U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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ONCOLOGIC DRUGS ADVISORY COMMITTEE

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62nd MEETING

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Monday, June 7, 1999

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The meeting took place in the Maryland Ballroom, Town Center Hotel, 8727 Colesville Road, Silver Spring, Maryland, at 9:30 a.m., Janice Dutcher, M.D., Chairperson, presiding.

PRESENT:

JANICE DUTCHER, M.D., Chairperson

KAREN M. TEMPLETON-SOMERS, Ph.D., Executive Secretary

JAMES KROOK, M.D., Member

KIM A. MARGOLIN, M.D., Member

PRESENT (Continued):

STACY R. NERENSTONE, M.D., Member

ROBERT OZOLS, M.D., Ph.D., Member

VICTOR M. SANTANA, M.D., Member

RICHARD L. SCHILSKY, M.D., Member

RICHARD M. SIMON, D.Sc., Member

GEORGE W. SLEDGE, JR., M.D., Member

E. CAROLYN BEAMAN, M.H.S., Consumer Representative

SANDRA SWAIN, M.D., Consultant

SANDRA ZOOK-FISCHLER, Patient Representative

JULIE BEITZ, M.D., FDA Representative

SUSAN HONIG, MD., FDA Representative

JOHN JOHNSON, M.D., FDA Representative

ROBERT JUSTICE, M.D., FDA Representative

ROBERT TEMPLE, M.D., FDA Representative

GRANT WILLIAMS, M.D., FDA Representative

LANGDON L. MILLER, M.D., Sponsor Representative

MARK LEVINE, M.D., Sponsor Representative

PRESENT (Continued):

KATHLEEN PRITCHARD, M.D., Sponsor

Representative

ALSO PRESENT:

ANN E. FONFA

ROBERT ERWIN

HELEN SCHIFF

KARIN NOSS

MARGARET BORWHAT

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(9:29 a.m.)

CHAIRPERSON DUTCHER: Good morning. Just so you know you're in the right place, this is the 62nd meeting of the Oncologic Drug Advisory Committee.

My name is Janice Dutcher. I'm chairing the committee.

We are going to start the two-day meeting with a discussion this morning about time to progression as a possible endpoint in breast cancer.

Before we get started, I'd like to go around the table and introduce the members of the committee sitting at the table. Dr. Swain.

DR. SWAIN: Dr. Sandra Swain, Bethesda, Maryland.

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

DR. SIMON: Richard Simon, National Cancer Institute.

DR. NERENSTONE: Stacy Nerenstone, medical oncologist, Hartford Hospital.

DR. KROOK: Jim Krook, SMDC Cancer Center,

Duluth.

DR. SCHILSKY: Richard Schilsky, University of Chicago.

CHAIRPERSON DUTCHER: Janice Dutcher, Our Lady of Mercy Cancer Center, New York.

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

DR. SLEDGE: George Sledge, Indiana University.

DR. MARGOLIN: Kim Margolin, City of Hope, Los Angeles, California.

MS. BEAMAN: Carolyn Beaman, Sisters Network. I'm the consumer rep. to the committee.

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

DR. BEITZ: Julie Beitz, Acting Deputy.

DR. WILLIAMS: Grant Williams, Team Leader, FDA.

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

DR. JUSTICE: Bob Justice, Acting Division Director.

CHAIRPERSON DUTCHER: Thank you.

We'll now have a reading of the conflict of interest statements.

DR. TEMPLETON-SOMERS: I'd like to welcome you all here this morning, and we will have individual conflict of interest statements for each session.

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 interests 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 18 USC 208(b), full waivers have been granted to Dr. Sandra Swain, Victor Santana, Stacy Nerenstone, Richard Schilsky, Robert Ozols, Kim Margolin, David Johnson, and Zook-Fischler.

Copies of these waiver statements may be

obtained by submitting a written request to the FDA's Freedom of Information Office located in Room 12A30 of the Parklawn Building.

DR. KROOK: In addition, we would like to disclose for the record that Dr. Sandra Swain, Richard Schilsky, and Robert Ozols have interests which do not constitute financial interests within the meaning of 18 USC 208(a), but which could create the appearance of a conflict. The agency has determined, notwithstanding these interests, that the interests of the government and their participation outweighs the concern that the integrity of the agency's programs and operations may be questioned.

In the event that 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 products they may wish to comment upon.

Thank you.

CHAIRPERSON DUTCHER: Thank you.

We are going to read one letter as part of the open public hearing, and then we will proceed to the presentations, and then we do have speakers for the open public hearing, which will be after the presentations.

DR. TEMPLETON-SOMERS: This letter is from Barbara A. Brenner, who is the Executive Director of Breast Cancer Action.

"Dear Committee Members:

"Thank you for the opportunity to address the issue of the use of time to progression as the primary endpoint in breast cancer clinical trials. Breast Cancer Action views this as a very complicated and important issue.

"Although we are, frankly, puzzled why the issue is being raised at this time, we urge you to address the question in a way that both acknowledges the complexity of the issue and continues to impress upon the pharmaceutical industry the need to develop

treatments that improve overall survival for breast cancer patients.

"Breast Cancer Action is a San Francisco based national education and advocacy organization founded and led by women living with breast cancer. Representing over 5,000 members throughout the United States and beyond, we carry the voices of people affected by breast cancer to inspire and compel the changes necessary to end the breast cancer epidemic.

"Since our founding in 1990, we have been calling for research, a more effective, less toxic treatment. The overriding context in which the appropriate primary endpoint for breast cancer clinical trials should be considered is the quality of life of the patients. Whether the endpoint is time to progression or overall survival is irrelevant if the patient's quality of life is so poor that more time is essentially meaningless.

"While we recognize that techniques currently used to measure quality of life measures are less than adequate, we believe that it is essential that how the patient lives, particularly for women

with metastatic disease, is equally important as how long she lives or how long she lives free of disease progression.

"Though Breast Cancer Action believes that the ultimate goal of all breast cancer treatment should be to improve overall survival, we recognize that in some limited circumstances, time to progression of disease may be an appropriate primary endpoint for clinical trials. The factors that determine which endpoint is appropriate are largely a function of stage of disease of the treated group, the agent to be used, and the protocol.

"One situation where time to progression should not be substituted for overall survival is a clinical trial designed to evaluate a drug or treatment intended to reduce the risk of recurrence of primary breast cancer. When patients are given chemotherapy or on a adjuvant basis, the quality of life impacts can be justified only if the treatment improves overall survival.

"On the opposite end of the spectrum are clinical trials that evaluate biologic treatments in

patients with metastatic disease. When a biologic treatment has few, if any, adverse health consequences, then quality of life and time to progression of disease are essentially synonymous.

"Even if the patient's life is not extended by the treatment, she presumably gets to live more fully in the time she has as a result of the treatment, and that represents progress in treatment.

"The hardest cases, of course, fall in between. One example is the case in which patients with metastatic disease are treated with both biologic and chemotherapeutic agents. If the patients must stay on the treatment to get the full benefit in terms of time to progression, then the quality of life issues become paramount. How sick do you have to be and for how long to get the benefit of the treatment? If there is no overall survival benefit in this setting and the quality of life advantages are significant, then extended time to progression is relatively meaningless.

"Breast Cancer Action understand the dilemma of determining overall survival in cases where

patients with metastatic disease either cross over to another arm of the trial or go off study to use other therapies when the treatment they are receiving in trial fails. Clearly, this crossover issue is not new to the field of cancer clinical trials.

"We wonder why the issue has taken on such importance now in the breast cancer context as to drive consideration of changing the primary endpoint to time to progression. Whatever the reason, it should be noted that if crossover patients so confound the overall survival statistics as to raise questions about treatment efficacy, then the treatment under study is clearly not a particularly powerful agent.

"Using time to progression as the primary endpoint for breast cancer clinical trials in the metastatic setting would make it impossible to see the benefit of the therapy in terms of overall survival. We have seen far too many drugs that showed promise in terms of time to progression that ultimately provided us only with the same steeply declining overall survival curves that have characterized most chemotherapeutic treatments for metastatic breast

cancer.

"Drug manufacturers must be given every incentive to produce treatments that improve both overall survival and quality of live of breast cancer patients. Accordingly, if time to progression is allowed to serve as the primary endpoint in some kinds of clinical trials for breast cancer, it must be done in a way that requires drug manufacturers to follow and report on overall survival with some recognition of quality of life considerations and gives the FDA authority to revoke approval if overall survival benefits are not ultimately demonstrated.

"The announcement for this meeting of the Oncologic Drug Advisory Committee is extremely vague in describing which issues are to be addressed regarding the use of time to progression as the primary endpoint in breast cancer clinical trials. We understand that the committee will release a series of questions to be posed at the hearing, but not until the day before the meeting itself.

"If those of us who due to distance and expense are required to submit our testimony in

writing must do so by May 28th, more than a week before the meeting, to allow for truly informed input from the public, members of the public need time to review and respond to the committee's questions.

"By the same token, the complicated nature of the issue of time to progression as the primary endpoint for breast cancer clinical trials highlights the need to assure that the perspective of those living with the disease is built into the development of protocols for those trials. Well informed breast cancer advocates bring a unique and invaluable point of view to the development of new therapies for the treatment of their disease. The FDA should include advocates in its process of approving protocols for breast cancer clinical trials.

"In conclusion, the issue of primary endpoint to be used in breast cancer clinical trials is a complicated one and, therefore, not amenable to simple answers. Breast Cancer Action urges you to recommend to the FDA that the issue be addressed through principles that put quality of life at their core, that consider stage of disease and agent in use,

and keep drug manufacturers' eyes on the prize of improving overall survival for men and women with breast cancer.

"Respectfully submitted, Barbara Brenner, Executive Director."

And copies of this letter and other letters from the public are available at the desk where you picked up agendas if you would like to see them. They're not for distribution, but they are there for viewing.

Thank you.

CHAIRPERSON DUTCHER: Thank you.

All right. We're going to then proceed with the presentations. First will be Dr. John Johnson from FDA.

DR. JOHNSON: Good morning, good morning.

It's necessary for me to speak from the table instead of standing at the lectern.

This morning's topic is considerations on the use of time to progression as the primary efficacy endpoint in randomized control trials of cytotoxic drugs for initial treatment of metastatic breast

cancer.

This is one of the most important matters the committee has considered because it involves not just a single drug or application, but all future applications for this use.

In addition, any committee recommendation may be extended to other kinds of cancer.

Before we decide where we are going, it is a good idea to review where we are and the reason we are there. My assignment this morning is to review the FDA's present efficacy requirements for marketing approval of the drug for this use and to explain the rationale for those requirements.

The present FDA efficacy requirement for marketing approval for this use is a favorable effect on survival demonstrated in randomized controlled trials. A favorable effect can be superiority to a control or equivalence to an effective standard regimen.

The FDA's reasons for requiring a favorable effect on survival fall into two categories. This slide describes the reasons associated with drug

toxicity.

First, cytotoxic drugs have significant toxicity. Usually only a minority of patients have tumor response, and most tumor responses are only partial. Time to progression effects are usually modest.

In view of the toxicity of cytotoxic drugs, the FDA has not considered tumor response rate or time to progression as adequate bases for marketing approval.

The second reason related to drug toxicity for requiring survival data is that survival in a randomized controlled trial can be viewed as a safety endpoint. In some patients it is not clear whether the cause of death is drug toxicity or tumor progression or both.

Survival is the net effect of deaths from both tumor and drug toxicity. Actually for this purpose a survival effect is not necessary. We only want assurance that the new treatment is not worse.

The reason related to efficacy for requiring a survival effect is that objective

cytotoxic drug regimens prolong life. Dr. Craig Henderson, a former ODAC Chairman, in a presentation to this committee on this issue at an earlier meeting, estimated that effective doxorubicin based combination drug regimens prolong life by about six months compared to no treatment.

The FDA wants assurance that these survival gains are not lost when a new drug is introduced.

By far the most common criticism of the requirement for survival effect is that secondary drug therapy after tumor progression might obscure any survival effect of the test drug. As indicated on this slide, one would expect that a drug used after tumor progress would have the same survival effect in both treatment groups and, thus, not obscure the survival effect of the test drug.

The effect of secondary treatment on survival can be analyzed. Usually there is a particular drug or drugs we are concerned about. WE can determine the proportion of patients in each treatment group that got the drug after tumor

progression. Usually it will be the same in each treatment group.

If there is an imbalance, the next step is to assess whether the drug had a survival effect. If so, an adjusted analysis can be done.

Recently this type of analysis has started to occur in clinical studies in advanced colorectal cancer. For many years, no one thought that available secondary therapies were likely to have a significant survival effect in colorectal cancer. After CPT 11 became available and was shown to prolong life when given secondarily, investigators started including analyses for this effect in their protocols.

In one recent protocol, the sponsor proposed that the primary efficacy analysis be a survival analysis adjusted for secondary use of CPT 11.

The potential effect on the survival analysis of crossing over patients after tumor progression from the control treatment to the test treatment is more serious. If the test drug is not marketed, the protocol should prohibit this. If the

test drug is marketed, the FDA looks at response rate, response duration, and time to progression after crossover to estimate the likelihood of an effect on survival.

Crossover from the control treatment to the test drug does not always obscure the survival effect of the test treatment. In the recent randomized controlled trial of herceptin in initial treatment of metastatic breast cancer, a five-month median survival advantage was shown even though 65 percent of the controlled patients crossed over to herceptin. It appears that the test drug may have less effect when given as second line treatment.

The herceptin randomized controlled trial supports the idea that the main problem is not our test methodology, but the lack of good new agents to test. In this trial it was not difficult to detect a good, new agent even in the face of a suboptimal study design.

This slide shows a comparison of survival and time to progression as efficacy endpoints. Survival is assessed every day and is 100 percent

accurate for the event and nearly 100 percent accurate for the day of the event.

Time to progression is assessed only every two to six months and is much less accurate for the event and even less accurate for the time of the event.

The importance of survival is unquestioned, while the importance of time to progression is less certain. Survival is both a safety and an efficacy endpoint. Time to progression is only an efficacy endpoint.

Of course, if death is counted as progression, time to progression also becomes a safety endpoint, but I believe we should not do this because tumor progression and death are qualitatively different.

Also, as presently implemented, including death as progression really serves as a cover-up for the lack of careful testing for progression.

In favor of time to progression is that it is faster, and a time to progression effect is not obscured by secondary therapy after progression. If

time to progression were used as the primary efficacy endpoint, time to progression would probably require more complete assessment and more frequent assessment than is presently done.

Would pharmaceutical companies be willing to provide the additional resources?

This slide shows some of the common time to progression assessment problems. Incomplete assessment at baseline is an occasional problem. More frequent problems are incomplete assessments at follow-up visits. In some protocols, only selected sites of known disease are followed. In other protocols, all known disease sites are followed, but not other sites where new disease is likely.

For example, a patient with lung metastases may be followed with a chest X-ray. No disease was present in the liver at baseline. So the liver is not followed. The liver fills up with metastases while the lung disease remains stable. The patient dies without any documented tumor progression.

This is then compounded by scoring the patient as progressed on the date of death, which

means she is scored as progression free until the date of death. This is obviously not believable.

Other problems are missed assessments and infrequent assessments.

This slide raises a very important question on which we will need the committee's input. If time to progression were used as the primary efficacy endpoint, what would be the effect on the availability of survival data? Three possible scenarios are listed on this slide.

In the first scenario, pharmaceutical companies may stop their studies and submit the NDA when data on time to progression is obtained. In this scenario, there would be little or no survival data ever. This scenario is unacceptable to everyone with whom I have discussed it at the FDA.

The second scenario would be accelerated approval based on time to progression with survival data required later to convert the accelerated approval to regular approval.

The third scenario would be regular approval based on time to progression with a promise

by the pharmaceutical company to submit survival data later for inclusion in the labeling.

In summary, there are only two real endpoints in cancer clinical trials. These are prolongation of life or a better life. Any other efficacy endpoints we use must be surrogates for one of these.

So were time to progression to be used as the primary endpoint in randomized controlled trials for initial treatment of metastatic breast cancer, time to progress must be a surrogate for a better life or a longer life.

In closing we remind the committee that any recommendation regarding use of time to progression as a primary endpoint in the initial treatment of metastatic breast cancer may have implications for its use in randomized controlled trials in other kinds of cancer.

Therefore, the FDA needs to know the specific reasons for any committee recommendations so that the FDA can assess whether they may apply to other kinds of cancer.

Madame Chair, that completes the FDA's presentation.

CHAIRPERSON DUTCHER: Thank you very much.

The next speaker is Dr. Sandra Swain.

DR. SWAIN: Thank you very much, Dr. Dutcher and members of ODAC, the FDA, and colleagues.

When I was originally asked to do this task several weeks ago, I thought that it would be relatively straightforward, but I have to say I found it most challenging, and I hope that what I will present to you today will help in our discussion, at least be a springboard for our discussion.

What I was asked to do was to review the literature on time to progression as an endpoint, and I thought, well, I'm going to be really smart. I'm going to call Dr. Simon up, and he's going to tell me the literature, and then it'll be easy.

But when I called him up, he said, "There is no literature. Write the paper."

(Laughter.)

DR. SWAIN: So that shows you where we are with this endpoint.

I think as was stated by the letter from, I think, Barbara Brenner at the beginning, it's a very, very complex issue, and what I'm going to try to address from the literature is should time to progression be a primary efficacy endpoint for first line chemotherapy trials in metastatic breast cancer. So it's a very specific topic.

What I'll first discuss are the drugs that have already been approved by the FDA throughout the history of treatment with cytotoxic drugs. Then I'll discuss the pros and cons, somewhat like Dr. Johnson's presentation, and then review the literature for first line treatment and second line treatment, looking at time to progression in those clinical trials.

Now, there have been only a total of nine drugs, cytotoxic drugs, that have been approved for metastatic breast cancer, and the first six seen here, methotrexate, cyclophosphamide, thiotepa, vinblastine, 5 FU, and doxorubicin, were all approved from 1953 to 1974 with a very broad and general based approval for stage of disease and also for other solid tumors.

It was only in 1994 when paclitaxel was

approved, the first breast cancer drug for 20 years, that more specific endpoints were really evaluated, and paclitaxel was approved based on a randomized, Phase 3 study some may call it, others a randomized Phase 2 because it was looking at two doses of paclitaxel, comparing them to each other, and a full approval was given based on a time to progression endpoint.

Docetaxel was approved in 1996 with an accelerated approval based on response rate and received full approval in 1998 based on three or -- excuse me -- two Phase 3 trials in second line treatment for metastatic breast cancer, one of which showed a survival benefit.

Capcitabine was approved in 1998, again, as an accelerated approval with the accelerated approval mechanism based on response rate data.

So you can see that we really haven't had a first line treatment that's been approved at all when we've had our more rigorous guidelines recently.

Now, before we start talking about it too much, I also wanted to mention that in biologics last

year -- and everyone on this committee, I'm sure, is familiar with this -- trastuzumab or herceptin was approved in 1998 based on a primary efficacy endpoint of time to tumor progression, and I think that is somewhat different in the Biologics Division, in which they do accept time to progression as their primary efficacy endpoint.

And before I go on further, I wanted to define a little bit what we're talking about, if I can, because I think if you try to read the literature, which I've done in the past several weeks, you realize that everyone uses a different definition. I think that's one of our big problems, and Dr. Johnson has pointed out some of the issues with that.

The term "time to treatment failure" was used in the 1970s through even the 1990s and is still used by ECOG, which is a similar definition for us as time to progression, but it makes reading the literature difficult because frequently the investigators don't define what exactly they mean by either treatment failure or progression.

The way we would define it today for most

studies would be that it is calculated from the date of randomization until either progressive disease or death.

Now, there are a lot of issues with this, and we don't need to go into detail about them here, but it's certainly something for the statisticians and other people to think about, is what do you do with patients who receive further anti-tumor treatment without progression. Should they be censored, that is, not counted as an event or should that be counted as an event? And I think that that makes a big difference in your results, and that's something that needs to be defined more definitively.

Now, I've noticed recently, and having been on the committee recently, many of the companies are bringing time to treatment failure data to the committee. This is to me a wastebasket endpoint in that it calculates from the date of randomization until almost anything you can think of, progressive disease, death, withdrawal due to an adverse event, patient refusal, patient being lost to follow-up, or further anti-tumor therapy. So it really can be

anything and, in my opinion, doesn't really give you a handle on the biologic activity or the clinical efficacy of the drug that's being tested. So I do not feel that this endpoint should be used as a primary endpoint.

Now, if you look at survival as an endpoint, as Dr. Johnson pointed out, this is easily measured at any time. It's certainly the easiest measurement that we can do, and it is clearly the ultimate patient benefit, that is, if quality of life is good with the treatment given.

Now, the negatives for using survival as an endpoint really all kind of are interrelated. Breast cancer, as we all know, is a very heterogeneous disease, and women can live for a very long time with metastatic breast cancer. The medians in the literature range anywhere, depending on prognostic factors, from ten to 47 months. Those women that have bone only disease have a median survival of four years. So that means some women will live much longer.

And that leads to the fact that many

secondary treatments are given. So, again, as we've heard discussed, the secondary treatment may affect outcome, and unfortunately the literature suggests that there's only a small survival benefit with most active agents. So it may be if you use a lot of active agents, one right after another, you're going to wash out your effect from your new agent since the survival benefit is probably two months with a lot of the therapies.

And finally, survival may not actually be directly related to treatment. That is, if a patient lives longer, there may be some other event that causes a decrease in survival or one of the other therapies that has been given.

Now, if you look at time to progression as an endpoint, the pros to using that is that you can relate it directly to the treatment that you are just giving to the patient. It's a shorter follow-up so that you can get your answer quicker, and there may be a patient benefit with this endpoint, with delaying progression, that is, a relief or delay of symptoms or complications.

Now, the negatives for time to progression, I think, are many, and I really think that Dr. Johnson did a nice job of presenting that. They're mainly in measuring time to progression. I think the pharmaceutical industry and all investigators really must look at this very carefully, and it has to be calculated very, very carefully because time to progression can be difficult to measure in patients, especially with bone disease.

If you're using a lot of evaluable patients in your trials, that date of progression is often difficult.

And then the dates are dependent on the times of evaluation. That is, there can be an ascertainment bias unless the times of evaluation are the same in both arms, and they are frequently rather far apart, every two or three cycles. So you can actually miss when the real progression date occurs.

And what I've found not only in reviewing the literature, but in working in this area of looking at clinical trials in breast cancer, the rules are often not prospectively defined. It just says you

measure time to progression, and that's really it, and all of these other issues, such as centering, et cetera, come later on. I think that is a real problem.

And time to progression may not be a surrogate for patient benefit if you have a very toxic therapy. I think that's clearly important. The time to progression can't be seen alone; that you have to have either a therapy that's nontoxic or has monotoxicity so that you maintain a good quality of life.

And finally, a small point, but it is evident in the literature. If you do continue treatment with an active drug versus stopping it, you will have a prolonged time to progression. So in the trials that are designed, those patients who are allowed to continue on treatment must be balanced between the two arms.

Now, I'm reviewing here. I looked at many, many trials, and surprisingly enough there are not a lot of trials that show a survival benefit in metastatic breast cancer. There are three that I'm

showing here that also show time to progression data, and I specifically chose them because of that.

The Engelsman trial looked at classic CMF versus an IV CMF, which was a less intensive form, and found about a 3.5 increase in time to progression with classic CMF and a five month increase in survival.

Two ECOG studies again looked at this issue and found there was a two month increase in time to progression with an adriamycin containing regimen versus a CMF-like regimen and a three to six month increase in survival.

And finally, another ECOG trial looked at CMF versus AV versus CMFP and found a time to progression and survival benefit in the CMF-prednisone arm. So you have three trials showing both time to progression and survival benefit, and in the review that I did of the literature, it was most frequent, number one, to not have time to progression data.

Number two, when the time to progress was the same on both arms, survival was the same.

And when time to progression was

increased, as in these cases, survival was increased, and in no situation was time to progression the same on both arms or increased and survival decreased.

Now, if you look at the herceptin trial specifically, this trial, as I said, the primary efficacy endpoint was time to progression, and I'm presenting it to show you the numbers on which this decision was based.

If you look at herceptin plus chemotherapy, there was about a 3. or 2.7 month increase in time to progress with the use of herceptin overall, and in the paclitaxel arm, it was about three or four months also and two months in the adriamycin-cyclophosphamide arm.

That was reviewed by the FDA and is in the package insert.

Now, the survival data was more recent. It was just presented at ASCO and has not been reviewed by the FDA, but I'm showing you the results here, and this shows a significant survival benefit in those patients who received the herceptin. The survival benefit is about 4.5 months.

And within the two substrata, it was not significant because the study was not powered. As I said at the beginning, time to progression was the primary endpoint. It wasn't powered really to look at survival in each of these individual strata, but you do have, again, a situation where time to progression is increased and survival is increased.

Though, as Dr. Johnson mentioned, there was significant crossover in about three-quarters of the patients, and it may be that somehow the biologic therapy is fundamentally different because it's a targeted therapy, and it's in a poor prognosis group of patients that you still do see a survival benefit, and maybe you would have even seen a greater survival benefit if you hadn't crossed over a lot of patients, but we'll never really know the answer to that.

Now, I wanted to specifically mention a very large trial that's been presented at ASCO, and I'm not just presenting it because George is sitting on the committee, but I really think it's probably one of the most important trials we've had in metastatic breast cancer, and we'll be able to get a lot of

information from this.

It's very large, 739 patients who was ECO 1193, and it's first line therapy for metastatic breast cancer, comparing paclitaxel to doxorubicin to the combination.

This trial showed a significant increase in response rate in the combination arm and an increase in time to treatment failure. Now, ECOG defines time to treatment failure as progression, a toxic death, death from breast cancer, and in patients who are crossed over without progression, those patients are censored. So it is somewhat like the time to progression definition that I gave you at the beginning.

There was a two month increase in this endpoint in the combination arm. This did not result in an increase in survival. As I said, there was a crossover in both of these arms, and the suggestion was that the crossover may have obliterated any potential increase in survival.

An interesting aspect of this is that quality of life was done. I have to mention at the

beginning that most of these patients were asymptomatic. They were ECOG performance status zero or one. So the quality of life actually was not improved in these patients because any time you get a toxic therapy and someone is no or a therapy that is going to give you toxicity and someone has no symptoms, you obviously are going to decrease the quality of life.

And it may be that there's a subset of patients here, and hopefully Dr. Sledge can enlighten us about this, that were symptomatic, had an increased response rate in time to treatment failure, and did actually benefit from the therapy as far as quality of life is concerned.

Now, I wanted to go over an overview that was published in 1993. Dr. Johnson mentioned in the beginning that Dr. Henderson said that there's a six month survival benefit in metastatic breast cancer with doxorubicin. I think that that is probably true.

However, it's not a huge survival benefit, and some studies will only show about a two month survival benefit. This meta analysis looked at five

trials that added doxorubicin into a Cooper type regimen and compared it to that Cooper type regimen and found that the hazard ratio for response rate, all the numbers less than one favor doxorubicin, by the way. The response rate was 50 percent increased in those patients who received doxorubicin. The time to treatment failure was about 30 percent increase, and this definition is similar to what I described as time to progression endpoint, and patients had 22 percent less chance of dying if they received the doxorubicin, and these were all significant.

Now, the caveats with this in any of these kind of what they call meta analysis are they really aren't true meta analyses in that the primary data is not reviewed, and in fact, in these trials I found it extremely difficult in one of the trials to find any number for the time to treatment failure. So I'm not sure how the author did it.

And in these five trials only two of them did show a survival benefit. The other three the survival was equal. All of them except one did show a time to treatment failure benefit from one to 4.5

months.

Now, another thing that I did was look at the Fossati, quote, unquote, meta analysis that was just published in the JCO. I used it really as a baseline for a literature review. They looked at 189 trials in breast cancer that were all randomized clinical trials published data only from 1975 to 1997, using Medline and M-base, and they found a total of 31,510 women who had participated in these trials.

They were looking at 12 different therapeutic comparisons, including things such as single agent versus polychemotherapy, CMF versus no CMF, and they were looking at response rates and mortality hazard ratio and side effects, and again, I do not consider this a meta analysis in that it was really a literature review and they did approximate many of the hazard ratios by looking at the curves in the paper, and many of the papers were really not well done with these endpoints and results not well defined.

But I used it as a basis to really do a literature review and looked at one of the different

comparisons where they reviewed the randomized trials with polychemotherapy, including an anthracycline versus no anthracycline, and in this analysis there were 22 separate first line randomized clinical trials. There were only nine trials -- there were ten comparisons because one was a three-arm study -- that did have time to treatment failure or time to progression data.

Many of the papers did not at all define what they meant by this endpoint, and in these nine trials seven of them had a time to progression date and survival which were -- medians which were equal or comparable.

In two of the trial, time to treatment failure and time to progression were increased and survival was increased, and in one of them, the time to progression was increased and survival was comparable.

So as you can see here, we don't have a lot of data available, but what is available shows that time to progression seems to correlate with survival, and as I said, in no case does it show a

decreased survival if time to progression is either equal or increased.

Now, I wanted to get to the second issue or one of the other issues looking at second line treatment for metastatic breast cancer because that seems to be the reason that most investigators use for not using survival as an endpoint.

There are several drugs that do confer survival benefit in the second line setting, and I'm showing you them here. Jones published this study, vinorelbine versus melphalan, showing an approximately one month increase in time to progression followed by a one month increase in survival, and I know that that agent, though it's not marketed, and Dr. Johnson made some comment about that, that it shouldn't be used, but it is used in breast cancer today.

Cowan in an older study looked at doxorubicin versus bisantrene and mitoxantrone, and if you could please, for the members of the committee, look at your handout, there's a mistake on this slide, and I'll tell the audience the mistakes.

Time to progression was 4.4 months, 2.2

months, and 2.3 months, with a p of .06. So doxorubicin did confer a prolonged time to progression in second line treatment, and also did increase survival when you compared it to mitoxantrone in a second line setting.

We don't see that situation very often now because most patients do receive adjuvant doxorubicin, but it is possible that it could be a second line treatment.

And finally, docetaxel was compared to mitomycin melphalan, and in this large study of about 400 patients, there was a two month increase in time to progression followed by about a 2.7 month increase in survival. So in this case, this study was reviewed by the committee, and as I said, this drug was approved last year showing that time to progression and survival were improved.

So to summarize those three trials, we've got at least three drugs in the second line treatment that can increase survival, though it's small amounts, one to four and a half months. It's about what we see for even some of these first line trials or the meta

analysis that I showed you.

In any studies we do not cure patients we're seeing survival benefits ranging from one to six months.

Now, finally on this slide I have the Nabholtz study looking at paclitaxel. As I mentioned in the beginning, this drug was approved comparing two different dose levels of paclitaxel in almost 500 patients, and this trial showed a 1.2 month increase in time to progression, and the drug was approved based on this data. There was not an increase in survival.

There was also other data presented from the TRC showing good efficacy and response rate. So there is a precedent for using time to progression even from this committee's deliberations.

Now, I wanted to turn to a couple of situations, and we all want the best for our patients. Everyone in this room wants the patient to have better quality of life, and I think that that is what's been very difficult in reviewing a lot of this literature, and there is not a lot of quality of life available.

I wanted to discuss first the study looking at symptomatic patients just to give you a basis for more discussion later, and this was an ECOG study which took a combination of three trials, took all of the patients who had a CR, complete response, after six cycles of a doxorubicin containing regimen, and randomized them to either further treatment with chemotherapy, and it was a CMF-like regimen or observation.

And what this trial showed was that there was an 11 month increase in time to progress if you continued treatment, and this study supports most of the studies in the literature looking at this issue not just in CR patients, but if you do continue treatment, you do have a prolonged time to progress, and I think it is a judgment call by the physician as to how the patient is doing. If they have had relief of their symptoms, then it may be wise to continue the treatment.

In this situation, it may be most likened to the adjuvant situation in which you do delay relapse or complications, so that it might be

worthwhile in some patients to continue also to prevent those circumstances.

The survival, however, was not increased at all in these patients.

Now, taking another situation, looking again at the same issue, if you have continuous treatment -- this is an Australian study that was published many years ago and is widely quoted. This study looked at continuous treatment versus intermittent treatment, and the intermittent treatment was three cycles of chemotherapy, which is much less than most of us would give to expect to get a response in patients. The median numbers of cycles is usually four to five cycles. So actually this is probably about the closest you could get to a placebo control from any of the breast cancer studied that I could find, though obviously they did get some treatment.

And in this study there was a 17 percent increase in response in those patients who got the continuous treatment. There was a two month increase in time to progression with a relative risk of 1.8, which was significant, and there was a survival

increase of 1. -- median survival increase of 1.3 month, which was borderline significant.

And the interesting aspect of this study and the part that's so widely quoted is that they did do quality of life data or questionnaires in this study. Unfortunately, it was only in about half of the patients, but patients did fill out the forms, and they found that quality of life was increased in both arms in the first three cycles.

It's interesting and important to note in this trial 80 percent of the patients were symptomatic. That's very different than George Sledge's trial where most of the patients had a performance status of zero or one. In the trial I just showed you, patients who had achieved a CR were for the most part asymptomatic.

So in this trial most patients were symptomatic. Their quality of life was increased with the continued treatment, and when the treatment was stopped, the quality of life decreased.

On the other hand, there was toxicity associated with the therapy. Even though there was

toxicity, which was significantly worse, such as nausea, the patients still felt that their quality of life was improved.

Now, the investigators were very surprised at this because I think they hypothesized many years ago that the quality of life would actually be worse when you continued treatment.

And to show you specifically the quality of life issues that they looked at, they looked at the linear assessment or linear analogue self-assessment scores, and as I said, these were improved for the first three cycles, but after the first three cycles the scores were worse for things such as physical well-being, mood, appetite, and then the quality of life index by both the patient and the physician showed that the quality of life was worse in the patients who stopped treatment.

Again, and the authors do point this out, it could be a placebo effect. Patients wanted to get treatment so they did feel better, but these data do support the use of time to progression as an endpoint, and they published a paper later on looking at the

change in quality of life scores and found that it could be predictive of survival, but, again, as I said, only about half of the patients filled out the form. But it is really one of the best trials we have for quality of life.

Now, to conclude, I unfortunately have to say that the survival benefit with active drugs is modest. I would say it's from two to six months, median increase in survival. I think I've showed you that time to progression does correlate with survival, and in the Coates study, the time to progression was increase and quality of life was also increased. So there's at least one study that does show that.

And I, again, would like to reiterate what Dr. Johnson said. It is essential that accurate reporting of the endpoints be done. It's just absolutely essential if we're going to use this as a primary efficacy endpoint.

And then to conclude, I wanted to put up here a few quotes from a white paper that was published in the Journal of Clinical Oncology in 1991, and this was a joint effort by the FDA and the NCI and

the senior author is sitting at the table, Dr. Temple, and it was really a quite articulate article, and I'm not just saying that because he's sitting there.

(Laughter.)

DR. SWAIN: But maybe.

But I wanted to bring back some of the quotes to him and to the audience of what it said because we're really revisiting this same issue ten years later. Though time to progression wasn't mentioned specifically in there, you can glean some information.

The clinical usefulness of a drug must reflect the relationship of risk to benefit for specific clinical conditions, and I think that is clear to all of us. Even if we are to use time to progression as an endpoint, the risk cannot outweigh any benefit that we might perceive this with endpoint.

The primary aim of cancer treatment is prolongation of life, but demonstration that a new agent causes tumor regression and improves patients' clinical condition also supports approval of a new agent even in the absence of improved survival. So

this was even said, as I said, about ten years ago with the FDA support.

And in breast cancer, a large fraction of recurrences are symptomatic, making improved disease free survival a valid surrogate for improved quality of life.

And the last quote really relates to adjuvant therapy, but I think we can put in there improved time to progression as a valid surrogate.

So finally, I would like to say that from my standpoint, though it's a very complex and difficult issue, I think time to progression is an acceptable endpoint which may confer patient benefit. However, as I've said repeatedly, the toxicity certainly must be taken into consideration, and it cannot outweigh any kind of benefit that we might see.

So I thank you very much, and I really look forward to the discussion.

CHAIRPERSON DUTCHER: Thank you very much. That was a very thorough review. We really appreciate it.

Before we get into the discussion by the

committee, we do have additional members of the audience who would like to present their views. So we will ask you to please come to the podium, if you can. Please identify yourself, your organization, and any financial sponsorship.

The first person is Ann fonfa from the Ann E. Appleseed Project.

There are copies of these presentations available at the table outside if you need them.

MS. FONFA: Hi. I'll start out by saying that no one has paid for me to come here today, and no pharmaceutical company has ever given me any money, and as I said last time I spoke, it's unlikely they ever will.

(Laughter.)

MS. FONFA: I prepared a text which has just been referred to, but I want to say right up front that survival, long term survival is the main factor that concerns me as a breast cancer patient.

Time to progression sounds like it may be an advantage over tumor response, which hasn't been correlated with increased survival and often not even

with delayed disease progression. The FDA has a long history of approving drugs that are only minimally better than the ones they're compared to.

I often speak of this as crawling on our hands and knees through a field of broken glass, and there are those of us who long to leap over this field. How can we do it? By holding oncologic drugs to the highest standards possible. After all, millions of dollars are spent on clinical trials, but from the patient perspective, this is about our lives.

We're wasting our precious time taking drugs that are little better than awfully expensive and extremely toxic placebos.

How much time in the time to progression are we talking about? In the presentation that I've just seen, it's relatively small. I would have to say very small.

If it's months, then I have to insist we also look at quality of life. For cancer patients, there are only two important imperatives: increased survival and decent quality of life. It's why I've spent many years asking for studies on and the use of

complementary and alternative treatments. These are almost always less toxic than the current chemotherapy drugs.

Can we correlate time to disease progression to improve survival? Since most trials are done using metastatic patients who by definition are close to death, I cannot understand why true survival is not reported after every trial. Indeed, a new standard for drug approval is long overdue and would be very welcome, but only if patients could then expect that our survival would be positively impacted.

I suggest, as I have for years, that we begin examining natural and nontoxic regimens. Patients are choosing to use these methods right now. Everyone in clinical practice acknowledges that. They haven't waited for studies.

Almost all of us now are into vitamin supplements and probably nutritional interventions. We don't use a single isolated element either. It's time for FDA and drug companies to recognize this situation. We have to begin studies immediately that offer an arm for patients who are utilizing these

substances.

Perhaps an arm for patients using natural substances will show greater efficacy. Some small studies have already indicated that many nutrients can potentiate treatments, possibly slow cancer cell growth and possibly encourage apoptosis.

Treatment failure is one of the most open secrets in oncology. It seems only the patients find out the hard way.

Discussions at ODAC, as reported in The Cancer Letter, among others, clearly shows that oncologists know that many drugs they offer us are little better than placebos, but they want to give the patients something under the theory that something, even a useless something, is better than nothing.

Where I come from this may be the same thing as false hope. I always said there was no such thing, but if a doctor already knows there's almost no chance of the administered drug being effective at all, then, indeed, that's false.

Of course, I would suggest turning to the alternative world and exploring the many possibilities

that exist there. One obvious advantage is that would be a less toxic way to go, and indeed, it would offer real hope as many of the possibilities have worked for others, and from my totally empirical viewpoint, if it's worked for someone, it could work again.

And I can personally testify that I have achieved disease stabilization using several nontoxic methods. This may be anecdotal, but it's my own story.

Oncologists have formed the practice of giving patients chemotherapy almost until the day they die, completely disregarding quality of life as an issue. This is no longer acceptable to patients.

As we've become more educated, our standards have changed. We want treatments that are effective, minimally toxic, and we want to discuss our options fully with our health care providers. I worry that the design of trials are set up so that we get information about the group, but not much that is really useful for an individual.

Take the example of Tamoxifen in the adjuvant setting. I know that there's a 50 percent

benefit in reducing further cancer by taking this drug. Yet upon further analysis, I find out that about ten women in 100 were likely to recur or get a new cancer. This has, indeed, been reduced by 50 percent to five of the 100. The end result is that 90 women take Tamoxifen, an extremely toxic drug, for whom it's completely unnecessary.

Additionally, another five women don't get the benefit since they're recurring anyway. A better method should be found to yield much more specific information so that we can clearly identify the women whose cancers will be stopped by any drug.

Of course, I wonder who will pay for such a trial. As a cancer patient I have had to face the fact that this is big business, and it's profit above patients. No company seems willing, no researchers seem to feel comfortable discovering how many newer patients need to take a drug, especially after it's been approved.

FDA needs to address the questions that may reduce market share because no one else will.

A magazine article recently published in

a bi-monthly news magazine for oncology professionals encourages their readers to tell patients dosages of drugs to be administered. This way the patient can help insure that appropriate drugs and correct dosages are given. Patients need and want to be involved in their treatment. We want to hold our health care providers to a much higher standard than previously.

When we're diagnosed with cancer, most of us don't know a damned thing about it. We usually welcome chemotherapy, especially if all we know is what we've read in the popular press. If, as is increasingly common, we have seen a family member or a loved one go through the treatment, we're less welcoming.

Patients' demands are changing the face of oncology treatment, and this is right, and it's very good.

In line with this change is FDA's need for a new standard for drug approval, but my challenge to you is will time to disease progression matter to patients. Will we see this new standard translate to longer life, better quality of life while we undergo

treatment? And it's a really, really important question.

When I decided to testify today, I thought about what's important, and I couldn't come up with anything more meaningful than improved survival. Can you demonstrate that for us? Will we see true progress with new drugs, not just approval faster and of more drugs, but will these drugs truly help us live longer? Will they make it easier for us to go through treatment because they take into account our need for a decent quality of life?

I worry about our current view that we can give a pill to reduce the unwanted effects of a treatment. So we have to offer the patient another drug to offset the unwanted effects of the first pill, and the second pill and the -- and so on. You notice I don't call these unwanted effects side effects because to patients they are not side effects. They're right there in our face at all the time.

A patient may end up with eight or nine medications to treat all of the unwanted effects in order to tolerate a truly toxic treatment that may be

relatively ineffective. It's a bad situation.

Think carefully as you enter this new era. Think of us as people with a disease, not only patients with cancer or disease targets.

We need standards from FDA that will offer our best hope for continue long term survival and useful quality of life.

Thank you very much.

CHAIRPERSON DUTCHER: Thank you very much.

The next speaker is Mr. Robert Erwin from the Marti Nelson Cancer Research Foundation.

MR. ERWIN: Thank you.

I'm Robert Erwin with the Marti Nelson Cancer Research Foundation.

This is a nonprofit organization that works with cancer patients to help them enroll in clinical trials and gain access to experimental medicine.

I'm also Chairman of the State of California Breast Cancer Research Council, which funds breast cancer research from cigarette tax money, and I work for a private biotech company which sponsors

cancer research, but which is not developing treatments for breast cancer.

Thanks to the excellent presentations of Drs. Johnson and Swain, I can delete a lot of what I had planned to say, and instead I'd like to just comment on some broader policy aspects of this debate.

I am a dedicated member of the nonprofit community and strongly advocate early and aggressive access to new and experimental treatment by informed patients and also the elimination of obstacles to such access.

But I'm also a participant in the free market. I believe it's the fastest and most efficient route to effective medical innovation. However, after 20 years in the pharmaceutical and biotech industries, I also have direct experience that warns me of the dangers of individual and institutional greed, and I think that's something that this committee needs to consider.

Hope is why we advocate aggressive access to experimental therapeutics. A desire for proof of efficacy is why we advocate careful and well funded

clinical research, and maintenance of the incentives for such well funded clinical research.

Appropriately, the current FDA procedures for accelerated approval provide for conditional marketing of new drugs for breast cancer and other cancers once reasonable safety has been established and other important endpoints, such as time to progression, have been met.

However, it also provides the FDA with a very strong and important oversight function post that marketing. This rapid access by patients through the accelerated approval process addresses our concern about aggressive access to potentially promising breakthrough therapies, and yet it also addresses a broader concern which has to do with the marketing of products that may in the long run prove to be ineffective.

I think it's very important that the FDA continue to have the authority to exert significant pressure on companies to thoroughly investigate the efficacy of the products they're selling. Under the accelerated approval regulations, the FDA does have

the power to revoke marketing approval, and I think that that's a very important point of leverage.

With the accelerated approval process as it's currently used, I think the need to grant full approval on the basis of secondary endpoints is less critical than it would be if these safeguards were not in place.

After many decades of FDA regulation and oversight, most consumers and most physicians do not now believe it is necessary to make careful independent judgments about medical products. The FDA stamp of approval is enough for most people.

Taken to a logical extreme, giving out that stamp of approval too lightly will blur the boundaries between effective pharmaceuticals and the highly profitable, but mostly valueless so-called nutritional supplements that are heavily promoted to people desperate for help.

Most consumers do not have the knowledge and most physicians who don't maintain an affiliation with major medical centers and teaching hospitals are too busy to pay attention to the technical nuances

that this committee considers. Those technical nuances are extremely important, but they're not always accurately reflected in the advertising campaigns that are launched by the companies whose products are approved.

I think there is adequate evidence of this by the number of times the FDA has had to shut down certain advertisements. So I'll leave out some examples.

I urge this committee to advise against full approval of drugs for the treatment of breast cancer with time to disease progression as the only primary clinical trial endpoint unless such approval is explicitly tied to quality of life and advertising implying data suggesting enhanced survival is prohibited.

I believe that maintaining the current accelerated approval mechanism combines the best features of free market incentives with rational consumer protection.

I also encourage the pharmaceutical and biotechnology industries to support increased funding

for FDA post marketing oversight, perhaps from an extension of the prescription drug user fee for those companies that receive accelerated approval of new drugs.

This would provide maximum potential benefit to cancer patients while reducing the probability of long term marketing of drugs that are safe but do not work. This is a clear benefit to a company selling a product that does work.

I also would like to once again remind all of you that properly designed crossover provisions and compassionate access during Phase 3 trials, although this is quite complicated, can provide important benefit to dying people, as well as accelerating the accumulation of both time to progression and survival data.

Thank you.

CHAIRPERSON DUTCHER: Thank you very much.

The next speak is Helen Schiff from SHARE-New York.

MS. SCHIFF: I would like to start my testimony by telling about two friends of mine in

SHARE who died of breast cancer.

Carole Hochberg died of breast cancer at age 40. When she metastasized two years after adjuvant treatment, she went on arimdex, a hormonal treatment for ER positive breast cancer. The side effects were nil, so her quality of life was wonderful. It lasted for a year.

When she progressed, she went into a herceptin plus weekly taxol trial. She was hoping for the miracle which some few women have gotten with herceptin.

When it didn't happen, she stopped all treatment and died two months later. She could have gone on to taxotere, xeloda, gemzar, navelbine, et cetera, but she didn't want to. She said to me, "It's not worth it. I don't want to go through the agony of being chemo'ed to death."

Another member of SHARE, Adrienne Asails, a young mother in her 30s with a four year old daughter. She did everything possible to prolong her life. She wanted to be there for her daughter as long as she could.

She did two stem cell transplants and had regular chemo before the transplants, in between, and after. She did get to go to Ireland for a wedding in which her daughter was a flower girl. She said that was a consolation for not being able to see her daughter be a bride.

So women make different decisions about the tradeoff between quality of life and prolongation of life. It is a terrible choice to have to make, but unfortunately that's where breast cancer treatment is right now.

We need the information of both of these endpoints, quality of life and survival, to make one of the most important decisions of our life: how and when to die. Perhaps these two endpoints should be combined into quality of life adjusted survival.

I do not believe that time to progression is a satisfactory substitute for either of these endpoints. We all know especially with chemotherapy that an increase in time to progression does not usually prolong survival, and even when it does, the quality of life sacrifice might not make the extension

of life worthwhile.

Survival should remain the primary endpoint for clinical trials for women with metastatic breast cancer. It is the gold standard, and the challenge is the pharmaceutical companies to come up with drugs that are other than the "me, too" chemotherapy drugs that we see so often.

I just want to tell a story. I was with the AACR convention, and I was talking to a woman from Burroughs-Wellcome. I asked her what they were doing there, and she said, "We're working really hard on a chemo where your hair doesn't fall out."

And I know that this is very important to women, but my feeling is, and I said to her, that you know, if we had a drug that was effective we wouldn't mind losing our hair once.

I think that we want to try to push the drug companies in a direction of finding drugs that really make a difference.

That being said, I would certainly not want to penalize some of the novel agents in the pipeline: angiogenesis inhibitors, vaccines,

monoclonals, and signal transduction modulators, as well as new hormonal manipulations and more targeted chemo. that may not show an overall survival benefit, but at much less toxic than conventional chemotherapy.

However, it looks like most of these new biologics will be used in combination with chemo. at least for metastatic disease. So the survival benefit along with the quality of life will still be important to women.

We will also want to know which of the novel agents either with or without chemo. extend life the longest and how they affect our quality of life.

I do think that time to progression is a better secondary endpoint than tumor response because it broadens our ability to detect the durability of treatment activity, not just the initial response.

It also allows us to determine the benefit of treatment, such as tumor stability, even when the therapy fails to achieve the standards of partial and complete response. However, TTP as an endpoint would not be able to determine if a drug simply slows progression, nor would it take into account the newer

angiogenesis inhibitors which sometimes do not stop progression for a while before they start to work because they're very slow acting.

This raises the question of time. I realize time to progression as a primary endpoint is a way to speed the approval of new breast cancer drugs to the market. We want new treatments as soon as possible, but we need to know if they increase survival and how toxic they are.

Why can't we continue with the fast track system of conditional approval with time to progression as an endpoint, but continue to collect data on survival and quality of life? I know this was done with herceptin, and I think it worked quite well.

Several oncologists that I have talked to think that it is unlikely that subsequent secondary therapy will have a major impact on survival, despite differences in subsequent treatment. Even with the crossover herceptin trial, survival advantage was shown in the second year.

I would like to add that survival must remain the primary endpoint in adjuvant and risk

reduction setting also. Treating millions of healthy women with a powerful drug should show a survival benefit before it is approved. In the adjuvant setting, we cannot substitute disease free survival for overall survival as a primary endpoint. We would never have found that lumpectomy is as good as mastectomy if we had only looked at disease free survival.

Another example. Tamoxifen in the adjuvant setting reduces the risk of recurrence by 46 percent, but only increases survival by 25 percent. The lesson is disease free survival does not always result in overall survival.

In closing, I would like to urge more advocate involvement in the FDA. It is good that advocates serve on ODAC panels and we can testify at ODAC hearings, but I would like to suggest that advocate involvement begin much earlier in the drug approval process. I would like to see us involved in the approval of protocol design.

It is my opinion that the more we are involved in the drug approval process, the more user

friendly clinical trials are, the more patients' concerns are address, the easier it will be to enroll clinical trials and get us closer to the goal which we mutually share: more effective and less toxic therapies for breast cancer.

Thank you.

CHAIRPERSON DUTCHER: Thank you.

I want to congratulate all of our speakers, Drs. Johnson and Swain and members of the breast cancer advocacy groups and clinical trials advocacy, for very carefully thought out and well presented presentations. I think it's really very helpful to the committee.

And we're going to take a break for 15 minutes. We'll be back here at about ten after 11, and then we'll begin the discussion.

(Whereupon, the foregoing matter went off the record at 10:48 a.m. and went back on the record at 11:10 a.m.)

CHAIRPERSON DUTCHER: Can you please take your seats? We're going to be starting the discussion.

You all should have a paper that has some comments, and then on the back of it there are some questions for the audience. I'm sure that they're at the desk, yeah. So you can pick up copies if you want to follow along.

Before we open up the discussion, Dr. Temple would like to make a few comments related to evaluating drugs based on different endpoints.

DR. TEMPLE: Thanks.

I just had a couple of observations. There have been a number of comments about the uncertainty of the time to progression endpoint because of variable times of observation and even because how to measure it isn't always built into the protocol very well.

I just want to observe that that problem is somewhat different depending on whether you're trying to show a difference between treatments and trying to show similarity between treatments. All of the things that people have described as being worrisome are biases toward the null. They tend to obscure difference if there is one.

So that if someone, despite that sloppiness, achieves a difference, it's not necessarily noncredible. Now, I'm ignoring the question of blinding here for the moment.

On the other hand, if one is trying to show that a therapy is just as good as another therapy, those are tremendous problems and make the data very noncredible.

Something that I don't believe came up is that blinding is particularly critical to something like time to progression, or at least might be, whereas of course in survival it's not. We don't see a great many blinded oncology trials, and attempts to have progression measured by people other than the investigator are also relatively unusual, but at things that could be considered.

It's worth pointing out that equivalent survival is also a problem. The committee probably needs to discuss this some other time. We've been seeing a lot of comparisons that involve looking at the total survival and comparing one drug with another and getting hazard ratios. I think that is very

dubious.

The figure of interest is the improved survival due to the control agent, not the total survival, most of which has nothing to do with the agent. That's for another time.

Maybe Rich might want to talk about this. Even if the advantage seen in time to progression is completely preserved in terms of survival, you know, six versus four versus 22 versus 20, the increased denominator would make it difficult to detect a problem in designing these trials. So that if there's going to be a fair delay after progression to survival, the trial is going to have to be clearly much larger.

We almost never see time to progression measured by symptoms, although that would be possible. I would say that if someone were able to show an improvement in symptomatic time to progression, there would be no argument about whether that would be credible. That's an improvement, and that's usually considered an improvement in quality of life. So it's worth pointing out that what we're talking about

here is time to progression measured by radiologic or other measurements at least for the most part.

Just to be sure, there's no issue about whether survival would be reported in a trial where time to progression was the primary endpoint. We would always insist on that. So anyone who was worried that we'd never find out that can be reassured.

There was some discussion in the public comments about accelerated approval or fast track approval. It's worth remembering that that's available only when you show an advantage in a serious or life threatening illness. That could never be a basis for using or maybe if the drug was dramatically less toxic or something, that would be a very hard way to be a basis for approval in an equivalence setting where no advantage over available therapy is intended.

But conceivably that is a possible basis for approval under our accelerated approval rule. If someone had an advantage, major advantage, and we thought that was a reasonable surrogate, we could use the accelerated approval rule conceivably, depending

on the advice from the committee, of course, as a basis for approval, but it wouldn't work very well in an equivalent setting.

That's it.

CHAIRPERSON DUTCHER: Could you just before we get started also just tell the committee what specifically you see as the issue with this discussion?

Because we did see a review that showed that time to progression was used recently for several agents, most recent breast cancer agents, as a matter of fact. So are you looking for sort of a statement that this is what we'll do in the future or just a discussion of how comfortable people are with the endpoint or where are you going with this?

DR. TEMPLE: Well, sometimes we do things case by case because they seem reasonable at the time, and then we step back and wonder whether we've been doing something that makes complete sense. I think that's what's going on here.

We've been affected by arguments that say survival benefits can be obliterated if the crossover

or -- let's not say crossover -- if the relapse treatment is beneficial, and of course, that's obviously true. That could be true.

Whether that's a reasonable argument to accept routinely, what kind of evidence there should be in support of it and things like that are major, major questions, and some of the questions that you're being asked touch on those.

We have done it where the secondary therapies were thought to be very beneficial, and I think we're asking whether we've been doing the right thing.

DR. JUSTICE: Actually the only case that was identified as paclitaxel, and that was not for initial therapy of metastatic breast cancer. That was second line, and it was not the sole basis for approval. Objective response rate was also supportive, although weakly supported.

DR. TEMPLE: The setting of third line therapy where we rely on response rates, clearly, in that case we would feel just as comfortable relying on time to progression. If anything, it's a somewhat

more persuasive endpoint.

The main question is whether that should be moved down into earlier therapies.

CHAIRPERSON DUTCHER: All right, and just to remind the committee, what we're discussing is time to progression as a possible basis for marketing approval of cytotoxic drugs for initial treatment of advanced metastatic breast cancer.

I can either take hands or I can go around the committee for comments. Hands? Okay, Dr. Schilsky.

DR. SCHILSKY: The discussion up to this point, I think, has been very interesting or at least the commentary, and I'm very impressed with the quality of the presentations by everyone who made a presentation.

I guess I'd like to begin by raising a question and perhaps asking Sandy Swain if she would want to comment further on it. To me it seems that the most persuasive argument in favor of using time to progression in place of survival is the notion that survival could be confounded by secondary therapies

that, therefore, may obscure survival benefit.

And what I'm wondering about is although I think we would all agree that that is a theoretical concern, what I'm wondering about is whether there so far is actually any evidence that that is the case. What I've seen presented so far, the data that Sandy presented which was, I think, fairly persuasive that time to progression correlates with survival, also demonstrated that in virtually every case where there was a time to progression advantage shown, there was also a survival advantage shown.

So it's not clear unless I misinterpreted something that there is an advantage to time to progression over survival, except for the fact that you might get to that endpoint a little bit sooner.

The other point is that in the second line therapy, at least in the data that we saw, in virtually all of the studies but one, the survival advantage for a second line therapy was pretty minimal, on the order of about four to five weeks. There was one study where it was more like three months, but in most of the other cases it was pretty

minimal.

And so it raises some question in my mind as to, you know, really whether a second line therapy really does have much potential to confound interpretation of results in the front line setting.

So maybe I'll just start it there because so far, I guess, I'm not persuaded that the theoretical concern about confounding interpretation of survival is actually a real concern based upon data that we actually have available to look at.

DR. SWAIN: Well, I think the other aspect of that when you look at the survival benefit, even for the first line treatments, it's again only one, two, three months. so you're looking at very small survival benefits. So I can only propose that it would -- these other secondary treatments which also only have a one or two month survival benefit if they're added onto each other may somehow, you know, really confuse or confound the outcome.

Certainly the herceptin trial doesn't support that. You still see a survival benefit of about five months even when a lot of patients are

crossed over, and I don't know how really to explain that, except that it's a fundamentally different type of therapy. It's a targeted therapy.

CHAIRPERSON DUTCHER: Dr. Simon.

DR. SIMON: I just want to comment on that one issue. I guess I can see how a crossover treatment could potentially influence the evaluation of survival of a regimen. I don't understand. If we're not talking about crossover treatments, and I guess the first question is not -- I don't really understand why that's of concern.

We're talking about a new drug. The issue is does it prolong survival or provide palliative benefit to the patient in the context of the other treatments that are available to the patient, including other secondary treatments, not some theoretical would it provide benefit if there were no secondary treatments.

So observing the survival benefit that it provides in the presence of the secondary treatments available is the correct medical question, and so I don't really see that there's any issue of has

something been obscured. I think the only -- the more complicated issue is trials done in which, for example, the herceptin trial, where there's a crossover to the experimental regimen after progression. Those could potentially obscure a survival benefit.

My own view is if you accept time to progression as the primary endpoint, then trials will be done in that way, and women will never know whether there is a real survival benefit to the treatment That has been approved.

MS. ZOOK-FISCHLER: I just wanted to call to the entire panel's attention my view is whichever way we go, whether it's the endpoint of time to progression or survival, I really feel we have to focus on quality of life issues, and I think you have to pay attention to it from some anecdotal evidence from patients who have been there.

It's been my experience that while there are some patients once they progress they have stable disease and the quality of life continues to be quite good, in the majority of cases women that I've been

that's not the case, and so I think quality of life has to be factored in.

If the endpoint is survival, I think that statistically it's probably very significant if a woman can survive two or three months longer, but personally for a woman who is suffering the side effects of whatever the new medication is, it's really quite irrelevant.

So I would like to see a longer period of survival. I don't know how you, you know, choose that number, but I think the quality of life is so important that unless you could offer a longer term survival, it isn't a very good answer for most people.

But I would hardly like to see time to progression as the primary, but I might like to see it for accelerated.

CHAIRPERSON DUTCHER: Dr. Santana.

DR. SANTANA: Having sat in this committee for a year and looked at some presentations on quality of life, I am quite concerned about how some of that data is presented, on the quality of some of that data and the robustness of some of that data.

So we have to be careful that if we are going to use time to progression in conjunction with quality of life and show or demonstrate improvement in quality of life, I'm concerned that that tool has not been utilized in the correct way or at least presented in the correct way.

So I caution all of us that we all talk about quality of life, but in the past year I have seen very few studies presented to this committee in which I was convinced that the quality of life data was very good.

CHAIRPERSON DUTCHER: Thank you.

Ms. Beaman.

MS. BEAMAN: I'd like to reemphasize something here that expresses my views quite well that was shared earlier this morning, and that is the overriding context in which the appropriate primary endpoint of breast cancer clinical trials should be considered is the quality of life of the patient, and whether the endpoint is time to progression or overall survival is really irrelevant if the patient's quality of life is so poor that it is meaningless.

Another thought, extension of that that comes to mind, of course, is that once the information is fully shared with the patient, if all of the side effects of all that is known is shared with the patient, and the patient agrees, that is one thing.

However, one month or three months in total agony is simply not something that should be hidden. I think totally revealing those known side effects would be of extreme importance here.

We're in a business here. We're looking at from one standpoint here dollars for desperation.

CHAIRPERSON DUTCHER: Thank you.

De. Sledge.

DR. SLEDGE: I actually appreciate greatly the presentations we've heard this morning, and one thing it's convinced me of is that despite the fact that we've been doing randomized trials in metastatic breast cancer for 30 years, we have an astonishingly small database to look at in terms of time to progression and, therefore, an astonishingly small database to make a conclusion on.

Now, I think we would all start off by

agreeing that what we want is, I guess, what you could call Vulcan oncology, you know: live long and prosper.

(Laughter.)

DR. SLEDGE: The question to my mind is whether or not time to progression represents a decent surrogate endpoint for either overall survival or quality of life. If it doesn't represent a decent surrogate endpoint for either of those, something that we can tie statistically to either of those, I'm not entirely sure what it is that we're measuring there.

Now, looking at it from a breast cancer standpoint, one of the problems I have is I'm not sure quality of life and overall survival are always the same endpoint, as we've just heard. If we look in E 1193, which is the trial Sandra referred to, in that trial, in a data analysis done by Donna Newburg of the ECOG Stats. Office, in essence, the only patients who had an improved quality of life were patients who started out symptomatic and then responded to therapy.

If you started out without symptoms and got therapy, your quality of life got worse, which I

guess is not particularly surprising. If you started out with symptoms and didn't respond, your quality of life got worse, again, not particularly surprising.

So in an American cooperative group trial where we're talking about patients who entering the trial are, in fact, in relatively good shape when they enter the trial, in fact, it's very difficult to show a quality of life benefit for most of the patients who enter into the trial.

Now, in terms of overall survival, overall survival, on the other hand, is most likely to be improved to my mind not in the patients who are really symptomatic with large bulk disease because we know from past experience that those the patients who tend to live the shortest, but rather the long term survival, at least in the data from M.D. Anderson where we have really long term follow-up, the long term survivors tend to be the patients who start asymptomatic with small bulk disease and small volume disease, and so from a survival standpoint those are probably the patients who are most likely to benefit.

So quality of life and overall survival

aren't necessarily the same endpoint, and so if you then go on to ask the question what is time to progression a surrogate for, I'd say from what I've heard this morning we don't have striking data that it's a surrogate for either.

You know, we have exactly one trial, the Coates trial, that looked at it as a surrogate for overall survival. That was a trial that was not comparing chemotherapy to no chemotherapy, but rather a very short duration of chemotherapy to a very long duration of therapy, and I personally don't consider that, even a single data point, to be able to ask whether or not it was a surrogate for overall survival.

Of course, we have no data, as far as I can tell, that relates time to progression to quality of life in any significant fashion. So I guess my overall feeling here is that this is a tremendously under studied area, and an area where we, in essence, don't have any striking data that would allow us even to make a conclusion about whether or not this represents an acceptable surrogate for either of what

we all consider the two most important points.

CHAIRPERSON DUTCHER: Dr. Margolin.

DR. MARGOLIN: I have a few things. I'll try to be very brief though because most of them are sort of reiteration and extend what some of the others have said.

I think those of us who haven't had cancer and those in the room who have demonstrate the fact that it's very hard for one person or one group of people to estimate the importance or the components of quality of life of another group of patients and depending on their disease and their treatment.

For example, Sandy gave us some data that suggested that quality of life could be superior just by virtue of being on therapy, but of course, we know that that's not always the case because many of the therapies are so toxic that they are expected to reduce the quality of life.

And for some patients, quality of life can simply be the importance of seeing their marker go up and down regardless of disease symptoms.

In the past few years we did have an

example of one study among many where some determinant of quality of life was able to be measured reliably and contributed to the approval of the drug. If I'm not mistaken that was the mitoxantrone and prednisone combination in prostate cancer, and I think since most of this discussion is directed at a large group of patients with metastatic breast cancer for whom a large proportion of patients is often excluded from trials, that is, those with the indolent bone only disease, which is hard to measure, but there's many analogies in this whole discussion with the group of prostate cancer patients and how we look at them in terms of measuring progression and quality of life.

So I'm not saying these things to take a stance, but just to remember that we still need to do this research to improve the quality of life assessments. It ought to be possible, and that we can apply these tools and then look back and see whether we've done it right after a few attempts.

CHAIRPERSON DUTCHER: Dr. Nerenstone.

DR. NERENSTONE: Just a couple of comments, and I also don't have any answers.

I think it's important for people who are looking at this question to understand the clinical problems and the biases that go into determining when somebody has progressed. I think it's not -- the time to progression question, you're talking about a very small number of months' difference that makes some sort of statistical argument, and that the biases of a physician who enrolls patients on these trials -- Mrs. Jones comes in. You know she's on the new drug arm. She has a new back ache. Are you going to immediately get a bone scan or are you going to say, "Well, it's because you lifted your child and therefore, we'll watch it, conservative measurements, and wait a month, and if it doesn't get in worse or it's better, then we're not going to do that indicated study"?

So you're talking, clearly, you're talking about investigator biases that are going to be able to make the difference between a drug that may or may not be statistically improved in the time to progression, and we're talking about very, very small amounts of time difference.

And I think it's very dangerous to say that that is really a -- shows that it's really a statistically improved drug when these are open studies, when there are clinical biases that are clearly apparent.

I also think that quality of life can be included. I think that drug companies and even the cooperative groups have had trouble getting the studies done, but that's because it's always been relegated as to a third main point. It's not the first point. It needs to be improved, and people need to pay more attention to it.

It's very intensive. You have to have that data manager making sure the baseline characteristics are billed out. You need to make sure those forms are done, and you need to make sure that the patients understand that these are not optional. It's part of the whole study design.

CHAIRPERSON DUTCHER: I'd just like to also comment that if this were to become an endpoint, I think that the standards for measuring this endpoint would change dramatically, as you point out, in terms

of what do you assess, and it could become actually -- I think there are two ways to do it. One way is to say, "Well, then we're going to get every single baseline study repeated every month to look at all sites of disease," which could become extremely expensive and complicated and probably very annoying for patients, or you say you wait until clinical progression, in which case you end up with somebody who becomes very sick from their disease, and either one is not sort of standard of care at the moment.

So I think that the ramifications of this could be quite major in terms of expense, and in terms of unnecessary testing that would end up being done to get the very moment at which there is progressive disease. At least it's a consideration.

Dr. Simon.

DR. SIMON: I think, as Dr. Sledge has pointed out, we really wouldn't want to consider time to progression as surrogate for quality of life, and I think in issues we're dealing with symptomatic patients or nonsymptomatic patients. Direct measures of palliation and quality of life are what's

appropriate.

The question is: has time to progression been demonstrated to be a surrogate for survival? Although I thought the presentation was excellent, I disagreed with the conclusion that it does correlate with survival. I think we had very little data there, and we had selected data, and on that basis, I really think you need sort of an unselected set of studies.

Time to progression is probably more related to response rate than it is to anything else, and we have a lot of data in the past to know that improvement in response rate is not predictive of improvement in survival.

I just will mention several years ago we did a study. My group did a study in ovarian cancer in which we looked at the relationship between the difference in response rate in randomized clinical trials in advanced ovarian cancer to difference in survival; tried to do it on unselected trials. And what we found was that there was very little relationship for overall response rate.

For complete response rate, there was more

of a relationship, but there was a substantial shrinkage. You needed to have a large difference in complete response rate to obtain any kind of a difference in survival, and I suspect if there's any sort of relationship here, it's similar.

Really if we had the database, when that database becomes available, you will need a large effect on time to progression for it to translate into any sort of difference in survival, and approving some drug based on some statistically significant, but very small differences in time to progression, which is what we've usually seen, will not translate into a meaningful difference in survival.

CHAIRPERSON DUTCHER: Dr. Ozols.

DR. OZOLS: But having heard that, the difference in survival that we've seen has also been very small. So what we've done over the last 30 year sis obviously just make a small dent in survival, and I think perhaps using time to progression,a nd I think it's important to use quality of life. It's a very important aspect of it, but I think if it can help us speed the drug delivery or drug discovery mechanism,

that may be a benefit in its own right.

I think patients want that choice. We also hear about the patients wanting the choice of agents even though the toxicities may be substantial. Certainly there's quality of life in not having a disease progress. So that's still a difficult thing to measure.

I agree with Dr. Santana that the quality of life instrument that we've seen here over the last several years at times have been giving us information that is not very easy to understand and to make sense of, other than if you're responding to treatment you do have a better quality of life at times. It comes down to something often that simple.

Measuring symptomatic progression would be very difficult, I think, at times because that would change how we practice medicine. Many patients want to know how they're doing on treatment. We want to know how they're doing on treatment as physicians.

So if you have somebody on treatment, they're asymptomatic, but their tumor is getting worse, you certainly wouldn't want to continue that

treatment, and even if there's any kind of toxicity.

So to make decisions just on the basis of change in symptoms would be very difficult. So I don't know what the answer is, but I think we should not ignore time to progression data. I think we should use it.

I think it's certainly better than response rate because there are certainly some of the newer drugs, the biological agents, in particular, that may have more of an effect not on producing a response perhaps, but perhaps on preventing disease from progressing, not from making it shrink, but making it not get worse. So that may be a good clinical endpoint.

So I think we should continue to use that, and exactly how we do it, obviously survival should and always will be the most important aspect, but time to progression, I think, is a good endpoint in selected cases.

CHAIRPERSON DUTCHER: Dr. Williams.

DR. WILLIAMS: Several of you have mentioned using quality of life or symptoms, et

cetera, with time to progression, but it seems to me that some of the most important data points are going to be after the time when you progress. So that if you're really going to seriously consider doing that, I think you'd have to design the study to collect quality of life endpoints perhaps until the patient died, and that would certainly be difficult to do, and you'd have to decide, you know, the effects of secondary therapy on those endpoints.

But I mean, if you just collect data up to the time when someone has an asymptomatic progression, I don't think you're going to get much from quality of life.

CHAIRPERSON DUTCHER: Dr. Sledge, did you want to ask a question?

DR. SLEDGE: Yes. Actually I wanted to ask some questions either of Dr. Swain or of our statisticians.

As a general rule of thumb, do you have a sense of what's the difference in either the number or the proportion of patients that are required to go from a time progression endpoint to an overall