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FOOD AND DRUG ADMINISTRATION

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Rajeshwari Sridhara, Ph.D. (p.m.)
Donna Griebel, M.D. (p.m.)

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P R O C E E D I N G S

Call to Order and Introductions

DR. NERENSTONE: I would like to start this morning's meeting. This is the Oncology Drugs Advisory Committee. Everyone make sure they are in the correct room.

I am Dr. Stacy Nerenstone and if you will bear with me a little bit, this is my first meeting that I am the chairperson.

I would like to start the meeting going around the room and having everyone introduce themselves for the public and for our audio which is recorded.

Dr. Taylor, if you would like to begin.

DR. TAYLOR: I am Dr. Sarah Taylor from the University of Kansas Medical Center. I am Director of Palliative Care and a Medical Oncologist.

DR. KELSEN: Dave Kelsen from Sloan-Kettering in New York. I am a Medical Oncologist.

DR. SIMON: Richard Simon. I am with the National Cancer Institute.

DR. SLEDGE: George Sledge, Indiana University, Medical Oncologist.

DR. LIPPMAN: Scott Lippman, M.D. Anderson Cancer Center, Medical Oncology.

DR. SANTANA: Victor Santana, St. Jude's Children's Research Hospital in Memphis, Tennessee.

DR. NERENSTONE: Stacy Nerenstone. I am a Medical Oncologist, Hartford, Connecticut.

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

DR. PRZEPIORKA: Donna Przepiorka, Baylor College of Medicine, Cell and Gene Therapy.

DR. PELUSI: Jody Pelusi from the Phoenix Indian Medical Center.

DR. REDMAN: Bruce Redman from the University of Michigan Comprehensive Cancer Center.

DR. ALBAIN: Kathy Albain, Loyola University Medical Center, Medical Oncologist.

DR. BLAYNEY: Douglas Blayney. I am a Medical Oncologist from Pasadena, California.

DR. COHEN: Martin Cohen, Medical Officer, FDA.

DR. JOHNSON: John Johnson, Clinical Team Leader, FDA.

DR. PAZDUR: Richard Pazdur, Division Director, FDA.

MS. ZOOK-FISCHLER: Sandra Zook-Fischler, patient representative.

Conflict of Interest Statement

DR. TEMPLETON-SOMERS: I have the Conflict of Interest Statement with regard to this session of this meeting.

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 and information provided by the participants, the Agency has determined that all reported interest in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exceptions.

In accordance with Section 208(b)(3), full waivers have been granted to Drs. Redman, Blayney, Lippman, Santana, Sledge, and Ms. Zook-Fischler. A copy of these waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of 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 financial involvement with any firm whose product

they may wish to comment upon.

Thank you very much.

DR. NERENSTONE: Thank you.

Open Public Hearing

We now move to the Open Public Hearing part of this morning's meeting. There are no speakers.

Is there anyone in the audience who had wished to address the application for Femara?

[No response.]

DR. NERENSTONE: Seeing none, we will continue on.

Dr. Johnson, if you would like to begin.

NDA 20-726/S-006 Femara (letrozole) Tablets

Novartis Pharmaceuticals Corporation

Introduction

DR. JOHNSON: Good morning.

[Slide.]

As a background for the committee session this morning on Femara, we will summarize the FDA's approval requirements for the initial treatment of advanced metastatic breast cancer. There are no absolute requirements. There are always exceptions to any set of requirements that we can write, but it is worthwhile to have a set of general requirements for approval.

[Slide.]

The approval requirements for cytotoxic drugs and

for hormonal drugs are somewhat different. Femara is a hormonal drug, but we will present the requirements for both cytotoxic drugs and hormonal drugs for completeness.

[Slide.]

Last year, the committee spent half a day on the approval requirements for new cytotoxic drugs for the initial treatment of advanced metastatic breast cancer.

This slide shows the committee's recommendations which have been accepted by the FDA. Randomized controlled trials are required, a favorable effect on survival is required for approval. A favorable effect on time to tumor progression is not adequate for approval, but may be adequate for accelerated approval provided the effect is impressive.

The committee made clear that a small but statistically significant effect on time to progression would not be adequate for accelerated approval. A favorable effect on tumor response alone is not adequate for approval.

[Slide.]

This slide shows the rationale for these requirements for the approval of cytotoxic drugs for the initial treatment of advanced metastatic breast cancer.

First, cytotoxic drugs have been shown to increase survival in this setting. Second, neither time to tumor progression nor tumor response is a proven surrogate for

survival. Finally, cytotoxic drugs for the most part have significant toxicity, and it is not clear that any of the modest effects on time to tumor progression or tumor response that are generally seen with available cytotoxic drugs are sufficient to overcome the toxicity of the drugs.

[Slide.]

This slide summarizes the approval requirements for new hormonal drugs for the initial treatment of advanced metastatic breast cancer. These are the requirements that Femara must meet.

Randomized controlled trials are required. Either a favorable effect on time to tumor progression or a favorable effect on tumor response is adequate for approval.

A favorable effect on survival is not required for approval. Usually, at the time these new hormonal drugs are being considered for approval by the FDA, survival data is not yet mature, but the FDA does require the submission of updated survival information at the time of approval because if survival were going badly in the wrong direction, the FDA would delay the approval until the survival situation became clear.

[Slide.]

The rationale for these requirements for approval of new hormonal drugs for the initial treatment of advanced metastatic breast cancer is shown on this slide.

First, hormonal drugs generally have modest toxicity and any favorable effect on time to tumor progression or tumor response is achieved at a lesser cost in toxicity than with cytotoxic drugs.

Second, a survival benefit has never been demonstrated for hormonal drugs in the initial treatment of advanced metastatic breast cancer. If we do have a new hormonal drug that improves survival, the FDA will probably require future hormonal drugs to have a favorable effect on survival to gain marketing approval, but at present, non-inferiority of survival is a safety endpoint and would not indicate that the drug had any efficacy in this respect.

[Slide.]

This slide shows the hormonal drugs that the FDA has approved for the initial treatment of advanced metastatic breast cancer. Nolvadex was approved in 1977. The basis of approval was a favorable effect on tumor response in non-randomized Phase II studies. Tamoxifen has never been shown to have a favorable effect on survival in this setting.

It was almost 20 years before additional hormonal drugs were developed for this use, but in the last five years the FDA has approved three additional drugs for this use, and the fourth drug, Femara, is on the agenda this morning.

This completes our summary. We can take questions now or later, but whichever you do, we would like to do it from the table.

DR. NERENSTONE: Are there any questions? I have a brief one. Dr. Johnson, from a regulatory standpoint, there is no need to compare a new hormone to an existing, already approved hormone, is that correct?

DR. JOHNSON: For the first-line use in the metastatic setting or certainly in the adjuvant setting, we have generally required comparative trials. Actually, this question has never arisen in our dealings with pharmaceutical companies because the competitive situation is such that they wouldn't be able to market their drug without large randomized trials.

DR. PAZDUR: But in addition to that, it would be very hard to understand or really analyze a single-arm study looking just at response rate or especially time to progression, it is a surrogate endpoint, just in a single-arm trial, exactly the meaning of it without putting it into a context of a randomized trial.

DR. NERENSTONE: So, you have no problem with them randomizing to the 1977 approved drug.

DR. JOHNSON: No, we have no problem with that.

DR. NERENSTONE: Dr. Temple.

DR. TEMPLE: Actually, as a general matter, there

isn't any requirement for comparisons at all, but there is a vice presidential proclamation about two years said that ir the case of serious life-threatening diseases, there is some requirement to compare a new therapy with old, so it is sort of an exception to the usual requirement.

DR. NERENSTONE: Dr. Blayney.

DR. BLAYNEY: Arimidex was recently approved. To my recollection, it was not brought before this committee. Could you refresh my memory on what basis and the indication for how it was approved?

DR. JOHNSON: All of these drugs were approved in the last five years. Actually, Arimidex was approved this summer. At the time they were being developed and clinical trials were initiated, there really wasn't anything else to compare them to except tamoxifen, so that wasn't an issue.

The Arimidex clinical trials, first, I should say that both Arimidex and Femara were approved some time ago for the second line treatment of metastatic breast cancer, and the comparator there was megestrol acetate in both cases. I believe one of them also compared their drug to aminoglutethimide.

Now, in first line, the Arimidex studies were really quite similar to what you will be hearing about Femara this morning. There were two studies with Arimidex in first line therapy of metastatic breast cancer, and the

comparator in each of those studies was tamoxifen, and the total number of patients in those two studies was a little over 1,000.

This morning we have one study with Femara that has 916 patients. So, both Arimidex and Femara are compared with tamoxifen, the total number of patients is about the same. Arimidex had a tumor response rate that was similar to tamoxifen in both of their randomized trials.

In the larger of their randomized trials, the time to tumor progression was identical to tamoxifen. It was eight months in both arms. In the smaller of their randomized trials, the time to progression on Arimidex I believe was about 11 months, and on tamoxifen was 5 months.

So, Arimidex did win on time to progression in the smaller of the two trials, but it didn't win on the tumor response in either of the trials, and the survival data on those trials is not yet mature.

DR. NERENSTONE: Dr. Simon.

DR. SIMON: Could you clarify for me what is the current FDA policy for approval of hormonal treatments for first line metastatic breast cancer? You indicated that the relevant endpoints were response rate and time to progression, but what do you have to show about those endpoints?

DR. JOHNSON: Well, it has to be shown to have a

favorable effect on either one of those two endpoints, and, of course, a favorable effect could be shown by beating the comparator, but if the comparator is effective, just being equivalent to the comparator is sufficient, and the tamoxifen is considered effective with respect to tumor response, so equivalent tumor response means the new drug is effective.

I don't believe tamoxifen has ever been shown to have a favorable effect on time to tumor progression, so equivalence to tamoxifen in that respect would not necessarily mean efficacy, so the new drug would have to win on tumor progression in order to be shown to be effective.

DR. NERENSTONE: Dr. Albain.

DR. ALBAIN: Dr. Johnson, I think I understood you to say that if this drug before us today, or any other future ones, shows a survival benefit, that all future hormonal agents would need to show a survival benefit with respect to the first showing of survival benefit, is that what you mentioned?

DR. JOHNSON: No, they would just have to show a survival benefit. It wouldn't have to beat the previous drug. It would have to be equal to it.

DR. ALBAIN: So, then, that would totally change how all the drugs have been approved up until this point. Then, we would have new guidelines saying all future drugs

would have to show a survival benefit?

DR. JOHNSON: Actually, I said probably, we would probably require future drugs to show a survival benefit, and, of course, the only way they could do that, they could beat something like tamoxifen or they could be equivalent to the new drug that did show the survival benefit.

DR. NERENSTONE: Thank you for that clarification, Dr. Johnson.

If there are no further questions, we will start now with the sponsor's presentation for Femara tablets for the indication as first line therapy in postmenopausal women with advanced breast cancer.

Dr. Hukkelhoven.

Sponsor Presentation

Introduction

DR. HUKKELHOVEN: Dr. Nerenstone, Dr. Temple, Dr. Pazdur, Members of the FDA Advisory Committee, FDA, and guests, good morning.

[Slide.]

My name is Mathias Hukkelhoven, Vice President of Drug Regulatory Affairs for Novartis Pharmaceuticals Corporation. On behalf of Novartis, I would like to thank you for the opportunity this morning to present and review Femara for a potentially new use in the treatment of advanced breast cancer. Specifically, we are seeking FDA

approval of Femara for the following indication.

[Slide.]

Femara (letrozole tablets) at a dose of 2.5 mg per day is indicated as first line hormonal therapy in postmenopausal women with advanced breast cancer.

[Slide.]

The current profile of Femara is as follows. Femara is a nonsteroidal aromatase inhibitor, blocking estrogen biosynthesis without influencing adrenal steroidogenesis. Since 1996, Femara has been approved as therapy for advanced breast cancer following anti-estrogen therapy in over 75 countries.

In the United States, Femara was approved in 1997. The specific indication in Femara's package insert reads that Femara is now indicated for treatment of advanced breast cancer in postmenopausal women with disease progression following anti-estrogen therapy.

[Slide.]

We estimate that since market introduction of Femara, more than 175,000 patients worldwide have received letrozole therapy at a dose of 2.5 mg per day. Since the introduction of Femara, very few serious adverse events were spontaneously reported to Novartis. This supports the current profile of Femara as a very well tolerated drug for endocrine therapy of breast cancer.

[Slide.]

Two Phase III studies form the basis for the NDA for first line breast cancer which was submitted in July of this year to the FDA. Study 25 is a pivotal, randomized, Phase III, double-blind, crossover study comparing Femara to tamoxifen in a first line therapy setting. Study 24 is a supportive double-blind study comparing Femara to tamoxifen in a preoperative treatment setting.

[Slide.]

In June of 1997, before the initiation of U.S. centers in Study 25, Novartis reached agreement with the FDA on the main characteristics of the study. Specifically it was agreed that the time to tumor progression was the primary endpoint for the study and that this single large study would be acceptable for registration of Femara as first line therapy in advanced breast cancer.

[Slide.]

The data derived from the pivotal Study 25, which is the largest randomized study in advanced breast cancer, support the following clinical profile for Femara. Femara at 2.5 mg once daily is more effective than tamoxifen in time to tumor progression, overall tumor response, clinical benefit and time to treatment failure.

As mentioned before, time to tumor progression is an accepted endpoint for efficacy of endocrine therapy in

cancer. The cumulative safety experience from all trials in first line treatment of advanced breast cancer further indicates that Femara is safe and well tolerated in this disease setting. This very favorable benefit-risk profile supports that Femara is a potential new standard of care in first line therapy of advanced breast cancer.

[Slide.]

This morning we would like to present to you detailed data on the role of Femara in the first line treatment of advanced breast cancer.

First, Dr. Harold Harvey will give an overview of current clinical practices in the endocrine therapy of advanced breast cancer. Dr. Harvey is Professor of Medicine at the Penn State College of Medicine in Hershey, Pennsylvania.

Subsequently, Dr. Ajay Bhatnagar will discuss the pharmacology of letrozole. Dr. Bhatnagar has been responsible for the preclinical research program for Femara within Novartis.

Then, Dr. Margaret Dugan will present the efficacy and safety data from the Femara clinical program in first line advanced breast cancer treatment. Dr. Dugan is group leader of the Femara program in the Clinical Research Department of Novartis.

[Slide.]

In addition to the presenters for this morning we also have several clinical experts and consultants attending this meeting. These experts are available for answering specific questions.

We have with us Dr. Henning Mouridsen who is the principal investigator for Study 25. Dr. Mouridsen is with the Rigs Hospital of the University of Copenhagen in Denmark. Also present today is the principal investigator for Study 24. His name is Dr. Matthew Ellis and he is an oncologist medical expert at Duke University in North Carolina.

Dr. Lloyd Fisher from the University of Washington in Seattle is our biostatistics consultant and finally the chairman of the Independent Femara Data Management Committee, Dr. Thomas Fleming is also attending. Dr. Fleming is Professor and Chair of the Department of Biostatistics at the University of Washington in Seattle.

[Slide.]

I would now like to turn the podium over to Dr. Harold Harvey for an overview of current clinical practices in the endocrine therapy of advanced breast cancer.

Current Clinical Practices

DR. HARVEY: Madam Chairman, colleagues and members of ODAC, Dr. Temple, Dr. Pazdur, Dr. Johnson, members of FDA, ladies and gentlemen.

As you have heard, I would like to present a brief overview of what I see as the current status of endocrine therapy in breast cancer.

[Slide.]

Hormone dependent breast cancer is I believe a very special subtype of breast cancer and indeed over the recent years we have recognized certain clinical and biologic features that help us identify this kind of disease and help us to choose patients for such therapies.

Hormone dependent breast cancer is characterized, first of all, by having a functional and intact estrogen and progesterone receptor apparatus. In general, these tumors tend to have a better histologic differentiation than the hormone independent counterpart.

Characteristically, the tumors have a low S phase, they tend to be diploid, and that goes along with the lesser degree of anaplasia one sees.

Patients who have hormone dependent breast cancer typically have a long disease-free interval, a long time between diagnosis and first metastasis, and the way metastasis does occur, we clinicians think that it tends to spread to sites of favorable disease, that is to say, the lungs, the chest wall or the pleura as opposed to, for example, deep visceral disease, such as the liver or lymphogenic spread to the lung.

Characteristically, then, for all the reasons I have stated, this kind of breast cancer will typically have an indolent course.

Two particular features I would like to draw to your attention are the following. In general, this kind of breast cancer is far more prevalent in older women, and in fact as women age, they are more likely to develop hormone dependent breast cancer.

Perhaps the most significant feature I think is the fact that we can treat this kind of breast cancer with sequential hormonal therapy, and I think this is a particularly important point.

In fact, I would suggest to you that this is a luxury that doesn't exist in all of oncology. We certainly can't treat endometrial cancer or prostate cancer and, heaven knows, not pancreatic cancer in this fashion, the same kinds of agents used in sequence.

[Slide.]

In fact, if you choose the patient correctly, use the features I have described, you can get an initial response that is anywhere from 30 to 60 percent, let's say, about 40 percent.

A subset of those responding patients will go on to respond to a second line of therapy, and a subset of those to a third line, a fourth line, and so on, until

ultimately we run up into the problem of hormone resistance.

Well, it would seem to me that if we can use these hormones in a sequential manner, we ought to determine what the optimal sequence of using these agents should be. As new agents become available, I think common sense dictates that the best agents be used earliest, and I think that is the strategy we should adopt as we go into the future.

[Slide.]

This slide looks at rough approximations of the prevalence of breast cancer in general and highlighted for you in yellow are the patients who would be candidates for endocrine therapy. These are large numbers, therefore, it is not a trivial problem.

[Slide.]

There are, as you know, several therapies currently available. These range from ovarian ablation through surgery or radiation therapy, or through the use of LHRH agonists, the role of antiestrogens and aromatase inhibitors, and older agents, as well as some newer promising agents, for example, the pure antiestrogens so called, or the newer LHRH antagonists.

[Slide.]

Now, as we choose patients for hormonal therapy, one of the things that we do is look at the age of the patient, and in an older patient, a postmenopausal patient,

our choices are a little bit different than a younger woman or the premenopausal subset. In older women, we tend to choose either antiestrogens or inhibitors of aromatase.

[Slide.]

A current concept in oncology, in fact a buzz word these days, is that of targeted therapy. We all want to treat our patients with targeted therapy, so we decrease toxicity and we target specific well-defined pathways.

What I would like to remind you, that, in fact, hormonal therapy is the first and, in my view, the most effective form of targeted therapy anywhere in oncology.

In the case of tamoxifen, for example, the target clearly is the estrogen receptor. We know that estrogen or tamoxifen compete for each other for binding to the receptor. After this happens, some series of downstream events occur that cause a cell to grow or, for examples, produce a new protein, such as a progesterone receptor.

This was the state of our knowledge up until fairly recently.

[Slide.]

More recently, we have understood that the function of the estrogen receptor is a great deal more complex. In fact, the estrogen receptor functions as a rather sophisticated transcription regulator.

We know now that estradiol or agents that we used

to call antiestrogens diffuse through the cell and they bind to an estrogen receptor. We understand the variance of estrogen receptor, so one can have, for example, estrogen receptor alpha and estrogen receptor beta.

This binding of the ligands to the receptor causes important conformational changes in the receptor and there is dimerization between the hormone of the ligand and the receptor protein. Once that occurs, there is induction of certain protein signals. These signals are referred to as either coactivators or corepressors, and they react with that transcription factors, forming a transcription complex which will then bind to the response element of DNA upstream from some estrogen target gene.

Once that occurs, then, the cell is instructed to either grow or divide or sometimes apoptose. I will show you later our understanding, our improved understanding of this receptor biology translates into therapy.

[Slide.]

Now, breast cancer compared to several other neoplasms is a relative indolent disease and particularly, as I said before, the hormone dependent subtype. I ask you to look at the natural history of this disease and realize that until recently we diagnosed this disease relatively late in its natural history.

Until recently, therefore, we intervened

therapeutically relatively late. What has happened in the last few years is increasing attention being paid to therapeutic intervention at earlier and earlier and earlier stages of this process.

[Slide.]

Now, bearing this curve in mind, let us look at the role of antiestrogens. Think, therefore, as breast cancer as a pathologic process in continuum.

I will submit to you that based on large, well-done, randomized clinical trials, many of which have in fact been approved here by ODAC in the past, that based on those trial, antiestrogens, and I am really talking about tamoxifen, tamoxifen has emerged as a drug which has had significant impact at every point along this continuum, certainly an effective agent in palliation of advanced disease, an agent which has improved the cure rate of breast cancer when used in the adjuvant setting, in some instances used neoadjuvantly to reduce primary tumors, and now used to prevent the progression of premalignant forms of the disease into invasive cancer, from DCIS to invasive carcinoma.

More recently, and I think quite excitingly, the possibility that this agent can prevent the disease in the first place. Tamoxifen, in my view, is perhaps the true wonder drug, the miracle that exists throughout all of medicine.

[Slide.]

As good and important a drug as tamoxifen has been, in contemporary times I ask you to think of two relatively new notions or concepts. What do we do once antiestrogen therapy, tamoxifen, has failed our patient, when the concept of blockade of the estrogen receptor is no longer viable or no longer effective?

I would submit that the next strategy is to investigate therapies which inhibit the synthesis of estrogen itself. A second notion is that as we conduct these clinical trials, we would hope to arrive at a family of agents which are as similarly effective as tamoxifen or perhaps even better than tamoxifen, the old previous gold standard.

[Slide.]

Now, talking about the synthesis of estrogen, let me remind you how this occurs and to sort of go over the pharmacology to the clinical setting. Think with me about an older woman who has been treated with tamoxifen, and that older woman, I used to think age 55 or so, but I was recently chastised, we can think of even older women, but in that postmenopausal woman or that woman who has become castrate either as a result of surgery or chemotherapy in the past, whose ovaries are no longer functioning, we can measure levels of estrogen in her blood.

Now, these estrogen levels derive from the conversion of androgenic precursors, primarily androstenedione and testosterone, and the conversion into estrogens is catalyzed by that Cytochrome p450 enzyme complex we refer to an aromatase.

[Slide.]

In this older woman, then, this postmenopausal woman, we understand that the adrenal gland secretes androgens and that these androgens undergo aromatization predominantly in peripheral tissues, peripheral tissues, such as muscle and especially adipose tissue or fat.

It has now been recognized that there is a second important site of conversion of androgens into estrogens, that in some tumors themselves, there is an important reservoir of aromatase activity. So, as we develop agents which target these pathways, in my mind these agents have to be sufficiently effective and potent to target both the peripheral site, as well as intratumoral site.

[Slide.]

I remind you that aromatization is, in fact, the terminal step in estrogen biosynthesis, and the drugs that affect this enzyme are either inactivators of the enzyme or competitive inhibitors, but it is this terminal step that is a target of specific therapy by modern day antiaromatase agents.

[Slide.]

In fact, as we have studied these agents in the laboratory and in the clinic, there has been a considerable evolution. We began by first reporting on what I would call a first generation compound, such as aminoglutethimide.

That compound offered significant toxicity. As time has gone on, we developed second and third generation compounds. These later compounds, such as anastrozole, exemestane, and letrozole, now have very exquisite specificity for the enzyme system - high selectivity, exact targeting for aromatase.

In addition, we now have compounds, such as letrozole, that are 100-, 1,000- to 10,000-fold more potent in inhibiting the enzyme than the earlier compounds, so we have made clear progress in the biology in this area.

[Slide.]

This slide indicates to you the structures of the available aromatase inhibitors. There are steroidal compounds, which are simple molecular changes of the major substrate androstenedione, and they are said to irreversibly inhibit the enzyme.

We have compounds that are nonsteroidal, and these are competitive inhibitors of the enzyme, letrozole and anastrozole.

[Slide.]

Well, why worry about new endocrine therapies in breast cancer? I think, as clinicians, we have to concede that faced with a patient with metastatic breast cancer, the likelihood of cure of this patient is very small.

Well, if cure is not our goal, I would submit to you that quality of life and a long duration of antitumor action is what we should be after. These then become the reasonable therapeutic goals as so beautifully outlined at the beginning by Dr. Johnson.

Aromatase inhibitors have been shown to offer an option to postmenopausal women who are no longer responding to antiestrogen, and they provide this option by, in fact, offering a better quality of life, better palliation, and a longer period of remission or response.

[Slide.]

You heard from the opening discussion that there have been three aromatase inhibitors approved relatively recently, and rather quickly I might add, by the FDA, and that is a good thing.

The first drug approved was anastrozole. Now, the three trials that led to the approval of these three aromatase inhibitors were similar in design for women who were postmenopausal whose disease had already progressed in the face of therapy with tamoxifen and who remained candidates for further endocrine therapy.

They were then randomized to receive either, in this study, anastrozole or at the time what we regarded as a standard second-line therapy, the standard of care for second-line hormonal therapy, the agent megestrol acetate.

So, in this first large trial, in fact two trials combined, anastrozole was compared to megestrol acetate. The second drug to be approved, as you have heard, was letrozole or Femara with similar design, again letrozole at 2.5 mg was compared to megestrol acetate.

Quite recently, the third drug, the steroidal inhibitor exemestane again compared to megestrol acetate.

Now, I am not asking you to make cross-study comparisons, but you will see that in every instance, anastrozole, letrozole, or exemestane, in every instance, the aromatase inhibitor was either equivalent to or better than the comparator megestrol acetate, for example.

[Slide.]

Well, that was second-line therapy. What could be the rationale, both clinical and scientific, for moving these agents up as first-line therapy? Well, these selective compounds, particularly anastrozole and letrozole, indeed represent a significant advantage over the then existing second-line drugs particularly in the older women, the postmenopausal women who had locally advanced or metastatic disease.

In clinical practice, they are, in fact, becoming rapidly established as the treatments of choice in this particular patient population. I believe that these results and this clinical experience then provide a rationale for studying aromatase inhibitors as first-line endocrine therapy in breast cancer.

In fact, as Dr. Johnson indicated, FDA, not ODAC, but FDA has fairly recently approved the first such indication for anastrozole. I remind you of this trial, which was a randomized, double-blind, double-dummy trial, in fact, two trials of identical design with the intent of combining the data.

Patients were randomized, these are all postmenopausal women with receptor-positive or presumed to have hormone-sensitive disease. They were then randomized to take anastrozole at 1 mg a day, the approved dose for this agent, or else tamoxifen at its approved dose, 20 mg a day.

[Slide.]

The major endpoint of this trial, as you have heard, was time to tumor progression, and these are the combined data from the two trials looking at the median time to progression comparing anastrozole with tamoxifen, and you can see that in this trial, anastrozole did every bit as well as tamoxifen, up until then the gold standard.

[Slide.]

The conclusions from that trial then would be that anastrozole is as effective as tamoxifen. In the course of the conduct of that trial, it was observed that was better tolerated, and specifically, it caused fewer thromboembolic events and less vaginal bleeding in these patients.

So, anastrozole became the first aromatase inhibitor to demonstrate at least equivalence to our old gold standard tamoxifen.

[Slide.]

The drug that you will be hearing about today is letrozole. There are many similarities between the two compounds letrozole and anastrozole, however, there are very interesting preclinical and pharmacologic differences and perhaps a richer preclinical profile attendant to letrozole.

We know, for example, that letrozole is fully capable of inhibiting both the aromatase targets I referred to at the very beginning, and, in fact, the next speaker, the discoverer of letrozole, will explain to you some of the differences between this drug and other available inhibitors.

[Slide.]

Now, you will remember at the beginning I tried to stress the importance in my mind of the sequential use of hormonal agents in breast cancer.

Let me in the end, then, get back to that and let me present to you my view of how hormonal therapies should be applied across the spectrum of breast cancer.

I suggest to you that tamoxifen or raloxifene depending on the results of the ongoing trial perhaps with diet or retinoids will be the mainstay of investigation of prevention of the disease, that until we have new data, tamoxifen will remain the major endocrine therapy used in the adjuvant setting, but that thereafter the paradigm ought to change and that the first line therapy, the first therapies for metastatic disease now ought to be aromatase inhibitors, effective potent aromatase inhibitors.

After that, there is second line therapy, perhaps using the newer agents, the so-called estrogen disrupters or estrogen downregulators, perhaps third line agents, such as progestins or androgens, and so on, until ultimately, we have solved the problem of resistance.

The real point, however, is that as we acquire new agents to treat this very prevalent form of breast cancer, we have to learn in what sequence to use them, use optimal agents early, and in so doing, offer our patients safe compounds, effective compounds, and significant greater palliation.

Thank you very much, Madam Chairman.

[Slide.]

Now, I would like to introduce Dr. Ajay Bhatnagar who has worked extensively with the compound letrozole.

Pharmacology of Letrozole

DR. BHATNAGAR: Dr. Nerenstone, members of the Oncologic Drugs Advisory Committee, ladies and gentlemen, good morning. My name is Ajay Bhatnagar and I am the Scientific Expert for Femara at Novartis Pharma in Basel, Switzerland.

[Slide.]

In my presentation today, I would first like to go through the mechanism of action of aromatase inhibitors and to compare this mechanism of action with that of the antiestrogens.

I would like to follow that with a discussion of intratumoral aromatase to show its importance and relevance to the pharmacology of aromatase inhibitors, and I would like to end by highlighting some of the data published since the submission of the NDA for Femara for second line treatment in 1996.

[Slide.]

Through the elegant work of the late Bill McGuire in Texas, we know that many breast cancers contain the estrogen receptor and that this estrogen receptor binds the estrogen and after that initiates a cascade of events both in tumor and non-tumor tissues that eventually leads to a

growth stimulus.

There are many other intracellular mechanisms which assist in this process, but the growth stimulus is initiated always by the binding of estrogen to its receptor.

The strategies have been developed for the treatment of hormone-dependent breast cancer that have one of two modalities. They can either antagonize the binding of estrogen to its receptor--and this is done, as Dr. Harvey told us, by a class of compounds called the antiestrogens, of which tamoxifen is the gold standard--or one can reduce the amount of estrogen to which the cell is exposed by inhibiting estrogen biosynthesis, and that is done using a class of compounds called aromatase inhibitors, of which letrozole and anastrozole are two members.

The one fundamental difference between the mechanism of action of these two agents is that whereas antiestrogens block the signal transmission from estrogen to the estrogen receptor and onto the growth stimulus, they have no effect whatsoever on one of the components of the growth stimulus, which is estrogen itself.

Aromatase inhibitors, on the other hand, inhibit the production of the growth stimulus itself and therefore have a more direct effect on the inhibition of growth.

[Slide.]

Now, in 1996, we presented to you the

pharmacologic profile of letrozole and characterized it by the three generic elements shown on this slide.

We showed you the inhibition of aromatase in vitro and in vivo, the selectivity of aromatase inhibition which meant maximal inhibition of estrogen biosynthesis at concentrations and doses where none of the other physiologically important hormones like cortisol were affected, and then we demonstrated the efficacy of estrogen deprivation in animals and in some early human studies.

[Slide.]

In that dossier for Femara we show letrozole to be highly potent, we showed it to be very selective, and we showed it to be an efficacious aromatase inhibitor in both endocrine and in non-tumor systems.

In addition, in some early results from our lab, we also showed it to be the more potent of the aromatase inhibitors compared to anastrozole.

[Slide.]

Now, in the last 10 years, the aromatase inhibitors that have been approved for use in the United States have been, as we have heard, Femara and Arimidex and Aromasin.

The other first and second generation inhibitors, like aminoglutethimide, Orimeten, fadrozole and formestane, are available in other countries outside the United States

like Europe.

However if we come back to the three compounds that are available to the U.S., we see that both letrozole and anastrozole belong to the sub-class of compounds called nonsteroidal aromatase inhibitors, whereas Aromasin is a steroidal aromatase inhibitor. Therefore we have tried to compare in the sub-class of nonsteroidal aromatase inhibitors the pharmacology of these compounds in a more special way.

[Slide.]

Over the past several years, Dr. Miller and his colleagues in Edinburgh, Scotland, have been showing something that is becoming of increasing importance to this area. They have demonstrated, like Bill McGuire did, that the tumor cells contain estrogen receptor. They have demonstrated that many breast cancer cells contain their own aromatase enzyme.

This enzyme is identical in its enzymatic properties to the enzyme found peripherally either in adipose tissue, in the ovary, or in human placenta. Therefore, it becomes important for us to look at the ability of aromatase inhibitors, not only to inhibit peripheral aromatase, but also to inhibit aromatase within the tumor.

Both these enzymes use the same precursor

androstenedione that comes from the adrenal gland in postmenopausal women.

[Slide.]

In collaboration with Dr. Miller in Edinburgh, Scotland, and Dr. Angela Brodie in Maryland, we took five different sources of aromatase. We took aromatase that comes from the placenta, extracted it in the form of microsomes, so we had a human source of aromatase in a cell-free environment.

We then took four cellular sources of aromatase. One was a rodent species, the hamster ovary, it was an endocrine tissue, cellular in nature. We took human breast adipose fibroblasts obtained from reduction mammoplasties, and then we took two cancer cell lines.

Now, most tumors contain relatively low amounts of aromatase, and so we took the most commonly used human breast cancer cell line, the MCF-7 cell, transfected it with the aromatase gene so that it could make its own aromatase enzyme, and we could then have adequate aromatase in the cell to study inhibition.

We also took a human choriocarcinoma cell line, the JEG-3 cell line. This is characterized by the fact that although it contains adequate amounts of aromatase, it doesn't contain any estrogen receptor.

Then, we took these five settings and compared the

inhibition of aromatase by letrozole or by anastrozole in these settings.

[Slide.]

So as to be able to show you the results on one slide, we have chosen to depict the potencies of these compounds as relative potencies. We chose arbitrarily anastrozole as having a relative potency of one, and compared letrozole to it.

You see here that in the placental aromatase from a cell-free source, the potencies of the two agents are almost identical. They are equipotent, only a factor of 2 for letrozole over anastrozole, which in this system is totally insignificant.

However, as soon as one introduces a cell membrane, whether it be in the rodent species or a human species, whether it be non-endocrine or in tumor cells, one sees that letrozole is at least a factor of 10 or more, more potent than anastrozole in these cellular systems.

Therefore, we felt that maybe that one of the differentiating factors in the potency of aromatase inhibitors in biological systems was their ability to inhibit the two types of enzymes.

[Slide.]

So, based on these results, a small research study was developed, which is shown on this slide.

Six breast cancer patients were randomized either to Femara at its approved dose of 2.5 mg once daily or to anastrozole at its approved dose of 1 mg once daily. They were treated for six weeks and then crossed over, the Femara patients being crossed over to anastrozole, and the anastrozole patients being crossed over to Femara, and these patients were treated for a subsequent six week period.

At the start of this study, at the crossover, and at the end of the study, blood was sampled and whole body in vivo aromatization was measured.

[Slide.]

The crossovers were arbitrarily defined as Crossover 1 going from anastrozole to Femara, and Crossover 2 going from Femara to anastrozole.

In Crossover 1, that is, those patients that started on anastrozole, we see that all six of the patients on anastrozole showed residual amounts of in vivo aromatization.

When they were crossed over to Femara, they all showed 100 percent inhibition of in vivo aromatization or complete inhibition of in vivo aromatization in the biological system.

In Crossover 2, those patients that started on Femara, you see they started with complete inhibition or 100 percent inhibition of in vivo aromatization, and when they

were crossed over to anastrozole, five of the six patients recovered some of their residual in vivo aromatization abilities that have been shown here. One patient, however, did remain in complete inhibition of in vivo aromatization.

This difference between Femara and anastrozole was statistically significant at the 0.003 level.

Now, these data and those in the cells that I showed you previously help in documenting that letrozole inhibits in vivo aromatization and aromatase in general more effectively than does anastrozole.

[Slide.]

We now come back to our original concept where we have now shown differences in the ability of aromatase inhibitors to inhibit aromatase of cellular origin.

We now would like to show you some results comparing the aromatase inhibitors to antiestrogens in a special experimental design. This design was created by Dr. Angela Brodie.

[Slide.]

What she did was to use the MCF-7 breast cancer cells that we had used in vitro, which had been transfected with aromatase gene. These were inoculated into nude mice to create a xenograft, and then animals were treated either with placebo, letrozole, anastrozole, or tamoxifen.

Those animals treated with placebo showed

substantial tumor growth after 56 days. Animals treated with letrozole, anastrozole, and tamoxifen were all three statistically significantly better than the control, however, letrozole was better than tamoxifen, and this difference was statistically significant, and letrozole was also better in reducing tumor weight than anastrozole, which goes to further document and complement the results we have shown you previously comparing anastrozole to letrozole.

[Slide.]

Thus, in conclusion, I hope I have shown you data that letrozole is a more potent aromatase inhibitor than anastrozole in the preclinical setting, is a more effective aromatase inhibitors than anastrozole in the human setting, and a more effective antitumor agent than both anastrozole and the antiestrogen tamoxifen in an animal tumor model.

Thank you.

I would now like to ask Dr. Margaret Dugan to present the clinical results of Femara versus tamoxifen.

Clinical Data and Conclusions

DR. DUGAN: Good morning. I will review the efficacy and safety results of the Femara Clinical Program which support FDA approval of Femara for first-line therapy in postmenopausal women with advanced breast cancer.

[Slide.]

Two, large prospective double-blind, randomized,

well-controlled, multinational studies in postmenopausal women with breast cancer comparing Femara 2.5 mg versus tamoxifen 20 mg have been conducted that document the superior efficacy of Femara over tamoxifen in previously treated and therapy-naive patients.

Study 25, the pivotal study, compared these treatments as first-line therapy in locally advanced and metastatic disease patients.

Study 24, a supportive study, compared the same treatments as preoperative therapy at an earlier stage of disease when patients were therapy-naive.

[Slide.]

I would now like to first review with you the conduct and results of pivotal study 25.

[Slide.]

In Study 25, eligible patients were randomly assigned double-blind treatments with either Femara or tamoxifen which they continued until disease progression or unacceptable toxicity.

This is defined as the core phase of the study. There was no stratification by baseline demographic or disease characteristics. At such time when a patient was discontinued from her initial treatment, if still suitable for further endocrine treatment, she was to receive crossover treatment, again in a double-blind fashion, until

further disease progression. All patients are being followed for survival.

It should be noted that as originally planned, Study 25 included a third arm of combination treatment with Femara and tamoxifen. The combination arm was discontinued early in the conduct of the trial when data became available of a pharmacokinetic interaction between these agents.

I will be presenting the results of the core phase of the study for the monotherapy arms only.

[Slide.]

Inclusion criteria for Study 25 included: postmenopausal women with Stage IIIB locally advanced or locoregional recurrence not amenable to surgery or radiation therapy or metastatic breast cancer.

ER and/or PgR positive or both hormone receptors unknown.

KPS of greater than or equal to 50 and measurable or evaluable disease.

[Slide.]

Exclusion criteria included: patients with a recurrence on adjuvant tamoxifen therapy or within 12 months of completing such adjuvant therapy. Prior endocrine therapy for metastatic disease. More than one systemic chemotherapy for recurrent or advanced disease.

These first two criteria were to insure that

endocrine-sensitive patients would be enrolled.

[Slide.]

The primary endpoint of the study was time to progression. Other major efficacy endpoints included: Time to treatment failure, objective overall response, confirmed CR or PR, clinical benefit rate, confirmed CR, PR, and stable disease greater than or equal to 24 weeks, duration of objective response, duration of clinical benefit and survival.

The completed primary analysis that I will present includes these efficacy and safety results on the initial treatments during the core phase of the study. Information is not yet available on the crossover treatments during the extension phase nor on survival.

The analysis plan for survival included two interims and a final analysis. Both interim analyses have been completed. It is the recommendation of an independent Data Monitoring Committee, under the chairmanship of Dr. Thomas Fleming, that the study has met its primary objective, that the study should continue follow-up for survival as specified per protocol and that the blinded results of the second interim analysis performed on November 10, 2000, not be disclosed at present.

This has been discussed and agreed to with the Agency. The Agency will make a statement with regard to

safety and survival during the Medical Reviewer's presentation.

[Slide.]

Scheduled evaluations were performed at regular intervals and included tumor measurements, performance status and laboratory assessments at baseline and every three months. Adverse events and survival were continually monitored.

[Slide.]

The primary assumption in the design of the trial was that treatment with Femara would demonstrate superiority as compared to tamoxifen, demonstrating a 20 percent reduction in the risk of progression, 80 percent power.

These treatment differences would be compared using an unadjusted Cox regression test, with two sided significance at a 5 percent level.

The required sample size was estimated at 450 patients per arm.

[Slide.]

Further prospectively-defined analyses included: Unadjusted analyses of rates of overall objective response and clinical benefit by logistic regression.

Adjusted multivariate analyses of time to progression and overall response rate adjusting for all predefined covariates. Three key baseline covariates were

defined as prior adjuvant tamoxifen, hormone receptor status, and dominant site of disease.

Stratified analyses of time to progression and overall response rate adjusting for each baseline covariate one at a time were also performed.

[Slide.]

The study enrolled a total of 916 patients, from 201 centers in 29 countries worldwide from November 1996 until January 1999. The cutoff date for this completed primary analysis is March 2000, 14 months after enrollment of the last patient.

[Slide.]

For all 916 randomized patients, 21 percent of patients remained on initial double-blind treatment at the time of data cutoff, with 79 percent having been discontinued from their initial treatment.

43 percent of all randomized patients received crossover treatment, again in a double-blind fashion.

The intent-to-treat analysis that I will present includes a total of 907 patients randomized. Nine patients were not included in this analysis, 5 patients with no evidence of active breast cancer at the time of study enrollment as prospectively designed, and 4 patients from one GCP non-compliant center.

The analyses of all randomized patients are nearly

identical to those that I will present. Two patients never received study medication.

[Slide.]

The baseline demographics were well-balanced between treatment groups. The median age for the study population was 65 years, with 33 percent of patients 70 years or older and 14 percent of patients less than 50 years of age, 92 percent of patients had a good performance status, KPS greater than or equal to 70, and 86 percent of patients were Caucasian.

[Slide.]

Receptor status was well balanced between treatment groups. 40 percent of patients had both ER and PgR positive, 26 percent had either receptor positive and approximately one-third of the population had both receptors unknown.

[Slide.]

Disease classification was well balanced between treatment groups, 70 percent of patients had at least one site of measurable disease, 27 percent had evaluable disease with or without non-evaluable disease, and only 3 percent had non-evaluable disease only.

The study was amended to allow patients with blastic bone only disease. The bone lesions in these patients were considered non-evaluable and therefore these

patients were assessed for disease progression only.

[Slide.]

Baseline disease characteristics were well balanced between treatment groups. Sites of disease were evaluated as either a dominant site or number of organ sites involved.

Dominant sites of disease were prospectively defined as soft tissue only, bone with or without soft tissue, and visceral dominant disease with or without bone or with or without soft tissue disease.

44 percent of all patients had visceral dominant disease with 13 percent having liver metastases. Approximately one-third of all patients had either one, two, or three or more organ sites involved.

[Slide.]

Baseline disease history was well balanced between treatment groups. The majority of patients had metastatic disease at study entry with only 6 percent having locally advanced Stage IIIB disease not amenable to surgery or radiation therapy. The median disease-free interval for all patients was 2.8 years.

[Slide.]

Prior therapies were well balanced between treatment groups - 37 percent of all patients having received any prior systemic adjuvant therapy, 19 percent

received prior chemotherapy alone, and a combined total of 18 percent received prior adjuvant tamoxifen with or without chemotherapy.

In those patients who received adjuvant tamoxifen, the median duration of adjuvant tamoxifen was 2.8 years for Femara and 2.3 years for tamoxifen.

A small percentage of patients, 10 percent received chemotherapy for recurrent or advanced disease.

[Slide.]

I would now like to describe to you the major efficacy results of pivotal Study 25 starting with the primary endpoint of time to progression.

This slide graphically represents the Kaplan-Meier curves for time to progression for both treatments, Femara and tamoxifen. The median time to progression was 9.4 months for Femara as compared to 6 months for tamoxifen, with 68 percent and 77 percent of patients, respectively, having progressed. The median time to progression was prolonged for Femara by 56 percent.

Femara was statistically significantly superior to tamoxifen in time to progression reducing the risk of progression by 30 percent, hazard ratio of 0.70, p-value of less than 0.0001.

More relevant, these treatment differences favoring Femara are clinically important to patients.

[Slide.]

As both treatments are relatively safe, time to progression and time to treatment failure should be similar. As demonstrated here, the results of time to treatment failure were also statistically significantly superior for Femara, with a 29 percent reduction in time to progression with a hazard ratio of 0.71 and a p-value of less than 0.0001. The median time to treatment failure was 9.1 months for Femara as compared to 5.7 months for tamoxifen.

[Slide.]

Treatment with Femara resulted in a significantly higher overall confirmed objective tumor response rate, 30 percent for Femara as compared to 20 percent for tamoxifen, with 71 percent higher odds of responding to Femara than tamoxifen, p-value 0.0006.

[Slide.]

Treatment with Femara also resulted in a significantly higher clinical benefit rate, 49 percent for Femara as compared to 38 percent for tamoxifen, with 55 percent higher odds of responding to Femara, p-value 0.001.

[Slide.]

The duration of response as well as the duration of clinical benefit in responding patients was similar between treatment group, although a significantly higher percentage of patients, 30 percent for Femara, 20 percent

for tamoxifen, responded with objective response, and 49 percent for Femara, 38 percent for tamoxifen with clinical benefit.

[Slide.]

A stratified log-rank analysis of time to progression was conducted on the prospectively defined key baseline covariates of prior adjuvant treatment, receptor status and dominant site of disease.

This analysis confirmed that the treatment difference adjusted over the strata for each covariate always statistically significantly favored treatment with Femara, p-value less than or equal to 0.0001 for each covariate.

Again, similar to the results of the intent-to-treat analysis, these treatment differences among these relevant subgroups are consistently demonstrated.

[Slide.]

A Cox regression analysis of time to progression within the strata for each key baseline covariate was performed. This forest plot represents the hazard ratios and the 95 percent confidence intervals for that analysis.

The hazard ratios, Femara compared to tamoxifen, are plotted on the x axis. A hazard ratio of less than 1 favors Femara, greater than 1 favors tamoxifen. A confidence interval which crosses a hazard ratio of 1 is not

significant.

The results for the intent-to-treat population as well as the within strata comparisons for each key baseline covariate are shown on the y axis. As shown by this analysis, treatment differences in time to progression are consistently and statistically significant favoring treatment with Femara.

As can be seen in this forest plot, the reduction in the risk of progression is consistently approximately 30 percent for all subgroups whether you received prior adjuvant tamoxifen, whether you are receptor positive, and independent of site of dominant disease.

These results were consistent with the overall intent-to-treat population. These data from this large double-blind, randomized study demonstrate that Femara is consistently superior to tamoxifen in time to progression, across relevant study subsets, and that these treatment differences are clinically important to the patient no matter which subgroup she may fall into.

[Slide.]

A Cochran Mantel-Haenzel analysis of overall objective response was conducted on the same prospectively defined key baseline covariates of prior adjuvant treatment with tamoxifen, receptor status, and dominant site of disease.

This analysis confirmed that the treatment difference adjusted over the strata for each baseline covariate always statistically significantly favored treatment with Femara, p less than 0.001 for each covariate.

Again, similar to the results of the intent-to-treat analysis, these treatment differences among these relevant subgroups are consistently demonstrated.

[Slide.]

A logistic regression analysis of overall response within the strata for the same key baseline covariates was performed. This forest plot represents the odds ratios and 95 percent confidence intervals for that analysis.

The odds ratios, Femara compared to tamoxifen are plotted on the x axis. In this case, an odds ratio of greater than 1 favors treatment with Femara and less than 1 favors tamoxifen.

The ITT population, as well as the within strata comparisons for each kay baseline covariate, are shown on the y axis. As shown by this analysis, treatment differences in overall response are consistently and in all but two subgroups statistically significant favoring treatment with Femara with a higher odds of responding.

Positive trends were demonstrated for the two subgroups of receptor unknown, p equals 0.07, and bone dominant disease, p equals 0.08. These data demonstrate

that Femara is consistently superior to tamoxifen in overall response across relevant study subsets. More importantly, patients with prior exposure to adjuvant tamoxifen had four times more odds of responding to Femara.

[Slide.]

In summary, Study 25 is the largest, single, double-blind, randomized Phase III adequate and well-controlled, multinational trial in first-line therapy of advanced breast cancer.

Study 25 has clearly demonstrated that Femara is consistently statistically significantly superior to tamoxifen in multiple efficacy endpoints. However, these advantages are clinically important to all subgroups of patients. These benefits include superiority in: time to progression, time to treatment failure, overall response rate, clinical benefit rate, and in all relevant subgroup analysis of time to progression, the primary endpoint.

[Slide.]

I would now like to briefly describe to you the conduct and results of the supportive study 24. This study was designed as an independent, Phase III, prospective, double-blind, randomized, multinational study to compare the efficacy of Femara and tamoxifen as preoperative treatments in a selected group of patients who were therapy-naive.

[Slide.]

In Study 24, eligible patients were randomly assigned double-blind treatments with either Femara or tamoxifen, which they were to continue for four months, at which time patients were to undergo surgical resection of the primary tumor, either mastectomy or, if eligible, breast conserving surgery.

Any additional therapies following surgery were left to the discretion of the individual investigator. All patients are being followed for relapse and survival yearly for five years.

[Slide.]

Entry criteria for Study 24 included: postmenopausal women with breast cancer, not eligible for breast conserving surgery, who were ER and/or PgR positive, clinical Stage T2 through T4c, nodal status up to N-2, no evidence of metastatic disease, and measurable disease at study entry.

[Slide.]

The primary endpoint of the study was response rate complete and partial by clinical palpation. Secondary endpoints included. Response rate by ultrasound and mammography, and rate of breast conserving surgery.

In addition, a correlative science substudy to evaluate tumor tissue both pre- and post-study treatments was included to evaluate various bimolecular markers.

[Slide.]

The primary assumption in the design of this study was that treatment with Femara would demonstrate superiority as compared to tamoxifen, demonstrating a 15 percent difference in clinical response rate, 80 percent power. This assumed that the response rate for tamoxifen was 65 percent.

These treatment differences would be compared using a Mantel-Haenszel test stratified by tumor size and lymph node involvement at the time of study entry, with two sided significance at a 5 percent level.

The required sample size was estimated at approximately 150 patients per arm.

[Slide.]

From March 1998 until August of 1999, a total of 55 centers in 16 countries worldwide enrolled 337 patients. There was a slight numeric difference in the randomization, leading to 162 patients on Femara and 175 patients on tamoxifen.

The intent-to-treat analysis that follows includes a total of 324 patients. Thirteen patients were not included in this analysis. Four patients with no evidence of active breast cancer at the time of study enrollment as prospectively designed and 9 patients from two GCP non-compliant centers.

[Slide.]

Baseline characteristics were well balanced between treatment groups. The median age was 67 years. As required by protocol, all but 3 patients in the tamoxifen group were ER and/or PgR positive, with 56 percent of all patients having both receptors positive. Fifty-two percent of all patients had T2 disease while the remainder of patients were evenly distributed between T3 and T4 disease.

[Slide.]

Fifty-five percent of patients had Stage IIA/IIB disease, 26 percent of patients had Stage IIIB disease.

[Slide.]

Treatment with Femara resulted in a significantly higher response rate as assessed by clinical palpation, 55 percent as compared to 36 percent for tamoxifen, p-value of less than 0.001.

Similarly, significantly higher response rates were demonstrated by ultrasound and mammography. In addition, the rate of breast-conserving surgery was also significantly higher for treatment with Femara, 45 percent as compared to 35 percent for tamoxifen, p-value of 0.022.

[Slide.]

In summary, Study 24 is a large, double-blind, randomized Phase III adequate and well-controlled multinational study. Study 24 has clearly demonstrated in

therapy-naive, hormone receptor-positive postmenopausal women with breast cancer that Femara is superior to tamoxifen in rate of response and rate of breast-conserving surgery.

[Slide.]

I would now like to review the safety data from both trials.

[Slide.]

All adverse events reported at least once greater than or equal to 10 percent of patients are shown for both studies 25 and 24. As can be seen here, the number of individual adverse events is low in both studies.

These adverse events are not unexpected and are reported with a similar incidence for each treatment group in each study. Study discontinuations due to adverse events or deaths were similar in both treatment groups and low.

For Study 25, in these most frequently reported adverse events, the percentage of CTC Grade 3 or 4 events was approximately 1 to 2 percent except for bone pain, arthralgia, and back pain where it was approximately 5 percent of patients.

[Slide.]

On review of selected adverse events known to these agents, the numbers of patients reporting either thromboembolic events, pulmonary embolism, cardiovascular

events, cerebrovascular events, or fractures, which were mostly related to tumor, were similar between treatment groups.

[Slide.]

In conclusion, Femara is well tolerated with a low incidence of adverse events.

[Slide.]

In summary, we have presented to you today the results of two large prospective, double-blind, randomized, adequate and well-controlled multinational trials. Study 25 forms the basis of approval for Femara as first-line therapy in postmenopausal women with advanced breast cancer.

[Slide.]

The efficacy results from Study 25 convincingly demonstrate in this largest single study conducted in first-line therapy, that Femara is consistently superior to tamoxifen in multiple efficacy endpoints - time to progression, time to treatment failure, overall response, and clinical benefit, that Femara is consistently superior to tamoxifen across prospectively defined relevant study subsets, including prior adjuvant tamoxifen, hormone receptor status and dominant site of disease, and that these treatment differences are clinically important to all patients.

In addition, Study 24 supports the superior

efficacy of Femara compared to tamoxifen. Femara is safe and well tolerated.

[Slide.]

Femara is indicated as first-line hormonal therapy of postmenopausal women with advanced breast cancer. The positive clinical benefits demonstrated in these studies clearly support approval of this indication.

[Slide.]

Breast cancer remains an important health issue worldwide. Newer endocrine therapies are needed in advanced breast cancer. Aromatase inhibitors are established second-line therapies. Femara is more potent and effective than either anastrozole or tamoxifen in preclinical models.

[Slide.]

Femara is superior to tamoxifen in the largest single, randomized clinical trial in first-line therapy. Femara sets a new standard of care in the treatment of postmenopausal women with advanced breast cancer.

Thank you very much for your attention. My colleagues and I, as well as our consulting medical experts, will be pleased to answer any questions that you may have.

DR. NERENSTONE: Thank you very much.

We will now open up questions from the committee.

Questions from the Committee

DR. PRZEPIORKA: One short question. Can you tell

us, please, were there any secondary malignancies in either of those two studies?

DR. DUGAN: One patient on the tamoxifen arm in Study 25 had an endometrial carcinoma that was reported, and she had received prior adjuvant tamoxifen therapy.

DR. NERENSTONE: Dr. Albain.

DR. ALBAIN: I have several questions. The first set pertains to sample size determinations, endpoints, and the survival look.

With regard to the latter first, as I understood it, there was no Data Monitoring Committee initially and that this was convened in the course of the analytical phase of the trial, and, as such, you have now conducted the second of the three planned looks by the Data Monitoring Committee. This was just done in November, is that correct?

DR. DUGAN: Correct.

DR. ALBAIN: What were the predetermined rules set up by the Data Monitoring Committee to report survival at this point since you are not choosing to report survival, what limits were set forth by the Data Monitoring Committee to give a report to us on survival would that have existed since none of that is in our materials?

DR. DUGAN: I would like to invite Dr. Thomas Fleming, the chairman of that committee, to address that issue.

DR. FLEMING: Hi, Kathy. This is Tom Fleming, University of Washington and chair of the Monitoring Committee. Maybe I can give just a little bit of background leading up into that.

As Dr. Dugan had pointed out, the sponsor gathered an independent group of international biostatisticians and clinicians to form the monitoring of this study in May of this year. I served as the chair of this committee and I had clinical investigators or clinical experts from five countries.

When we first met, we realized that the study had completed its core phase and the primary endpoint information that has been presented to you today was complete.

We also recognized that the survival data was essentially early and that it was still very timely to do standard independent monitoring of evolving survival information, so we made a recommendation in May of this year that we proceed with standard monitoring of the trial that essentially involved our committee having sole access to evolving survival information and that we would follow group sequential guidelines, as you had suggested or had referred to, and that specifically the interim analyses would occur in May, a second interim analyses six to nine months later, and then the final analysis in November of next year.

That second interim analysis actually occurred November 10th, specifically to have information in advance of this meeting. The committee was using a standard O'Brian-Fleming group sequential guideline for monitoring strength of evidence.

DR. ALBAIN: Would you refresh our memory what that was? Usually, in a protocol that is spelled out upfront, and since this trial did not have it, what did you establish that you would allow a reporting at the second analysis?

DR. FLEMING: Very good point. It was certainly our perspective that ideally, exactly as you say, this should have been established upfront, and looking at the glass is half-empty or half-full, our perspective was at this point it was still timely to implement such a procedure.

The O'Brian-Fleming guideline looking at survival differences is May used a significance level, one sided, of approximately 0.001, and looking in November, used a one-sided significance level of approximately 0.01.

I just might quickly give you what our three key recommendations were at the time of this November look. In November, our conclusions were that the current interim survival data reviewed at this November 2000 meeting remained inconclusive, neither establishing that Femara

provides superior survival relative to tamoxifen, nor ruling out that Femara can provide a clinically meaningful survival advantage, so neither conclusively positive nor conclusively negative.

But important insights remain to be gained regarding the relative effects of these endocrine therapies on longer term survival outcomes both overall and in important subgroups.

Secondly, we recommended that available evidence suggests that it is ethically and scientifically appropriate for patients to continue their treatment in the blinded trial, and finally, we again recommended that efforts should be made to continue to maintain confidentiality of the survival data in this trial in order to preserve the integrity of the ongoing blinded study.

DR. NERENSTONE: Dr. Blayney.

DR. BLAYNEY: Dr. Fleming, then, I am given to understand, based on what you said, that it could go either way, survival could be worse or it could be no worse or better, I didn't quite understand.

DR. FLEMING: It is a fair clarification you are looking for. If what you are saying is to be better you have to rule out equality, it is not at this point sufficiently convincingly better to rule out equality, nor is it sufficiently unfavorable to rule out that it is still

very likely you could prove benefit, so I am not saying that there is evidence of harm, evidence of benefit, but rather to say that the results still remain consistent with either establishing benefit or eventually, in the end, not achieving statistical significance for benefit.

DR. BLAYNEY: Have you ruled out that this is a harmful therapy?

DR. FLEMING: That is a very fair question and let me touch on that, because John gave an excellent summary, in essence, of where the Division at least views survival data to be.

In essence, I think he pointed out that survival information is important in an assessment of this nature, at least from the safety context, ruling out inferiority. This is a tension here for someone who is, on the one hand, wanting to see that survival data confidentiality be maintained in order to preserve the integrity of this information, on the other hand, realizing the importance of your weighing all relevant information.

So, whereas, at this point I have indicated that the data are not conclusively positive, there is a lower standard which is can you rule out that at least it is favorable enough to rule out it is meaningfully worse, and whereas this type of information normally wouldn't be conveyed, I can convey that yes, the results do rule out

that there is a meaningfully worse result on survival.

Now, recognizing that this is not information that you directly have, in discussions with the Agency, we have agreed to provide to them the Kaplan-Meier survival curves, so that they would have access to this information that we had.

Our understanding is they are planning to keep that information confidential, but they in essence do have the Kaplan-Meier survival curves that we reviewed in November, so that they would be able to in essence validate the comments that I have just made to you.

DR. BLAYNEY: And the November 10th date of analysis was picked, not because as might be designed a priori, because a certain number of events had occurred, but was driven by the date of this meeting?

DR. FLEMING: It is a combination of the two, which frequently is what guides when monitoring committees meet. There were 300 events in May, and we were looking at meeting again when we got approximately half increments of additional information of additional deaths.

We had projected six to nine months, which would have been between November and February of 01. We essentially did approach an additional 100 events in a manner that allowed for the meeting to occur in November. Certainly, though, there was added interest in holding this

meeting early enough in November, such that if results were conclusive, they could be provided to you.

DR. BLAYNEY: I have two more questions, if I may, Madam Chair.

DR. NERENSTONE: Yes, go ahead.

DR. BLAYNEY: Let me go to the nubbin of the issue here, and it goes to the efficacy of the tamoxifen placebo. First of all, the double-dummy technique that you employed, a woman who was on the study was given two pills.

Could you go to how you assured that the tamoxifen, which is marked pretty distinctively, was hidden from that patient, study entrant, and the identity was hidden, and how you assured bioequivalence, if there was some extra coding or some other attempt to hide the distinguishing mark on the placebo.

I am struck by the low incidence of hot flashes that she reported. Californians report much more hot flashes than what you have here, and I am concerned about the bioequivalence of both the placebo and your drug.

DR. DUGAN: I see your question as being with regard to how is the study package kept double-blind and double-dummy to the patients.

DR. BLAYNEY: And the double-dummy is equivalent to the tamoxifen to which it is putatively being compared.

DR. DUGAN: I would like to ask if the

statistician--

DR. NERENSTONE: Maybe we should have just a brief discussion of exactly how the pills were given. I think maybe there is some confusion about that. Describe the double-placebo procedure.

DR. FISHER: I am not sure that a statistician is the person to reply.

DR. NERENSTONE: Could you please introduce yourself for the recorder.

DR. FISHER: Lloyd Fisher, University of Washington.

The tamoxifen used in the study was actually not the tamoxifen used in the U.S. as you saw in your briefing document, but there have been bioequivalence, so this somewhat negates the marking concerns that you had, because it is a different tamoxifen, but there have been bioequivalence studies, and the Agency has looked into this for the obvious reason that we want something bioequivalent to what is being used in the United States.

As I understand it, that has been established, but I personally have not reviewed those data, and so on, so if you want more detail, someone else here would have to answer.

DR. NERENSTONE: I think Dr. Temple has a comment.

DR. TEMPLE: The usual reason for using a double-

dummy is so that you don't have to encase any of the drugs in some new coding, so you just give the regular drugs and then you have placebos that look identical to tamoxifen and identical to the other.

So, if you know the bioavailability of the other product, and you know that it is okay or if it is regular tamoxifen, you avoid all those problems, you shouldn't have any. Now, I don't know that that is what they did, but that is what double-dummy is usually for.

DR. FISHER: No, that is the case here.

DR. DUGAN: Right. That is what we did. They looked identical.

DR. TEMPLE: So, you don't alter the active drugs at all in any way. You just give something that looks like an active drug.

DR. BLAYNEY: Okay. Then, the hot flashes that you reported on Slide CP-40, on page 20 of your briefing document, look a lot lower than what I am used to seeing.

DR. DUGAN: Do you have the slide?

[Slide.]

Again, the study was double-blind. This was spontaneous reporting. In p24, the women were newly diagnosed and perhaps the lower percentage of reporting of hot flushes could be attributed perhaps to that, but again the study was double-blind.

DR. BLAYNEY: I would have an alternate explanation that these are women that don't have bone pain, that only have local disease, and perhaps they are more focused on actually systemic symptoms rather than the bone pain from their metastasis.

DR. DUGAN: That could be.

DR. BLAYNEY: I still think that is fairly low.

My last question. In Study 24, did you look at breast tissue that was resected, and was there a difference in the number of complete responses in the breast tissue resected?

DR. DUGAN: The number of pathologic complete responses were two on Femara and three on tamoxifen. Approximately 80 percent of those patients enrolled went on to have surgical resections.

DR. BLAYNEY: Thank you.

DR. NERENSTONE: Other questions from the committee? Go ahead.

DR. SLEDGE: Dr. Bhatnagar, you went to considerable lengths to show us data on aromatase inhibition, comparing your drug to another drug. Is there any clinical data, percent aromatase inhibition, 97 percent versus 100 percent makes any difference whatsoever in terms of clinical outcome?

DR. BHATNAGAR: Could I have MOA-2, please.

The data that I showed you, Dr. Sledge, was an especially designed study only to compare anastrozole and letrozole. Now, this in vivo aromatization has been done several times on each of the agents, but in historical comparisons.

If you look at this slide, this has all come from the laboratories of Mitch Douset [ph] and Pierre Lonnig [ph], and you see that aminoglutethimide, formestane, and anastrozole, exemestane, and letrozole have been studied in this setting. They are ranked by the residual aromatase, in vivo aromatization seen from 9.4 percent for aminoglutethimide to 1.1 percent for letrozole.

Now, in this list, letrozole and aminoglutethimide are the only two agents that have been compared to one another in a large antitumor trial, ARBC-3 in the second-line setting. In this setting, letrozole was significantly better than aminoglutethimide in several time points including survival.

The only other direct comparison has been the small study between letrozole and anastrozole.

So, if one can use this historical data and speculate that there is a clinical benefit to be derived by reducing the residual aromatization to zero or close to zero, the only data we would have would be the letrozole versus aminoglutethimide to base this on.

DR. SLEDGE: I doubt you can use that data, I mean given what an awful drug aminoglutethimide is for the average patient taking it.

So, how about within individual studies for individual drugs looking at patients stratified by greater or lesser aromatase inhibition, is there any data whatsoever?

DR. BHATNAGAR: No, there isn't because these studies are very difficult to do. They are usually smaller studies and they are carried out separately as individual studies rather than part of a large clinical trial.

DR. SLEDGE: Because this database, you are talking about a 2 percent difference in aromatase inhibition, which is perhaps not huge in the grand scheme of things.

Actually, for Dr. Harvey. Harold, in the year 2000, is it acceptable to do a trial of a hormonal agent in a group of patients, a third of whom you don't know the estrogen receptor status?

DR. HARVEY: In my very strong opinion, no, and I would be rather perturbed if into the future, other studies allowed such a large percentage of receptor unknown patients.

I suppose, in retrospect, in defense of this particular trial, it isn't quite as bad as it looks in the

sense that the patients who were receptor unknown were chosen based on their responsiveness using other clinical considerations.

So, receptor measurement is absolutely, I think, ideal, to be preferred, but there are other criteria, as you know, for determining responsiveness to hormones. But I agree, I would strongly urge all comparative groups, as of this point forward, to adopt the stance you suggest.

DR. SLEDGE: A question perhaps Dr. Ellis could answer. You presented some interesting data last week in San Antonio on the O24 study in terms of the HER-2 interaction with response. I wonder if you could share that with us.

DR. ELLIS: Yes. One of the advantages of the preoperative endocrine setting is you can address questions concerning predictive markers in a prospective and blinded manner, so that is what we did.

With respect to the HER-B family member of receptors, we actually looked at HER-B1 or EGF receptor and HER-B2, and we looked at these factors separately and then as a combined characteristic of HER-B1 and/or HER-B2 positive, and what we found is very provocative.

Essentially, we were able to confirm that the presence of these HER-B family members are resistance markers for tamoxifen, but they are not resistance markers

for letrozole.

In fact, if you look at the subgroup of patients that were receptor positive and also expressed one of these two receptors, EGFR family members, the difference in response rate between letrozole and tamoxifen was 88 percent versus 21 percent with a hazard ratio of 28, and it was significant to the fourth decimal place.

So, it does look like this was part of the explanation for why letrozole is more effective than tamoxifen specifically within this group, although when we took this particular factor out of the 024 data and said, well, is there any difference between the two drugs, even when these EGFR family members are not expressed, we still saw differences, so this is a partial explanation for the difference in efficacy.

It would also be considered exploratory in these prospective further examination.

DR. NERENSTONE: Dr. Simon.

DR. SIMON: I have a couple of questions. One is was there any kind of central review of the response assessment or progression assessment, and if the assessment was primarily based on local center evaluation, was there any attempt to validate that the people doing the assessment were actually blind and could not guess the identity of the treatments that the patients were on, and was there anyone

at the center who knew the identity of the treatment?

DR. DUGAN: I will address the first question first. There was not any central review that was done in this study. The results from the second-line studies where we had extensive radiology review, there were essentially no differences in the response and progression that affected the analyses.

What was placed prospectively into this trial was, as you said, a central radiologist at each institution who was blinded to the treatment assignment and who was to review all the relevant x-rays at that institution. Worksheets were kept.

What was done internally is that the clinical team blindedly reviewed all of the data listings without knowledge to the treatment assignment, and any discrepancies that were noted were then queried to the investigators and resolved.

DR. SIMON: Could you say that again? What discrepancies or what potential discrepancies?

DR. DUGAN: Anything with regard to the categorization of a response usually involving calculations of numbers.

DR. SIMON: Did anyone at the center know the identity of the treatment?

DR. DUGAN: No, they were blinded.

DR. SIMON: And you said--maybe I missed it--you didn't present the crossover results, but you are saying now that there were no differences on the crossover treatments with regard to response or time to progression?

DR. DUGAN: No, we have made no comments in the briefing book with regard to the crossover data. We have not looked at that crossover data. As specified in the protocol, that data will be evaluated approximately 18 months after the completion of the core, which is estimated in September of 2000 when approximately 75 percent of patients will have had an event.

DR. SIMON: Will have a second event you mean?

DR. DUGAN: Yes, on the crossover treatment.

DR. SIMON: But isn't the crossover data sort of relevant in terms of evaluating the overall effect of the treatment on palliation of the patient? In other words, if your drug produced some benefit for initial treatment, but it meant that on crossover treatment, that somehow it had some negative effect that you might otherwise have as a second-line treatment, would that be relevant?

DR. DUGAN: With regard to this application for approval, time to progression on the initial double-blind treatment is the primary endpoint for the study. It should be remembered that the treatment assignment after first-line failure was not random. Forty-three percent of these

patients did go on as they were felt still suitable for further endocrine therapy, 60 percent did not.

With regard to the issue of the crossover therapy, I would like to ask Dr. Mouridsen, who is the principal investigator on the trial to comment.

DR. MOURIDSEN: I do believe that time to first progression is a very valued endpoint in this study of endocrine therapy in advanced breast cancer. The reason is that as you saw from the data, approximately 60 percent of the patients at progression did not crossover to any other endocrine therapy, so they received as second-line, the vast majority of these patients chemotherapy.

So, the prolonged time to progression means for these 60 percent of the patients, a prolonged time during their life before they should have the chemotherapy.

For the last 40 percent of the patients who did crossover, we think it is unlikely that the response to tamoxifen in that second-line situation would be highly significantly better than the response to second-line Femara. That means that we should lose in the second-line setting what we gained in the first-line setting.

I admit we don't have solid data from randomized trials to make this conclusion, but we have indirect comparisons from the literature indicating that second-line Femara is as effective as second-line tamoxifen.

We have also the data from the preliminary analysis of the first-line Arimidex versus tamoxifen trial who in the subset of patients analyzed response to the second-line treatment with either tamoxifen and/or Arimidex, and they demonstrated completely similarity as concerns efficacy in the second-line setting.

DR. SIMON: I have one final question. Maybe I missed this in the material. What percentage of the patients were not evaluable at three months for response or progression assessment?

DR. DUGAN: The percentage of patients who were not evaluable overall for response was low. With regard to the--while they are looking for the slide--with regard to the time to progression, if you are asking, we can show you the overall patients who were not evaluable for progression.

DR. SIMON: The reason I ask is because it looks like the major difference was based on the evaluation at three months.

DR. DUGAN: Right. If we can have the curves with the censoring marks for time to progression for Dr. Simon.

Again, to remind you that the patients remaining on trial are at least 14 months into their therapies.

[Slide.]

If we go back to the time to progression curves, again you can see the censoring marks that are noted. Most

of the censoring that occurred early on for discontinuation without evidence of progression would be most of these marks early on before the 12-month period. Most of these patients out here are censored, but are still on treatment and still continuing on study.

[Slide.]

If you look at the number of patients who are censored, 32 percent on Femara, 23 percent on tamoxifen. You can see here that 25 percent and 15 percent remain on core study without progression, patients who died, not cancer-related deaths, and also those who didn't receive treatment were censored.

There is this group here of 6 percent of patients who were discontinued without evidence of disease progression or clinical deterioration. What we have done is done a worst case scenario analysis where we took these patients here and considered them as progression events for the Femara arm, leaving these patients here still censored, and the results are still highly statistically significant, favoring Femara with a p-value of 0.0015.

DR. SIMON: Thank you.

DR. NERENSTONE: Dr. Albain.

DR. ALBAIN: I have three other questions.

First, in follow-up, regarding the statistical design, this did not have stratification variables built

into the initial design as I understand it, and that is of some concern given, in this particular population, the demographic and tumor-related characteristics could highly influence even how the disease does without any treatment, in other words, one or two sites of bone metastases or one subcutaneous nodule, that patient could go for a while with some stabilization even without treatment.

So, why were there not up-front stratification variables? Then, since they were not there, you have done a number of post-hoc adjustments in your Cox modeling, are you confident that that rules out these potential concerns given there were no up-front stratification variables as we standardly use?

DR. FISHER: Stratification, there is stratification and analysis, and stratification for randomization, and in a large study where you get a lot of people with the different characteristics, as long as they are measured, you can look within strata.

Even though you didn't randomize separately, you can compare the treatment groups within strata, and indeed, you already saw quite a few subset analyses where it was very consistent.

The Cox models were not post hoc. They actually were prospectively defined in the analysis plan before unblinding, but they were not part of the primary analysis,

which is why you have some material in your briefing document, but it was not presented here. The results are essentially the same.

Does that answer all your questions?

DR. ALBAIN: I just was curious why, with so many known standard variables that influence outcome, why that wasn't taken into account up-front. I am not concerned that the results are in doubt, but--

DR. FISHER: I wasn't around during the design stage. I would conjecture in a study this worldwide, with so many different countries, and so on, that to set up, for example, if you going to stratify and block by traits, you either have to have clinics that are going to enroll a lot of people, because you have to remember you have a separate block within each cross subset of the strates, and, in fact, a number of these clinics enrolled small numbers, or you have to have some sort of phone-in central randomization available in all kinds of languages, and so on, and so forth, but maybe somebody from the sponsor of the study--

DR. ALBAIN: Thank you. I also have two questions regarding Table 8 in the briefing document, not the slides.

First of all, commendably, there is a very large number of patients over the age of 70 enrolled in this clinical trial, way beyond I think anything we have seen before, and even though that would truly be a post-hoc

subset analysis, have you looked at outcome just in that subset?

DR. DUGAN: Yes. We have looked at distribution of age by decade and by integrals of 5, and for those women older than 70, the results are highly statistically significant favoring treatment with Femara.

DR. ALBAIN: The second question has to do with bis-phosphonate use. If I am reading this table correctly, again a subset analysis in a much smaller group of women, the patients did worse on Femara if they had bis-phosphonates onboard, is that correct?

DR. DUGAN: That is correct for that analysis, but one would question that analysis. We took everybody who was randomized and asked the question if bis-phosphonates was used or not. What we have done subsequently is asked the question in patients who have had bone metastases, with the use of bis-phosphonates, were there any differences with Femara, and they were not worse with Femara.

DR. ALBAIN: Did you look in a little more detail on when the bis-phosphonates were started, because sometimes it does take longer than that interval you used in the protocol to see a benefit?

DR. DUGAN: Bis-phosphonates were required to be used at the time of randomization if patients had documented bone metastases, and not to be added on during the study

with few exceptions. If it were used for hypercalcemia, maybe one or two doses.

DR. ALBAIN: Right, but if you had started it two weeks before randomization, you may not see the bis-phosphonate effect until into your study treatment.

DR. DUGAN: Right. We did not analyze it by time prior to coming on to study.

DR. NERENSTONE: Dr. Kelsen.

DR. KELSEN: I think my question has been partly answered, my question regarding crossover, how many patients were unable to crossover, what happened to them, I think I have got the answer, they went on to chemotherapy.

I think your table actually is a little stronger than your argument. I get the impression from this table, which is CP-12, it is not that 60 percent of patients or 55 percent of patients have not crossed over, about a quarter of the patients who started on Femara are still on trial according to this table, only 15 percent of the tamoxifen patients are, and it is really that there were three-quarters of patients exited, 44 percent of the ones who exited Femara were able to crossover.

I assume that means they were well enough to crossover, their physicians were comfortable that they had the time to try a second hormonal treatment, but in 30 percent of patients felt that they had to go to

chemotherapy, they were too ill to wait for hormones.

You have demonstrated on the tamoxifen arm, I think, that of the 84 percent of patients who exited, a higher percentage were felt to be too ill or for some reason their physicians felt pressed that they must go on to chemotherapy, they were unable to wait for another hormone, which actually I think is more supportive of your argument rather than less supportive of the argument. Is that correct?

DR. DUGAN: Yes, you are correct. Thank you.

DR. NERENSTONE: Dr. Pelusi.

DR. PELUSI: Along another note, when we look at the side effects on 25, I too was, like Dr. Blayney, surprised at the low incidence of hot flashes, and actually bone pain, as well.

So, I attribute it to perhaps if we put patients on study, maybe we have less side effects, but in reality, I think all of us struggle with side effects and how that translates into quality of life for patients, and was there any attempt made to look at any quality of life studies within that particular 025 study.

DR. DUGAN: There was no prospective implementation of a validated quality of life instrument. I could ask Dr. Mouridsen, who was instrumental in the design of the trial, to address your issue about quality of life.

DR. MOURIDSEN: The major objective in the treatment of advanced breast cancer is to postpone as long as possible the time to progression and deterioration of the physical condition of the patient, and maintain as long as possible the best possible quality of life.

We did really consider when the study was planned to run quality of life studies, however, it was decided not to do it, to do formal quality control studies, the reason being that we know from the literature that quality of life is determined primarily by the response to the treatment, and only to a minor extent by side effects, although we know, for instance, that with heavy cytotoxic therapy, this may impair quality of life.

So, when the study was planned, we didn't expect major toxicities from the treatment, nor did we expect major differences in toxicities, so we concluded that probably if any change in quality of life in the study, that would be due or be determined by the efficacy of the therapies.

So, that was the reason why we decided not to do the quality of life studies as we these were unlikely to contribute with data which would change the overall conclusion which could be drawn from the efficacy data.

DR. PELUSI: I can appreciate that, but I still think it is important for us to look at quality of life issues for our patients.

It would be interesting in a crossover study, as well, when you go back and look at that data, at what point we are talking about performance status and also what the effects are and really compare those two as that crossover goes. I think that is going to be important in the future, as well.

DR. NERENSTONE: Thank you. We are going to take a break now and I ask that everybody be ready to reconvene at 10:55.

[Recess.]

DR. NERENSTONE: One more question for the sponsor.

DR. TEMPLE: I wasn't quick enough before. I had two questions. One, a pharmacokinetic interaction apparently interrupted the third arm, but the effect wasn't very large, it was like a 30 percent reduction in the letrozole concentration.

I wonder what you knew about the dose-response for letrozole that made you think that study, that arm would no longer be useful, because it is a little disappointing not to know what the result of the combination was.

DR. ELLIS: Matthew Ellis, Duke University.

This issue of dose-response with aromatase inhibitors came up in two out of the three trials in the second-line setting with 2.5 mg a bit more active than 0.5

mg in a three-way comparison with megestrol acetate, and then in a second trial with aminoglutethimide, although a third trial, which in fact wasn't available at the time this decision was being made, didn't suggest a dose response between 0.5 and 0.25. There was, of course, concern that the decrease in letrozole levels could compromise efficacy.

DR. TEMPLE: Well, it wouldn't have compromised the efficacy of the direct comparison, it would only have made the combination not look as much better as it might otherwise have, and the reduction would have been to about, what, 1.8 mg, so it wouldn't have taken you all the way down to 0.5. Oh, well, I mean that is water over the dam, I guess.

The other question I had was Dr. Bhatnagar, as Dr. Sledge pointed out, spent most of his time describing comparisons with another aromatase inhibitor. The obvious question is do you plan to actually get clinical data on that comparison?

DR. DUGAN: There is presently a second-line study looking at a comparison between Femara and anastrozole. That has completed enrollment, and those results should be available within a year's time when it has met the number of events.

DR. TEMPLE: What about first line?

DR. DUGAN: There are no prospective plans to do

such a comparison. We are looking forward to the adjuvant trials, one of which is nearly completely enrolled, and the other one that is halfway through its enrollment.

DR. TEMPLE: And what are those in comparison to, however?

DR. DUGAN: That is to tamoxifen.

DR. TEMPLE: I mean this doesn't signal some intent to promote those nonclinically documented differences, does it?

DR. DUGAN: No.

DR. TEMPLE: I didn't think so.

FDA Presentation

DR. COHEN: Good morning, everyone. My name is Martin Cohen and I am going to present the FDA analysis of the data.

[Slide.]

The proposed indication for letrozole is as first-line therapy in postmenopausal women with advanced breast cancer. As you have heard earlier, letrozole has had a prior approval for second-line therapy in the identical patient population following progression on antiestrogen treatment.

[Slide.]

The letrozole pivotal trial was a double-blind, double-dummy, randomized, multicenter, two-arm, Phase III

trial comparing letrozole to tamoxifen in postmenopausal women with advanced breast cancer.

As you have heard, the design of this trial changed a little bit over time. Initially, there was the third arm combined letrozole/tamoxifen arm, and that was dropped following the pharmacokinetic interaction that Dr. Temple mentioned, and there is also a crossover feature to this study at the time of progression.

I am also not going to present any crossover data because it is too premature at this time.

[Slide.]

The comparator treatment for the study was a generic tamoxifen that was manufactured in Finland. Bioequivalence studies were conducted, and the Tamofen was found to be bioequivalent to Nolvadex.

[Slide.]

The primary endpoint of the study was time to progression. Secondary endpoints are as listed on the slide. Of these secondary endpoints, I am not going to discuss clinical benefit because clinical benefit is primarily driven by response rate data and adds little independent information.

I am also not going to discuss time to treatment failure because that is really a composite endpoint rather than efficacy endpoint.

The FDA agrees that survival data is premature at this time, and I am not going to present any survival data although I will comment on survival at the end of this presentation.

[Slide.]

As you have heard, the eligibility criteria for postmenopausal women, Stage IIIB or IV primarily, although a few Stage II patients were entered on the trial, receptor positive or unknown, measurable or evaluable disease except patients with bone-only disease were eligible.

Patients may have had adjuvant chemotherapy or one chemotherapy regimen for advanced disease, and they may have had adjuvant tamoxifen if they recurred more than one year after stopping therapy.

[Slide.]

Tumor evaluations were performed at baseline. There was an optional one month evaluation, and then tumor evaluations were conducted every three months thereafter. I mention this because it probably impacts on the observed response rates in the study.

To be declared a responder, a patient had to meet the response criteria on two consecutive evaluations. By spacing the evaluations every three months, one might expect that the response rates would be lower than if the evaluations were performed monthly or every other month.

[Slide.]

It was a little bit complicated, but logical in terms of the method of determining response. One had three categories of disease - measurable disease, non-measurable, but evaluable disease, and non-measurable/non-evaluable.

In addition, one had to count the number of lesions to find what category comprised the bulk of disease because, as you can see on this slide, bulk of disease drove the response determination.

If you just look at the first line, patients who were CR's or PR's for their measurable disease, but no change for non-measurable/evaluable disease, and non-measurable/evaluable disease constituted the bulk of disease, and the overall response was no change, and so forth, as you go down the table.

[Slide.]

Patients studied, as you have heard earlier, the study started with the first patient in November 1996. The last patient was enrolled January 1999. 939 patients were randomized. Twenty-nine countries participated.

The two leading accruers to the study were institutions in the Soviet Union. The third largest contributor was in Beijing, China. The institutions in the United States contributed approximately 10 percent of the study population.

[Slide.]

There were 458 patients randomized to the letrozole and tamoxifen arms, 4 patients came from a single institution that did not meet good clinical practice regulations, 5 patients had no active cancer, and so the intent-to-treat population was 453 for letrozole and 454 for tamoxifen.

[Slide.]

You can see here a breakdown of the study patients. Approximately 6 percent of patients were Stage IIIB. You have heard two-thirds were receptor-positive, approximately one-third were receptor unknown. 38 percent letrozole and 40 percent tamoxifen patients had received prior adjuvant therapy.

The breakdown in terms of the type of adjuvant therapy, numbers of patients are listed on this slide, and 19 percent and 18 percent of letrozole and tamoxifen patients respectively received prior tamoxifen, and 6 percent of patients on both arms had prior advanced disease chemotherapy.

[Slide.]

Patient characteristics. Patients were comparable for age. As you have heard, the median age was 65; for race, approximately 85 percent of patients in both arms were Caucasian.

The performance status, greater than 90 percent of patients were performance status zero or one by ECOG or WHO classification. Twenty-five percent soft tissue dominant disease, 33 percent bone, and 42 percent visceral disease. Approximately 12 to 13 percent had liver metastases. The number of involved sites, as you have heard before, median was two.

[Slide.]

In terms of presenting efficacy results, I am going to present the results of the FDA analysis. I might state here that the FDA analysis did not differ substantially from the sponsor's analysis.

[Slide.]

In terms of median duration, patients randomized to letrozole remained on study for a median of 11 months versus 6 months for tamoxifen. Since disease progression was the major reason for coming off study, one might get from this slide an indication that disease progression was prolonged by letrozole, and that data is presented on this slide.

[Slide.]

The median time to progression for letrozole-treated patients was 9.87 months versus 6.15 months. This result was highly statistically significant, and the hazard ratio is indicated on the slide.

[Slide.]

In terms of response rate, for the letrozole treatment there were 9 percent CR's, 24 percent PR's, and overall response rate of 32 percent versus 3 percent CR's, 18 percent PR's, and overall response rate of 21 percent for tamoxifen. This was also highly significant.

For those of you who look at the tamoxifen response rate of 21 percent and think that it might be low, considering Dr. Harvey's slide where he expected a first-line response rate of about 40 percent, I would say two things.

One, that this response rate is similar to the response rates that we have seen in other first-line advanced breast cancer studies where tamoxifen was a comparator treatment, and two, I would say it is probably a little bit low because of the every three month tumor evaluation.

[Slide.]

The response duration was comparable for the two treatments, 11.5 months median for letrozole, 10.3 months median for tamoxifen.

[Slide.]

In terms of response by dominant site, for all sites listed on the slide, the letrozole response rate was either superior or equivalent to that of tamoxifen. In no

case was it inferior.

As you can see, for soft tissue dominant disease, the response differences approached statistical significance, and for visceral disease, leaving out liver disease, the response differences were statistically significant.

[Slide.]

In terms of response by receptor status, for patients who were receptor-positive, the letrozole response rate, 33 percent, was significantly superior to the tamoxifen response rate of 22 percent, and there was not a striking difference in response rates for the ER and PR unknown group, suggesting that most of these patients were likely also receptor positive.

[Slide.]

The FDA--well, I did an exploratory analysis looking at improvement in performance status, and the glasses should be a greater than or equal sign. The criteria for improvement was a 10 percent improvement in Karnofsky performance status that lasted for two or more consecutive observations.

The reason why this is exploratory is that we really don't have good data on how reproducibly investigators can measure a 10 percent improvement in performance status, and, secondly, we also don't have data

suggestive that it is a clinically meaningful improvement in performance status.

But be that as it may, 32 percent of letrozole-treated patients achieved this improvement in performance status during treatment versus 19 percent of tamoxifen-treated patients, and this result was also highly statistically significant.

[Slide.]

I looked at one other category. That was patients with an initial performance status at 50 to 70, and again we are looking at performance status for greater than or equal to two consecutive visits.

You can see here there were 83 letrozole patients whose initial performance status was in this range, and 79 tamoxifen patients, and 18 letrozole, 13 tamoxifen improved their performance status by 10 points, 16 versus 6 by 20 points, 6 versus 4 by 30 points.

[Slide.]

Turning now to safety, looking at serious vascular adverse events, for cardiovascular events, this included angina, myocardial infarction, and the diagnosis of either coronary heart disease or atherosclerotic heart disease, and you see that a small percentage of patients in both arms had serious cardiovascular complications.

The cerebrovascular complications included TIA's,

hemorrhagic or ischemic strokes or hemiparesis, and again a relatively comparable number of patients in both arms and both being small percentages, and peripheral thromboembolic complications included thrombophlebitis and pulmonary emboli, and again relatively comparable numbers and relatively small numbers for the two treatment groups.

[Slide.]

Twenty-one letrozole patients had a total of 26 fractures, 18 tamoxifen patients had a total of 20 fractures. Those fractures appeared to be disease related.

Ocular toxicity occurred in similar numbers of patients on the two arms. As was mentioned this morning, one patient developed endometrial carcinoma on study. I included hot flashes and vaginal discomfort under serious adverse events in that these complications, if severe, might lead a patient to discontinue taking study medicine and going off study.

[Slide.]

Early therapy discontinuations were observed in small numbers of patients, 11 patients on letrozole versus 18 patients on tamoxifen. The major reason for early therapy discontinuation was bone pain. In nearly all cases, that bone pain was disease related rather than treatment related.

Again, you see here the second most common cause

was thrombosis and then small numbers of the other listed causes.

[Slide.]

We have more interesting symbols here. In terms of age, the scissors is less than or equal to, and the glasses are greater than or equal to.

So, for age, we looked at adverse events for patients who were age less than 55, 56 to 69 years of age, and greater than or equal to 70 years of age. The adverse events were comparable for each age group. We were unable to look at adverse events by ethnicity because of the large majority of Caucasian patients.

[Slide.]

So, to summarize the efficacy results, letrozole had a significantly superior response rate to tamoxifen, 32 percent versus 21 percent, comparable response durations for the two treatments. Time to progression favored letrozole 9.87 months versus 6.15 months, and improved performance status was 32 percent versus 19 percent.

In terms of survival, we had the chance to look at the November 10th survival curves that were generated for this study. We agree with Novartis that in terms of reviewing survival as an efficacy endpoint, it is too early, there were too few events to evaluate survival for efficacy.

In terms of safety, the FDA is convinced that