central core lab should be reading and sorting these things out.

DR. LIPSCHULTZ: I will give you an example. We just completed for the NHLBI a 10-year study of patients at risk for cardiotoxicity in a different setting, and it was a multicenter study, and shortening fraction of 31 percent, which is basically an ejection fraction cut in half, and when you compare the local measurement to a central core remeasurement of the exact same studies of 21-51 percent -- very wide, and when you are dealing with relatively small

numbers like this and trying to really understand this, it certainly behooves us to have some quality assurance similar to what you were talking about with your receptor central core labs. There are also quantitative ways to assess acute myocardial injury that the FDA has approved that are relatively noninvasive. We are using those on a variety of pediatric POG and CCG studies in a national way, and they seem to be easily standardized in another marker for injury.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: Perhaps the FDA can help the sponsor design some very directed studies for defining a set of pretreatment cardiac parameters that would allow presumed safer treatment, you know, with central lab, and then some very specific, precise, uniform monitory, even, say, a Phase 2 study of Herceptin and Adriamycin or something like that in a defined population of patients so that a post-marketing report could be generated.

DR. SEIGEL: As I am sure most or all of you are aware that when we head toward drug approval we have the opportunity to negotiate with the company commitments to address key issues. In that regard, and it doesn't come out explicitly in these questions but you mentioned looking more at toxicity and how to monitor it in the setting of use with anthracyclines. What about use with other unknown or other likely drugs to be used in this setting? Is that another

area where there is significant concern that we should be getting toxicity data?

DR. DUTCHER: Dr. Doroshow?

DR. DOROSHOW: Well, I think there are two things to be said. One is that if it is going to be used with anthracyclines, irrespective of the preclinical data that are available in terms of pharmacokinetics, it would seem mandatory to know if there are any toxic interactions that could be related to pharmacokinetic antibody interactions that could lead to an enhanced cardiac toxicity with Adriamycin. So, that is a simple thing to do. It really ought to be done.

I think it is also true that since we don't know the mechanism of the interaction either at the tumor cell level or in the heart, these kinds of things really will be required with agents that could potentially have cardiac toxicity. Taxol is not a major cardiotoxin but together with Herceptin we have results that are very significant, and I think that you can't exclude potential -- that has to be studied in humans because the preclinical models are not available.

DR. WEISS: And, I think it is important to point out one way or another post-marketing what we all now know, that this is potentially a quite cardiotoxic agent, and that it is very important to know what kind of ventricular

function you are dealing with before you give this to a patient with or without the various agents under discussion.

DR. DUTCHER: In terms of other agents, I mean it has acted very differently with Taxol or AC. So, I don't know that you would know how it is going to behave in combination with other chemotherapeutic agents. So, you know, I don't think that there should be an onerous burden of a Phase 1 with every chemotherapeutic agent by any stretch, but I do think that there needs to be additional information gathering as the drug is used more widely and in combination with other agents. That just is prudent.

DR. WEISS: A possible suggestion of follow-up is noninvasive studies over time, I don't exactly know how many or how often, but some sort of follow-up monitoring would be important to consider.

DR. SEIGEL: Let me solicit a little more advice regarding the first part of this question, which deals less with what studies might be done and more perhaps with what might go into labeling. I gather, as I have noted before, that you have indicated that there is a consensus that patients ought to be pre-screened for heart failure and probably with ejection fraction determinations, although we have certainly heard loud and clear what we also see, which is you can't determine from the database that those patients are at higher risk. I guess the concern is that they may

have less reserve and, so, we haven't specifically heard but I would like to hear, if anyone felt this, that patients with any particular amount of heart failure at baseline ought to be contraindicated or not treated. I would be interested in your thinking about that.

Another thing, I guess, that I would like to think through is what then ought to be recommended follow-up. You do all of this; you get the information. Then, do you simply follow the patient clinically for symptoms, or should there also be recommendation for any further routine evaluation even in the asymptomatic patient for cardiac toxicity?

DR. WEISS: There might be a recommendation with regard to heart failure, but if a person is having some degree of heart failure, which the group could agree on, class III or class IV failure, or whatever, that the drug either be used with extreme caution or not at all.

I do agree with the need for some sort of noninvasive follow-up monitoring over time. As I said, I don't know how often that might be done, but I don't think that the monitoring should stop once the drug has been given.

DR. LIPSCHULTZ: I believe it is clinical practice by most physicians that if a patient has clinical congestive heart failure that they not continue to receive

anthracycline. I would continue to hold that true for this situation as well.

DR. SEIGEL: Would you also say that patients with clinical heart failure should not be begun on this regimen?

DR. LIPSCHULTZ: That is the usual practice with anthracycline therapy as well.

DR. DUTCHER: Jay, I guess the only problem is we don't really know what this drug is doing to the heart. So, I think that that would be probably your gut feeling, but you might have somebody who has had four different drugs, you know, and they understand that it is a risk and they want to have this treatment, and I don't think that that should preclude it. I just think we have to get more information. I mean, maybe it is HLA related; or maybe it is Crest toothpaste related. We just need to find out what it predicts for, and is it everybody; is it a certain group. So. Okay, can we go on?

Question five revolves around schedule and duration of treatment. In all studies, Herceptin was administered weekly until disease progression. A shorter duration of therapy may be equally efficacious. If Herceptin is approved, what post-marketing commitments should be made to verify that administration to time of progression disease is optimal?

DR. SCHILSKY: It has to be studied in an

appropriately designed clinical trial. I mean, it may be that a shorter duration of administration will not be equally efficacious. The only way to find out is to do the appropriate trial.

DR. VOSE: But I don't know that we need to mandate that for them as part of a mandated post-marketing study. I think that the field will do those studies appropriately.

DR. SIMON: We don't know that information for most chemotherapeutic drugs, and to really get that information would be very difficult because it would require essentially doing a therapeutic equivalence trial in a setting where the size of the benefit is actually very small. So, you would have to size it -- first of all, you would have to only include responders probably in the randomization, and then you would have to size it so you could detect whether you were losing, say, half the benefit. It would be a very, very large trial.

DR. DUTCHER: Okay. I think we did address some of number six, which is about pharmacokinetics. Pharmacokinetic data from the clinical and preclinical studies suggest that following administration in combination with paclitaxel, Herceptin serum concentrations are higher compared to those following administration of Herceptin as a single agent. This same effect is not apparent for the

combination of Herceptin with AC therapy. In addition, unexpected toxicities have been observed which were not predicted by preclinical testing. There is only anecdotal data to date on the combination of Herceptin with other anti-tumor agents. Given this information, if Herceptin is approved, should its indication as a combination therapy be limited to use only in those combinations whose pharmacokinetic interactions have been studied in a specific, prospective fashion?

DR. SEIGEL: We have received a lot of comments on it. If there are more, they are welcome but I don't think we need any more discussion.

DR. DUTCHER: Okay, question number seven is the immunohistochemistry question. Going to the last two sentences, in patients with 2+ overexpression -- let's see, no, I am going to go up a sentence.

While neither study 648 nor 649 was designed to determine the difference in clinical benefit between patients whose tumors were 2+ and those whose tumors were 3+ by immunohistochemistry testing for HER2/neu protein overexpression, exploratory analyses suggest that the benefits conferred by the addition of Herceptin to AC or T are largely or entirely seen in patients whose tumors exhibited 3+ overexpression of HER2/neu in study 648. In patients with 2+ overexpression, there was no suggestion of

benefit in time to progression, overall response rate, or survival. The response rate to single agent Herceptin in study 649 was also significantly lower for patients with 2+ overexpressing tumors as compared to those with 3+ overexpressing tumors.

(a) Given the known risk-benefit profile, should the indication for single agent Herceptin as second- or third-line therapy for metastatic breast cancer be limited to those patients who are 3+ by immunohistochemistry testing? Dr. Margolin?

DR. MARGOLIN: I think that given the fact that the data we looked at were exploratory and not based on pre-stratification, and the fact that there is still a pretty big overlap in those assays between 2+ and 3+, we are not ready to limit this indication to patients who are 3+.

DR. DUTCHER: Dr. O'Leary?

DR. O'LEARY: I would like to emphatically disagree, and I would like to disagree because of looking at the confusion matrix between the DAKO antibody and the test data set, considering the fact that about 80 percent of these tumors are expected to be not overexpressing.

If you were to include the 2+ in the DAKO assay you would have about as many people showing up who would be positive in the DAKO assay, 2+ and above, who were not in the group shown to have clinical benefit as you would in the

group shown to have clinical benefit. If you restrict it to 3+, it looks like you probably would be expected to exclude perhaps 20 percent of folks that might possibly benefit.

It seems to me that that lab interaction right now and the fact that this has been validated against, you know, sort of the wrong assay, and the principle of "do no harm" in this case would suggest that if you use the DAKO assay you are going to be including a lot of patients in therapy for whom benefit has not been demonstrated.

DR. DUTCHER: Dr. Miller?

DR. MILLER: I agree with Dr. O'Leary. I think that this drug should be used where we think it has the most chance of being efficacious. So, I would use the patients who are 3+.

DR. DUTCHER: Dr. Vose?

DR. VOSE: I have to disagree with that. I think that there is enough question about the assays and I wouldn't want to exclude 20 percent of patients that could possibly get a benefit from this when we have put out all these other stipulations as far as not using it with AC and doing the cardiac monitoring, and doing everything else. I think that would be a problem, to exclude that 20 percent of patients given that the we have to really evaluate that.

DR. SEIGEL: I am sorry, 20 percent is which?

DR. VOSE: Well, using the numbers that you were

saying, that 20 percent of patients, if we just go with using the 3+, we would exclude 20 percent of patients that could potentially get benefit from the Herceptin.

DR. MILLER: Yes, but that is 20 percent of patients who would be read as 3+ --

DR. VOSE: Right.

DR. MILLER: -- and 17-30 percent of those patients would respond. So, you are actually benefiting 30 percent of 20 percent. It is a much smaller number --

DR. VOSE: I understand it is a smaller number overall, but I think given the stipulations that we have said and the fact that the test is not perfect and needs to be further validated, I don't think it is proper to exclude those patients.

DR. SEIGEL: If we go with 1+ we are excluding 5 or so percent of the people that were 3+ by the study assay probably, and if we go with 2+ we would be excluding maybe 6, I guess. I guess we are really in the range of 3-5 percent of the patients. Is that okay, or should we just not use a test?

By the way, we are not going to ask for a vote here, and I should explain that these data will be presented in considerably greater length and detail, with a lot more time for discussion, to the device panel on Friday. We are going to integrate all of that information. Having had you

suffer with us, if you will, or having had the benefit with us of this extensive data, we really want to appreciate and integrate your advice.

DR. VOSE: It just seems to me that it hasn't been validated or not validated enough that we can answer this question. I think it needs further study.

DR. MILLER: I think the device panel, on Friday, is going to ask different questions than what you are asking as a clinical panel here. I mean, I think the vote on that would be much here than on Friday. I am going to be there on Friday but I think this is the panel you want to ask.

DR. DUTCHER: Dr. Simon?

DR. SIMON: I think there are two aspects to it. One is the aspect that Dr. Margolin was alluding to. In general, it is dangerous to sort of say, well, post hoc I am going to require demonstrating an effect in every subset. In this case, however, it is not every subset; it is a subset which, although it may not have been defined prospectively, is a subset which is inherently relevant. So, even though it is not a clear-cut situation, I feel, given that it looked like there was not one iota of evidence that there was a benefit of including the antibody with chemotherapy in the patients who were 2+, that in itself would start getting into issues of assay reproducibility. So, I would say you probably shouldn't restrict it to 3+.

But then when you get to issues of assay reproducibility, I think it even becomes more compelling to restrict it to patients with 3+ because if you look at the matrix that was put up there, if you look at the row that corresponded to 2+, 12 percent of the patients in that row were 3+. All the rest of them were either 2+, 1+ or 0+, and there were many, many more of them who were 1 and 0+ than there were who were 3+.

So, whereas you may say, well, yeah, if I included the 2+ -- it really works with the 3+ patient and, therefore, I want to do 2+ because I don't want to lose those 12 percent, by doing that you are just including a whole ton of women in whom there doesn't seem biologically or empirically to be any benefit.

DR. VOSE: Do you think there are enough numbers?

DR. SIMON: There were 150-something women in the second row.

DR. VOSE: Right. Do you think that is enough to validate that assay?

DR. SIMON: Well, I think immunohistochemical assays are notoriously unreproducible.

DR. VOSE: Right. That is the problem.

DR. SIMON: I mean, I believe that. I believe you have that spread.

DR. DUTCHER: Why don't we let Dr. Shak make one

rebuttal comment? Be very brief.

DR. SHAK: Being very brief at this late hour, we did point out the interaction but I want to reemphasize just two points. Number one, it is an interaction and not a test that excludes benefit, and that is very important. In the study that was overall negative it would be inappropriate to identify a subgroup that was positive and try to make a claim for proof of efficacy.

The second point is that in the exploration, in fact, there are examples of benefit in 2+ patients. It was pointed out in the single-agent study that there was a 6 percent response rate. Well, those are real and meaningful for those patients. Again, the confidence intervals around that are large, and those could be a significant number of women who have few other options in a very advanced setting.

[Slide]

Probably even more important is now a subgroup of a stratum, namely the paclitaxel group. In the paclitaxel group in 648 in the 2+ subgroup the response rate was 21 percent with Herceptin plus paclitaxel, and 11 percent with paclitaxel alone.

DR. SIMON: That doesn't seem to agree with the data that the FDA presented.

DR. SHAK: Well, the FDA presented data overall, which showed that overall there was no difference in

response rates.

[Slide]

With regard to time to progression, again, there is clearly evidence of a lesser magnitude of benefit but, again, we would be cautious in concluding from this that it would indicate that there was no benefit.

We would recommend, and I think it is what we have recommended, that it be that the insert clearly state and inform patients and physicians that it may be the case that there are lesser magnitudes of benefit with lower levels of HER2 overexpression. That would then allow within the context of the overall information provided with benefits and risks for individual treatment decisions to be made.

DR. DUTCHER: Thank you. Dr. Simon?

DR. SIMON: As a practical matter, given what was shown on that slide in terms of the reproducibility of that assay for 2+, the only way you are going to try to reclaim the small potential gain is by including the vast majority of patients -- I mean, more of them are going to be 1+ and 0+ than are even going to be 2+.

DR. DUTCHER: Dr. Schilsky?

DR. SCHILSKY: This is a tough issue, and I brought his up earlier. I think under most circumstances I would actually completely agree with Rich Simon's analysis, but that depends on having a lot of confidence in the data

that we have at the moment and on that concordance chart that was shown, which was based on specimens not even derived from the trial.

I actually come down on the side of thinking it would be a mistake at this point to restrict the use of this to just the 3+ patients because I don't actually know what 3+ means. There are going to be other assay methodologies that are available in the future, and I think that it is going to take some time in the context of the prospective use of Herceptin, with clearly defined assay methodologies, to sort this all out, and it probably would not be wise to limit it at this point.

DR. DUTCHER: Mixed reviews.

DR. SEIGEL: Let me ask another question which isn't exactly here but is related to that. Is there a relatively strong sense, if I read between the lines, that if there were to be approval of this drug and of the DAKO test kit, that there ought to be studies looking at it? We heard in the comment period that there are studies of 0 and 1+ patients under way now. I don't know with what test kit or what studies, but it seems like whatever is out there clinically available for screening for overexpression, it would be nice to have information as to extent to which results from that correlate, if not with survival which would require a randomized control, at least with response

rate outcome.

DR. DUTCHER: I think what you would like to see is some kind of a kit so that you really could show reproducibility in terms of multiple different people using it because right now, you know, some people call another pathologist and say, "is this positive or negative? Look what I see." So, I am concerned that, you know, there is going to be a lot of variability for a long time, but that doesn't mean that we are not going to treat patients based on that data. Dr. O'Leary?

DR. O'LEARY: My comment is that even if you address the reproducibility issues perfectly, it is the fact that the test kit that is being looked at is not the test kit that was being used to determine clinical benefit. It becomes a real issue here, and it would be awfully nice to see a rather direct relationship established at some point, assuming these are approved eventually, between the test kit performance and the clinical responses of the patients because this is a very, to me, unsatisfying surrogate.

DR. SEIGEL: Yes, in that regard, I would like to put out a little bit of a public plea. In many cases, and I can't speak specifically to this one, where studies are done, and we have a lot of them, where therapy is dependent on expression of a specific antigen, we ask, where possible and storable -- or on circulating levels of cytokines or

whatever they are based on, that specimens from the patients in the study be saved and stored so that subsequent tests for whatever that is can be used to study those patients to see what determinations are made on the basis of the results of that test. So, just a little plea for anybody listening or watching, and I certainly hope that that will more often than not be the case.

One thing perhaps I should toss out just as a flyer and, again, we are not on the verge of making decisions without a lot more discussion, but in integrating a lot of disparate comments, it occurs to me that one possible approach would be to write an indication that says that this should be used in patients who are strongly positive overexpresssors, and then to put into the labeling both the data showing that 2+ with the study assay had -- I wouldn't say not an iota but certainly not a lot of evidence in terms of efficacy, and the data showing the lack of correlation, with some commentary but leaving perhaps the indication not specifically linked to a specific outcome or a specific test, but with some commentary, as I said, pointing out, as I think Dr. Simon has, the fact that patients 2+ with DAKO are all over the board, for example. Would that be a consistent way to address a number of the concerns that we have heard?

DR. VOSE: I think that would be very acceptable.

If you say strongly positive, that would rule out those patients --

DR. SEIGEL: And then provide the data --

DR. VOSE: Provide the data and then they could make the decision.

DR. SEIGEL: Yes. Again, I am not saying we have decided to do that, but that would be one of the options that we might consider.

DR. DUTCHER: Dr. Norton?

DR. NORTON: Just as a clinician who has used the drug a lot, it is almost a plea -- we had any number of patients that tested 2+ with polyclonal antibodies that we used, and then tested 3+ with the Genentech antibody and had very good responses to therapy. I can just see, you know, the panic of having a situation where somebody was excluded from being able to treat these patients because of a very subjective test -- 2+, 3+ -- 3+ usually is obvious; 0 is usually obvious; 2+ can be all over the place and it is a very subjective test, and I think, you know, putting this sort of artificial numerical descriptor on it could be very dangerous and very destructive.

DR. DUTCHER: I don't see any more pages for the questions so I think we are dismissed.

DR. SEIGEL: Thank you very much.

DR. DUTCHER: We will be back here in twelve

hours.

[Whereupon, at 7:45 p.m., the proceedings were recessed until 8:00 a.m., Thursday, September 3, 1998]

- - -

CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Alice Toigo

ALICE TOIGO