survival endpoint?

And similarly, what's the difference in the time that's required to go from a time to treatment endpoint to an overall survival endpoint?

Because if the differences are trivial, then this doesn't seem to be a very important question. Whereas if the differences are large, then it's an imminently practical question.

DR. SIMON: Well, if you wanted to have a specified power for detecting a specified, say, hazard ration of survival, it requires you do that calculation and you find out you need so many events, events being deaths.

If you want to identify, target that same hazard ratio in time to progression, you need those same number of events, those events now being progressions. So if you wanted to say, well, we want to be able to detect a 25 percent reduction in the hazard of death, you need a certain number of deaths. If you want to be able to detect a certain percent reduction in the hazard of time to progression, you need that exact same number of progressors.

The only question becomes whether you would target the same size of an effect of survival or time to progression, but actually what you target should be based on what's medically important.

CHAIRPERSON DUTCHER: Dr. Temple.

DR. TEMPLE: Rich, it seems to me that begs a crucial question. If you were, for example, to convert time to progression from ten to five months and have a five month change, it would be hard to expect the improvement in survival at some distance to be more than five months. So you wouldn't expect a 20 month survival to be converted to ten. You'd expect a 20 month survival to be converted to 15. That's a smaller effect when you're talking about hazard ratios.

So doesn't that mean that the sample size will have to be considerably?

DR. TEMPLE: Well, as I said, I think you should -- the decision as to what size effect you should target should be determined based on what's medically important relative to the toxicities of the therapy. To compare it based on -- well, I think

that's what it should be based on.

The only difference would be to observe those number of events will take longer follow-up in the survival situation than it will in the time to even situation.

You know, I don't really understand your point, Bob, because to say, you know, you'll be able to -- you know, basically the power depends upon the hazard ratio you want to be able to detect, and you're sort of relating it to an absolute difference in --

DR. SIMON: I'm suggesting that it's hard to imagine that survival will be improved by much more than the delay in progression. Let's say a delay in progression translates one to one to improved survival by the exact same number of months. If the difference in months is five at the time of, you know, median or something like that, then as the denominator for survival increases, the impact on the hazard ratio is inevitably going to be smaller.

So, I mean, that's part of the answer to Dr. Sledge's question. You're going to be looking for inevitably, I mean, unless something magic is going

on, a much smaller effect on the hazard ratio even if the amount of months change is the same.

DR. TEMPLE: Okay, but the issue there really is that it's not really a statistical power issue. It's an issue that a certain effect on time to progression may actually translate into a much smaller effect on survival.

DR. SIMON: That depends on how you're measuring effect. If you just counted months, which may not be how a statistician would do it, then it's the same effect. If you're counting hazard ratio, then it's a much smaller effect, right, but if it's all in months, I think the right answer to Dr. Sledge's question is you're going to need a substantially larger study for the same duration of benefit.

DR. TEMPLE: Well, in hazard ratio, what we found in ovarian cancer was that the effect measured on actually a log odds basis for response rate translated into a smaller effect in hazard ratio for survival, and therefore, if you wanted to do studies based on targeting what would be a medically

meaningful difference in survival, you would probably need a larger study than if you designed it based on detecting a difference in response rate that you didn't know the medical relevance of.

DR. SLEDGE: So again, I'm trying to put this in terms that a nonstatistician can understand. Are we talking about minimal or relatively trivial differences in numbers of patients, you know, like ten percent, 20, 30 percent increase? Are we talking about doubling the size of studies? What's your sense?

DR. SIMON: I think the kinds of studies that the cooperative groups for example are doing for metastatic breast cancer are large enough to detect medically meaningful effects on survival. I don't think we're talking about doing -- you know, right now the cooperative groups are doing studies of metastatic breast cancer with, you know, 100-plus patients per arm, and your study had what, about 250 patients per arm?

We're certainly not talking about studies any bigger than that.

CHAIRPERSON DUTCHER: Do you want to continue this?

DR. WILLIAMS: Well, just one last thing. If you look at Andy Engelsman's study, the time to progression difference is 4.5 months, and the survival difference is five months. The statistical significance of the time to progression is as long as your arm. It's .000-something. The survival difference, even though it's numerically larger, is .016, more marginal. That just says it's harder to show that 17 versus 12 is significant than it is to show that nine versus 5.5 is --

DR. SIMON: But the important point is that with the size of studies we're doing right now in the cooperative groups, those studies are large enough to detect medically relevant differences in survival.

DR. TEMPLE: Yeah, I'm not arguing that at all, but to show the same thing with a much larger denominator is obviously going to be harder.

CHAIRPERSON DUTCHER: Dr. Johnson.

DR. JOHNSON: Yes. I'd like to agree with Dr. Simon. What Dr. Temple is omitting is he doesn't

know how mature that study is, and you probably had a lot more events for progression than you did for survival at the time that analysis was done, and therefore, the P value is larger for survival, but once you get the same number of events, if the effect is the same, the P value is going to be the same.

DR. TEMPLE: I'm sorry. You're just missing the point that the effect the same could refer to hazard ratio or it could refer to number of months an the implications are different.

You're right. If the hazard ratio is the same, it'll be just as easy, but if you're talking about five months added to 12 or five months added to four, that is different, and you know, it's just not something -- I don't think it's debatable. It doesn't go to which one you should ask for. You know, that's a totally different question, but you will need a larger study.

DR. SIMON: But people don't plan studies based on looking for an absolute difference in number of months.

DR. JOHNSON: Yeah, i wanted to make --

that wasn't really the point I wanted to make. Dr. Sledge asked about how much longer it would take, and that occurred to me yesterday, and at the last minute I had 21 published randomized control trials on my desk. So I looked at the median survivals in these trials, and the survival range, median survival range from ten months to 32 months, the median time to progression ranged from four months to 14 months. The average median survival was 17 months, and the average median time to progression was nine months.

So based on these 21 studies, on average you'd have to wait eight months longer to get the survival data.

DR. SIMON: I guess another way of what you're saying, Bob, is that for the kinds of -- you're just going back to what I said before. For the sizes of effects on time to progression that we're seeing, it really does not represent much in terms of even a potential survival benefit.

DR. SLEDGE: So if the argument is that we want to use time to progression as an important surrogate for overall survival, then we're talking

about an eight month difference on average between the two. Does that represent something important in terms of speeding up drug delivery?

DR. TEMPLE: That's the delay for the median to be achieved or something. There's also an implication for the ability to detect an effect of a given size measured in months, and that I think is the more important determinant of how much bigger the study is going to have to be, which again, I want to emphasize I'm not saying whether it should be or shouldn't be. I'm just making the observation it's going to have to be bigger.

It's like whether you look at three months survival or one month survival after a heart attack. It's a guarantee that in the course of the additional nine months, there will be deaths from a large number of reasons so that the advantage seen at three months will be diluted as a hazard ratio even if the difference in survival stays exactly the same. I mean, even if it's a ten percent more survival, it'll be ten percent added to a larger denominator.

So the P values will shrink. I mean

that's just inevitable, and then you can argue about which is more important and what you do in the cardiovascular area. If you're not way better at one year, what does it matter if you're better at five days? But you need a bigger study.

CHAIRPERSON DUTCHER: Dr. Schilsky.

DR. SCHILSKY: A different topic, I guess. I wanted to just briefly come back to the issue of if time to progression were to be used as an endpoint, what would it take to have it be reliable as an endpoint because it seems to me that it is conceivable to me that time to progression might be demonstrated to be a surrogate for survival. I don't think the data suggests so far that it is, but I don't think that we have sufficient data to make a judgment one way or the other.

So if we wanted to try to get that data, what would it take, and one of the concerns that I have is that I think it's exceptionally difficult to conduct a study in such a way that the data would be reliable.

To begin with there's the issue of the

variable natural history of the disease that Dr. Swain pointed out, and it seems to me that in order to demonstrate that someone's tumor has actually stopped progressing with the therapy that you probably need to demonstrate first that the tumor is actually progressing when the patient is enrolled in the study, and that's something that oftentimes is not done.

So many of us have watched patients without any therapy for prolonged periods of time, and the tumors have remained completely stable, and had those patients been on treatment, we would all be patting ourselves on the back about the effectiveness of the therapy that we were using.

So I think that that's an area of some concern. Then there's the issue that has been raised about evaluating all potential sites of disease so that when you go back to compare to a baseline, you know what the patient was like at the baseline.

And then, of course, there are the issues of the frequency of the valuations that are required and, in fact, the definitions that are used for what constitutes progressive disease.

The National Cancer Institute has published and will be circulating again new criteria for both response and progression, and the new criteria for progression are different from old criteria for progression. Now, in a randomized trial that may not make a difference, although it will make it more difficult to compare things in the future to historical experiences.

Then there's the whole issue of the importance of quality of life that I think everybody agrees has to be an important consideration, and the ability to do those analyses appropriately and without missing data, which is a frequent confounder in studies that we've seen up to this point.

So in order to do the study well, it seems to me, will make the study exceedingly complex and perhaps prohibitively expensive, but if someone is willing to make the investment to do it right, I think that it could provide exceptionally valuable data for us on which to be able to begin to formulate judgments about the role of time to progression as a surrogate.

I'm just concerned that these studies will

be expensive. They will be subject to having lots of missing data points because of the complexity of the evaluations that will have to be done, and at the end of the day it will be very difficult to have data that will be of the quality that we would ultimately like.

CHAIRPERSON DUTCHER: Dr. Krook.

DR. KROOK: Just a couple of comments. I guess I've been on this committee long enough that there was one drug that we did approve in pancreas cancer, gemzar, that I remember clinical benefit which was toxicity survival was one month, but one of the things, and I listen to my colleagues here, and I think there's three things in the equation here that lean me towards the questions which are going to come, and one is the what I guess I call three variables: a variable of the disease I heard Rick talk about; I heard Stacy talk about the variability of the physician; and I heard some of our presenters talk about the variance of the patient obviously taking what we call alternative drugs.

I think perhaps going back, what I think Stacy said is I as a clinical physician, I will delay

telling that person the progression as long as I'm not sure because I think telling somebody that they've progressed not only perhaps affects the disease. Obviously just that statement along as a physician affects the quality of life of that person. I think we've heard that in the room.

Therefore, I think all of these three variables -- and I think we could add biostatistician to the variable, but that's another question --

(Laughter.)

DR. KROOK: -- as we've heard here, all of these will affect -- I don't think the disease, the patient, or the physician can perhaps all together agree on time to progression. They all agree on survival.

CHAIRPERSON DUTCHER: Interesting. Any other comments?

Now, remember the discussion is really regarding cytotoxic agents.

DR. KROOK: Right.

CHAIRPERSON DUTCHER: We haven't really thrown in to the mix the issue of some of the new

biologic agents that are coming in where it is going to be an issue in terms of assessing outcomes.

Shall we go through the questions? I think we've talked about a lot of them, but you want -- yes?

DR. TEMPLE: I just have one question before. Quality of life has come up a number of times, and it would be helpful to hear some discussion of how you're thinking of that.

Presumably if someone could show that a person's tumor related quality of life, whatever that means, was improved, we wouldn't be arguing about surrogates because that would be a benefit, but there's another sense in which people seem to be using it by saying, "Well, at least it shouldn't be worse," taking into account both the tumor related symptoms and the toxicity of the drug, and it would be helpful to know whether what you're saying is at least it shouldn't be worse in return for this putative grain or just how are people thinking of that?

I guess I should add we've seen very few examples of improved quality of life. The only real

examples are where someone studied pain, and that was improved in prostate cancer, but global quality of lives have been hard to find.

CHAIRPERSON DUTCHER: I think that some of the issues that have been brought up are legitimate and probably hard to quantitate, but you know, the issue of taking chemotherapy until you die is an issue for some patients because their lifestyle is revolving around going back and forth to the clinic.

Now, for some people that's psychologically beneficial because they're, quote, unquote, doing something, and for other people it's a terror. So I think that quality of life in this setting is not just tumor changes. It's lifestyle changes. It's getting to family events. It's a lot of things that we haven't really figured out how to measure.

And I think that's what some of our people that were speaking at the open public hearing were saying. I mean, they want a drug that they can get off of and survive, not that they will take to their grave, and I think that that's a real serious issue in

looking at agents that do have significant toxicity that do require additional supportive care measures to maintain patients as an out patient.

DR. TEMPLE: So how would one use those measurements? Let's say you had a drug that improved -- increased time to progression by three months. What would the observation in quality of life be that one would need to accompany that to be reassuring on this point? How would you do that?

DR. SLEDGE: Well, again, the big problem is that you're only likely to see a quality of life improvement in patients who are symptomatic when they go on therapy. Most American trials require patients to have a performance status of zero to two, ECOG performance status. Most of the patients who actually go on the trials have a performance status of zero or one. So you're automatically introducing an a priori bias against being able to see a quality of life endpoint for most of the patients who are going onto your trial.

So the only way that I could see that you could reasonably even do that sort of analysis would

be to restrict it to the patients who are symptomatic going on the trial.

DR. SCHILSKY: Or you'd want to presume -- I agree with everything you've said, and it's probably 80 percent of patients who go on front line metastatic disease trials are asymptomatic or minimally symptomatic. So the issue really is if you can't demonstrate relief of symptoms very easily, can you demonstrate no decrement in quality of life, you know, as a result of the therapy?

That really, I guess, basically gets to toxicity assessment and the impact of that toxicity on quality of life, and so I suppose that would need to be the focus of these types of assessments, would be a demonstration of lack of a decrement as a result of the therapy.

CHAIRPERSON DUTCHER: Let me just say that I think the issue is the people that might have a survival advantage are probably not necessarily the people where you can demonstrate at least during the treatment a quality of life advantage.

Dr. Williams.

DR. WILLIAMS: Aren't we forgetting the control arm? I mean these are almost always compared to front line treatment, and we usually have a comparative analysis, not compared to own baseline.

CHAIRPERSON DUTCHER: Dr. Margolin?

DR. MARGOLIN: That was what I was going to say also, but really what I wanted to ask was a clarification question, if this isn't premature, which has to do with an assumption when we try to answer or vote on these questions.

Will we be making the assumption, Dr. Temple and Dr. Johnson, that everywhere where it says TTP here means reliably assessed where the measurements really are not the issue and we don't have to deal with Dr. Nerenstone's very well described ascertainment bias?

DR. TEMPLE: Well, I think Dr. Nerenstone raised the question that nobody has addressed, which is the lack of blinding, which if there's any subjective component to when a person gets referred to evaluation could make a two to three month difference. It's sort of ridiculous.

In other areas where blinding is impossible, like surgical trials, people have a different person assessing outcomes. That's not common in cancer trials as far as I know either. So that strikes me as a major question, and I think we'd like your advice on that question. I'm not sure I would assume anything.

As I did say before, noise and scatter tends to obscure differences. So personally I'm less worried about that as a factor when you're looking for differences. If differences emerge from noise, that doesn't argue against them. In an equivalence trial it's fatal, of course, but bias is a worry when you're looking for differences, too. Noise may not be, but bias is. That seems a very important question.

CHAIRPERSON DUTCHER: Anyone like to comment? Dr. Margolin.

DR. MARGOLIN: Well, I think nothing here is trivial. Everything is actually very challenging, but I think relative to all the other challenges that we're facing, if you were to look at a fairly straightforward trial design in which you are using

both subjective from the point of view of the patient and physician, as well as the extremely important objective measures, it's easy to have central review committees assigned for -- and companies are usually quite willing to do that -- for the objective testing, and careful documentation with appropriately designed case report forms, et cetera, both for patients who would have to be doing high quality of life self-assessments anyway, as well as their physicians, and then appropriate uninvolved auditors doing chart audits; I don't think it's an impossible task.

DR. SCHILSKY: I would agree. I think blinding is tough in most of these cases, you know, particularly if the experimental drug has some different toxicity profile. You know, it's almost irrelevant to try to blind.

I do think independent review of progression events is certainly possible and probably appropriate in these sorts of circumstances. Again, it would depend heavily upon predetermined definitions of what constitutes progression.

DR. SLEDGE: Actually, and we do that all

the time in the cooperative group certainly. I mean, you have a review of it in a central office by someone independent of the initial investigator who has done the trial. The standard rule of thumb is that those tend to decrease time to progression.

DR. SCHILSKY: Sure.

DR. SLEDGE: It virtually never increases. It virtually always decreases when you have an independent review.

DR. SCHILSKY: Well, that's fine as long as it, you know, applies equally in both arms. You just get more reliable results.

DR. TEMPLE: Such a review would be blind to the treatment, I would presume, if a central review.

DR. SCHILSKY: Sure.

DR. TEMPLE: Dr. Nerenstone suggested that someone confronted with back pain might have a different attitude depending on which therapy the person was on. That's not easy to fix through a central review. How worried about that sort of thing are you?

DR. SLEDGE: I think to a certain extent that comes out in the wash. I mean there are patients who want to know immediately whether or not they're progressing. There are patients who don't want to know. There's doctors who want to know; there's doctors who don't want to know.

My sense is that that tends to come out in the wash -- I mean, tends to be a wash by and large.

DR. NERENSTONE: I disagree with that a little bit. Having looked at a number of years ago studies done by the cooperative group in hepatoma, which we know is notoriously unresponsive, in looking at a series of three different sets of trials, drug A was always better than drug B in response rate. In fact, drug A as soon as it became drug B failed to drug B of other studies.

I think that there is an inherent bias in physicians, that if that patient has the better sequence of drugs, and we all know that we're looking at new drugs; we're looking at new ways of giving them; we're looking at higher doses; that that kind of bias definitely play into when we're going to pick up

on subjective complaints.

And my concern is that I think maybe -- and I guess Rich would have to comment on this -- one way is to target. If you are going to use time to progression, one way would be to target a time to progression increase bigger than your set intervals of monitoring. That is, if you're going to tighten up your time to progression rules, you're going to have to tighten up on how you're going to monitor these patients. Instead of every three months you do it every two months. Then a three month increase in time to progression might actually have some validity.

But if you're in a three month bone scan and you have a two month increased time to progression. I'm not sure that has any real significance scientifically to telling you that one drug is more active than the other.

CHAIRPERSON DUTCHER: Dr. Ozols.

DR. OZOLS: Now, the bias you're talking about, Stacy, comes into play when you have an experimental drug that is available off study or you're looking for a new indication. So if somebody

thinks that herceptin is better or taxol is better and the patients were not randomized to that, and you would look for an earlier progression because you wanted to get them off. If that drug was available, you could get it if they progressed.

Now, on the other hand, if the drug is not available off study, then it sort of comes out in the wash.

DR. SCHILSKY: One other comment about ascertainment bias that occurs to me. The example that Stacy gave was sort of an ascertainment bias based on a clinical report from the patient. The other kind of ascertainment bias I think that we may have to deal with increasingly in unblinded studies has to do with the, you know, unspecified use of tumor markers. There'll be more and more tumor markers that are available, that are commercially available, that physicians have different levels of belief in as being relevant to oncologic practice, and to the extent that physicians may harbor biases about, you know, a particular therapy that a patient is getting, you know, if someone orders a tumor marker, believes the

result, that may prompt an evaluation or may delay an evaluation.

And then what do you do in the circumstance when the protocol specifies an evaluation at a particular endpoint and the physician has undertaken an evaluation a few weeks sooner than that, which is then an unspecified evaluation in the protocol? You know, is that the result that you use in your final analysis or not?

So my point is that, you know, there are many more types of ascertainment biases that are likely to have to be dealt with in studies where progression is an endpoint.

CHAIRPERSON DUTCHER: Dr. Margolin.

DR. MARGOLIN: Well, I think this is probably overly concrete and perhaps fantasy, but I would take Dr. Schilsky's example as a suggestion as a way to get more information in a prospectively planned way about what those markers do mean.

So if you do a study in ovarian cancer, if you do a study in breast cancer, mandate the markers and how they're going to be used and how they're going

to be followed, and then when you look back at the data, you'll actually have something to say for the next study about the correlation between those and the time to progression and the survival and the quality of life, et cetera.

CHAIRPERSON DUTCHER: Dr. Temple.

DR. TEMPLE: One of the things we encounter is that when a tumor marker progresses, the patient is then put on additional therapy, and they tend to get censored from the time to progression analysis. So you lose the patient's record.

One of the things you might want to talk about is whether that makes sense or whether we should just wait until the person actually progresses anyway and keep them in the analysis.

CHAIRPERSON DUTCHER: Well, I think that's what Dr. Margolin is saying. How meaningful is the market and when does it mean something, if at all?

Dr. Ozols.

DR. OZOLS: And it's not only, again, the physician who uses the marker. It's something that the patients use at times, which makes it difficult

for us. Patients come in with their CA 125 plotted out on a weekly basis to three decimal points, you know, and there's a lot of misinformation about that, how that should be used and the concept of immediately acting on something before it gets out of control is something that is in many patients' minds.

CHAIRPERSON DUTCHER: A good discussion.

Well, shall we go through these? Do you want to do this? Okay. All right.

The following questions address issues regarding marketing approval of new cytotoxic drugs for initial treatment of metastatic breast cancer and assume that we are dealing with randomized controlled trials.

Can secondary but not crossover treatments after tumor progression in a randomized controlled trial prolong survival in the control group and not the test group, thus obscuring a favorable survival effect of the test group?

So this suggests that a second treatment is given in the control group, not a crossover, but another drug, and therefore, the survival advantage

from the new agent is not seen.

Dr. Simon?

DR. SIMON: Well, as I said before, I wouldn't know how to answer this because I think it's essentially misguided. I don't --

(Laughter.)

DR. SIMON: The real question on survival is in the context of the secondary treatments that are available. I don't think that it's a -- even if secondary treatments can provide some effect on survival, I don't think that they're obscuring a favorable survival benefit.

CHAIRPERSON DUTCHER: Dr. Nerenstone.

DR. NERENSTONE: And in a large enough randomized trial, both groups would be able to get that at the time of progression, not just one group. So, therefore, if there is a survival advantage, if there is a secondary drug or third drug with activity, both groups would be allowed to get it at the time of progression. So I don't think that's really an issue.

CHAIRPERSON DUTCHER: Dr. Temple.

DR. TEMPLE: Well, you can imagine a case

where it could be. For example, if the test drug is an anthracycline and the control drug is not, control drug A is not, you might think people might cross somebody over -- wrong word -- might use salvage anthracycline, whereas they might think it's pointless to do that in the group that got the anthracycline.

So you can think of cases where it could obscure it.

DR. OZOLS: Well, in that situation the anthracycline test drug that you're testing has no survival benefit in the context of where you already have anthracyclines available to patients.

DR. TEMPLE: Oh, but that isn't the question. The question is whether it has a survival advantage. There are many questions.

DR. OZOLS: Well, the medically important question to the patient is the survival difference you would actually see.

CHAIRPERSON DUTCHER: Dr. Beitz.

DR. BEITZ: Yeah. A point to consider on this matter is the issue of global studies and that some patients in certain countries may not have

available to them marketed products in the United States.

DR. SCHILSKY: So I'm still a little unclear. Is this a hypothetical question or are you asking us to answer this based upon whether there is actually data available to suggest that there could be an obscuring effect?

DR. TEMPLE: Well, people have come forth with the idea that it was the secondary therapy that obscured the really terrific benefit shown in the time to progression part of the study. How to provide evidence that that's true is an interesting and difficult question, but it's been offered as a theoretical possibility.

DR. SCHILSKY: Right.

DR. TEMPLE: Most of the time, as Stacy said, everybody who progresses is going to get the same therapy. So it would be hard to think of why it should advantage or disadvantage one group, but as in the case I cited, you can imagine some circumstances where that might be true.

DR. SCHILSKY: Well, that's what I'm

asking. Is this question meant to be can we imagine a scenario where this would be true or are you asking us are we aware of any data to suggest that this is actually true?

DR. TEMPLE: I think it's more how credible do you find that assertion.

CHAIRPERSON DUTCHER: Dr. Margolin.

DR. MARGOLIN: Well, I think there's only one answer to this question, which is yes, because if you ask a question that starts with "can" and there's nothing to absolutely rule it out in medicine or biology, the answer has to be yes, and let's move on.

CHAIRPERSON DUTCHER: Okay. I think the answer should be not obvious that this exists as a problem.

DR. NERENSTONE: But just a question, which is in your specific case, Bob, the question -- shouldn't that study then be designed as an equivalent study? Because if you're looking to see if anthracycline A is better than no treatment, those studies have been done. If you're looking to see if anthracycline A is just as good as anthracycline B,

given some time else during the time of the patient's life, shouldn't that have to be an equivalent study to make sure there's no detriment to survival?

And really, would you think time to progression in that specific case is even appropriate? Because there are other options available.

DR. TEMPLE: How to exactly design the studies is going to get complicated, but I can imagine a trial where you compared drug A with A plus an anthracycline, but as soon as anybody progresses, maybe they go on to some other therapy. That seems like an intelligent trial to do, but it seems like the group that didn't get the anthracycline initially and then did, if anthracycline has had a benefit, might benefit -- that might obscure the apparent advantage.

I don't think that's a crazy trial. I guess what I hear is this isn't known to be a problem very often, but someone might make a case in a particular instance that it was, and it shouldn't be considered a very general problem, but I thought the case I posed was one where you could make that argument.

How you'd support it I have no idea.

DR. WILLIAMS: Jan, I was just talking to Dr. Johnson. He believes we have the sense of the committee on this and can move on.

(Laughter.)

CHAIRPERSON DUTCHER: Okay. Can data from a randomized controlled trial be analyzed to assess whether secondary treatments after tumor progression may have obscured a survival advantage for one of the treatments?

Dr. Sledge.

DR. SLEDGE: I think the answer to this one from a practical standpoint is no. Anyone who's ever tried to do this, and many of us around the table have tried to do this, realize that there's an infinite variety in terms of what physicians offer to patients as salvage therapies, and so for practical purpose, this sort of data dredging virtually never gives you a reasonable answer.

CHAIRPERSON DUTCHER: Okay. Is time to progression a surrogate for survival?

DR. SLEDGE: Well, we don't know.

CHAIRPERSON DUTCHER: Anybody who thinks it is?

DR. SIMON: Maybe.

CHAIRPERSON DUTCHER: Maybe. One maybe? Maybe, maybe, maybe?

I don't think there's anyone who would not look at it, correct?

DR. SIMON: Well, I think the situation is it has not been demonstrated from the data available to be a valid surrogate for survival.

DR. SWAIN: And what would you need to demonstrate that?

DR. SIMON: I think you'd want a body of data not selected based on those that had tended to have found a survival difference and then looked back at time to progression, but on a more unselected body of data of clinical trials that perhaps found and did not find a difference in time to progression, and what did that tend to be associated with in terms of the survival difference.

DR. SWAIN: Well, I think I showed that in one of the slides. There were nine trials, and seven

of them did have comparable survival and time to progress. Both had an increase. I mean that's what you're asking.

DR. SIMON: Well, you showed also the Falksen trial with a very large difference in time to progression and no difference in survival, and under the set you did show, I felt like there was a lot of trials that you did not have data on time to progression, and therefore, I wasn't convinced that there wasn't some not selection on your part, but selection on the part of those who reported the results.

CHAIRPERSON DUTCHER: Dr. Temple?

DR. TEMPLE: I mean, one could describe this as a diagnostic test in which you would like to know what the sensitivity and specificity of a finding of improved time to progression is with respect to the gold standard of improved survival. We can look among what data we have. I'm not sure how much we're going to be able to contribute, but we can.

DR. SIMON: I don't actually think that's the way to look at it because I think the medically

important difference is what size difference in time to progression corresponds to what size difference in survival, if there's a relationship at all, and under what situations is there a relationship, but saying it either is correlated or isn't correlated, I think really the medical decision making is based on size of effects relative to toxicity of therapy, and so you really -- we really want to relate what size difference in time to progression translates into what size difference in survival, if there is a relationship.

CHAIRPERSON DUTCHER: People feel comfortable with those comments?

Dr. Temple.

DR. TEMPLE: Just to be sure we get help when we get down to some of the later questions, we now use with your concurrence from time to time tumor response rates as a reasonable surrogate for clinical benefit in the refractory tumor setting. Now, you could probably say all the same things about response rate that you just said about time to progression, but in that setting under the accelerated approval rule we

have made use of that in a setting where there was thought to be no other alternative sort of weighing benefits and risk.

So in commenting on the adequacy of the surrogate here, it's worth keeping the potential use of it in mind.

CHAIRPERSON DUTCHER: I agree with you. I think the issue that Rich brought up is real. I mean is one month difference of clinical meaning to people? You know, if it's six months and the survival is better, too, then wonderful, but you know, we haven't seen data that suggests there's big incremental differences by either of these measures with the kinds of drugs that we've been seeing and the disease that we've been talking about.

So I think that, you know, home runs will certainly -- time to progression would be wonderful. If it's a year, that would be great. So I think that's the maybe part of it, but I think the committee would like to be flexible in terms of looking at all of the information that's presented and trying to tease out some things that might suggest an

improvement with any new drug.

Is TTP a surrogate for a patient benefit other than survival?

DR. OZOLS: Well, coupled with toxicity, yeah. I mean I don't think we should underestimate the benefit, the quality of life benefit to a patient who is getting treatment and she is not getting worse when she comes in to see you every month, and you tell her she's not getting worse. That's much better than if she leaves when you tell her she is getting worse. So there's just no question about how that impacts upon her quality of life until the next time you see her, but of course, you can't divorce that from the toxicity of the treatment.

So it's something that by itself is important, but it has to be taken in context as we've heard over and over again with the toxicity of the therapy and the length. We mentioned the length of this benefit.

DR. SLEDGE: I will say that in 1193 where we did see a statistically significant improvement in time to treatment failure, we saw no improvement in

quality of life.

DR. SWAIN: But, George, you said 80-something percent of those patients were asymptomatic.

DR. SLEDGE: Absolutely true, but basically what you're saying here is chemotherapy is psychotherapy, and I don't think it is. I mean, you know, walking into a room and saying, "Oh, you haven't progressed," may make the patient feel better for ten minutes, but to use that as a valid endpoint for approving a drug is making chemotherapy psychotherapy.

DR. OZOLS: Oh, no, no, no. Psychotherapy would be if you're giving chemotherapy to somebody who was asymptomatic but the disease is getting worse and you're still giving the chemotherapy.

I mean this is a different situation. This is a disease where the patient has had a response or her disease is not progressing on treatment. She knows she has disease. You know she has disease, but it's not getting worse on any measure that you can tell. I think that's an important consideration, and it's different than giving somebody chemotherapy when they're progressing even though they're asymptomatic.

CHAIRPERSON DUTCHER: Dr. Krock.

DR. KROOK: I want to follow up on what George said here. I'm going to change my comments. When I got into a room with a patient with metastatic breast cancer, I think there's three choices. I can go in and say, "You're better." I said say, "You're the same," or I can say, "You're worse." I think that lady in this case leaves with a different quality of life depends on which of those three that I say. If I say, "You're the same," okay, I got through another month. If I'm better, hey, maybe I'm going to get that magic cure, but if I say to that person that you're worse, her quality of life changes.

Now, time to progression is worse. If I say she's the same or I say, "You're better," she doesn't get -- well, time to progression is not a point on the curve.

CHAIRPERSON DUTCHER: Dr. Williams.

DR. WILLIAMS: I'd like to make a distinction between the term "quality of life," especially as George was using it, which is measured by some scale and measuring something we don't really

know what it means, perhaps, versus I think perhaps what Bob is saying, that at some time in the future the patient is going to progress and going to have symptoms.

And I think of both of this in this term "quality of life" here, and one of them, I think, is perhaps just in your mind that you're delaying the time the patient is going to progress in the future, and the other is at some scale that we may or may not know what it means.

And so I don't know that having a negative finding on this scale means that you haven't delayed this person's ultimate time to symptomatic progression, which we haven't measured and don't know if it really does.

CHAIRPERSON DUTCHER: Dr. Margolin.

DR. MARGOLIN: Well, I think it's pretty clear from this discussion from all of our practices that we just don't know. This concept of quality of life and what the patient gets versus what they give and where they start, it's not possible to generalize for all patients. Some patients would rather be on

chemo. till they die because they're doing something even if you show them a scan that's worse. Other patients only want to be on it if you can assure them it's absolutely working.

But I completely agree with Dr. Krook. When you're going to talk to a patient, even when you start therapy, you say there are three possible outcomes. In order of preference, you have a response, you remain stable and one assumes that that's in some way attributable to effect of the therapy, or you get worse, in which case things don't go so well.

And for most patients if they're on a therapy and you cannot achieve choice number one, you settle for choice number two, and you do the best you can, and we're trying to make generalizations here to please all the patients, but there's quite a big spectrum of what patients are expecting and what they will put up with, and I think we have to live with that sort of variability and just vote with what we think is the majority.

CHAIRPERSON DUTCHER: Dr. Schilsky.

DR. SCHILSKY: I guess I'm uncomfortable with accepting the notion of time to progression by itself, meaning time to some radiographically demonstrable growth of the tumor, that that represents any sort of a surrogate for patient benefit.

I think what I would be more comfortable with would be either the notion of time to symptomatic progression, that is, if you have a therapy that can delay worsening of someone's symptoms, tumor related symptoms, or delay the onset of tumor related symptoms in an asymptomatic patient, I would be more persuaded by that or in the asymptomatic patient, I guess, would be the issue of preservation of that asymptomatic period without significant toxicity from the therapy.

But I'm just reacting to the language of this question. I mean just to say time to progression by itself, is that a surrogate for patient benefit, I wouldn't think so.

DR. OZOLS: Yes, but you know, we heard, Rich, as well about survival. You could replace survival then. You know, supposing a two month improvement in survival is statistically significant,

but at a horrendous cost. That likewise wouldn't. So --

DR. SCHILSKY: I agree. I agree with that. I agree with you. I think one could make the same arguments with respect to survival, and there would be patients who would say, "Gee, if I'm going to live another two months but I have to go through hell to achieve that, it's not going to be worth it."

CHAIRPERSON DUTCHER: Dr. Temple.

DR. TEMPLE: The point you raise is critical. If someone can show increased time to symptomatic progression, then they've already shown something that's a benefit. Of course, you weigh it against toxicity and all of that. So that's not really an issue for us.

If anybody could manage to show that, which I can't recall anybody who has, but if anybody managed to show that, we would love that. That's an exception.

The question here is suppose you don't have that, can we use the endpoint.

DR. JOHNSON: Well, you know, Bob, we've

taken this up with companies, and people are just not willing to conduct clinical trials that way. When they see radiographic progression, they want a change.

DR. TEMPLE: Yeah, that's what I said.

DR. JOHNSON: They're not willing to wait until the patient become symptomatic.

DR. TEMPLE: Right. That's why this is an issue.

DR. JOHNSON: But really we can't do that.

DR. OZOLS: But are you saying that's not appropriate practice?

DR. JOHNSON: I'm saying that most people aren't willing to do that.

DR. OZOLS: Right, but I'm saying on or off study if a patient's tumor is growing or they're getting new lesion and they're on treatment, you certainly aren't going to continue that treatment even if they're asymptomatic.

DR. JOHNSON: Well --

DR. OZOLS: So you can't ask someone on clinical trial to do something that they wouldn't do in standard practice.

DR. JOHNSON: That's what we just said.

DR. TEMPLE: Right.

DR. JOHNSON: We discussed this in the context of tumor markers, if you recall, and you said you would be willing to continue a patient on therapy or at least willing not to start a new therapy in the face of a rising tumor market, but many of your colleagues wouldn't be willing to do that.

DR. TEMPLE: There is another possible answer. I wonder what you think of this, which is even if someone crosses -- sorry. Wrong word -- gets salvage therapy, you could still measure time to progression and not just censor the patient, which is what we typically do now.

In other words, you'd be looking at symptomatic progress sort of as the study is randomized. That's unusual for us, but we could -- you could do that, and a positive finding there would be pretty credible.

DR. SLEDGE: I just don't know how you could do that though. When you say time to symptomatic progression, you know, it's not entirely

easy for me to know which symptom is due to the treatment and which symptom is due to the disease in every patient.

DR. TEMPLE: Well, that's why you have a committee to do it, I guess.

(Laughter.)

CHAIRPERSON DUTCHER: But, you know, the unfortunate or the fortunate -- the unfortunate? -- the fortunate thing is that in metastatic breast cancer there are so many drugs that do show some effect, call it, positive effect. In other malignancies where you have a very limited armamentarium, we are often put in the position of watching something grow slowly or grow quickly, but you do definitely see some change in the clinical behavior.

So your problem here, I think, is confounded by your wealth of agents.

Kim.

DR. MARGOLIN: I think paying attention to the word "surrogate" in that question is really important because I think we all agree that we cannot

possibly know that increasing the time to progression actually benefits a patient, but is it a surrogate? Does it correlate most of the time with survival, the gold standard? Is it likely to correlate with quality of life and, most importantly, with objective responses?

It seems like the answer to that is yes. So as a surrogate, we know that surrogate is not an equivalent. It's just a representative. It seems safe to think of it as a surrogate.

CHAIRPERSON DUTCHER: Dr. Nerenstone.

DR. NERENSTONE: I think that as a clinician there's no question that a longer time to progression is worthwhile. My concern is that at the levels of increased time to progression that we're seeing, that they may not be real.

And so that I think that there are two issues. One is a clinical issue. Is increased time to progression important? And I would say, yes, it is. But as a regulatory issue, is time to progression, especially at the small times that we're seeing, is that a clear marker of active drugs? I

think that's a much harder question to ask.

CHAIRPERSON DUTCHER: Dr. Simon.

DR. SIMON: Well, I think "surrogate" is a fairly strong statement. It means it represents an effect on what it's purporting to be a surrogate of, and I think I guess my impression here is the only thing you could potentially know about quality of life, I guess, is is time to progression a surrogate for symptomatic improvement, and I think we have two potential bases for doing that.

Either we have studies that have correlated time to progression with symptomatic improvement in patients who had perhaps symptoms when they went on study, and I don't think we have that body of data. So on that basis, I don't think we could conclude that time to progression is a surrogate for patient benefit in terms of symptomatic improvement.

The other thing we could have to go on would be clinical impressions. That is, does tumor progression seem in the clinician's view to be associated with symptomatic deterioration?

But other than that, I don't see how we could conclude that time to progression is a surrogate for some other kind of patient benefit.

DR. SWAIN: I'd just make one last comment, and I would agree with you after having tried to review all the data and presenting the data that certainly we do not have data. The only data that would even remotely support it is the Coates trial because the time to progression was longer in that study.

But I think that still we need something. We intuitively, as you said, think that if time to progression is increased, that the patient is going to benefit, that their symptoms are going to be lessened. So I think we can't throw it out.

I agree that the statement is strong, and if you noticed in my presentation I did not make that statement at all that it was the surrogate because I do think that you need hard data for that, and I don't think we have it.

DR. SLEDGE: You know, the other thing is I'm not sure we're always treating the patient. As

often as not we're treating the physician in this sort of setting.

Again, I don't think we should use this, chemotherapy, as a form of psychotherapy, and to claim that there's a surrogate here which implies a statistical association based upon a single weak data point in the literature I think is perhaps claiming a little bit too much.

CHAIRPERSON DUTCHER: Dr. Temple.

DR. TEMPLE: Just one word about what our regulations say. The standard for a putative surrogate in the setting of accelerated approval is that the surrogate is, quote, reasonably likely to predict clinical benefit based on pathophysiclogic, et cetera, et cetera, reasons.

I guess one reason is what Rich said, that people sort of believe it for a variety of reasons.

A surrogate outside the context of accelerated approval has to be better than that, although there's no formal definition. So the reasonably likely standard is the one for accelerated approval, and something considerably stronger is what

would be needed for ordinary approval.

DR. JUSTICE: And that's what we're getting to in Questions 5(a) and (b).

CHAIRPERSON DUTCHER: Right. All right. So is TTP -- I can't say that -- time to progression -- it reminds me of another disease.

(Laughter.)

CHAIRPERSON DUTCHER: If time to progression is a reasonably likely surrogate for survival or other patient benefit, is TTP, is time to progression a sufficiently reliable surrogate only for accelerated approval with confirmation of effect on survival or other patient benefit needed in a Phase IV to quality for regular approval, or is it sufficiently reliable to be the basis for unqualified regular approval?

DR. SLEDGE: Are we to assume here that we answered Questions 3 and 4 yes?

CHAIRPERSON DUTCHER: No, I think we are to assume we answered those questions as we answered them, which to me three was maybe and four was possible.

(Laughter.)

DR. SWAIN: That we believe it is, but we can't prove it.

CHAIRPERSON DUTCHER: I mean, you're never going to see a study coming in for accelerated approval that doesn't have a response rate in addition to time to progression in a cytotoxic drug, I would think. I mean, am I overstating?

For a cytotoxic agent --

DR. TEMPLE: Only for pancreatic cancer.

CHAIRPERSON DUTCHER: Well, but you gave us a new drug. Okay?

That's true. In pancreatic, we didn't require a response, zero, yeah.

DR. SIMON: I thought we were only supposed to answer five if the answer to three or four was yes.

CHAIRPERSON DUTCHER: I think five is the crux of the questions.

DR. SIMON: Well, five starts off with "if TTP is a surrogate for survival or other patient benefit, then" you do 5(a) and 5(b), but I didn't

think that we -- so it depends on the answer to three and four, which I don't think either of those was yes.

CHAIRPERSON DUTCHER: But it wasn't no either.

DR. WILLIAMS: Since five has two levels or requirements for a surrogate, it might be helpful to go ahead and answer five anyway.

CHAIRPERSON DUTCHER: Well, I think you're right. I think it's important for us to kind of -- I think what these folks need is for us to come to some level of comfort. Either it's not comfortable at all or it's a little bit comfortable or, of course, as time to progression in the spectrum of things that we would accept for accelerated approval, and I think we've heard quite a spectrum from the group.

Dr. Margolin.

DR. MARGOLIN: Well, it seems like given the degree of divisiveness on Questions 3 and 4, but assuming we've agreed that we do need to go on to Question 5 that it's pretty obvious that the answer to (a) would be yes and that (b) would be no, that nobody is willing to use time to progression as full fledged

approval of a new drug.

CHAIRPERSON DUTCHER: Well, I would think that on (a) there may also be some concerns from the discussion.

Dr. Ozols.

DR. OZOLS: Yeah, I think (a) at this point should be yes. I think we should continue to study this and we should take the opportunity to hone down, perhaps better define what time to progression is and make it a more useful clinical indicator, but I think we should ignore the data that we have, and obviously we interpret data differently. Therefore, there's a good possibility there's something good in that data and that we can learn something from that, another clinical marker.

So I think if we do (a) and do a few studies and get some information, I think that may be very useful for us.

CHAIRPERSON DUTCHER: Dr. Schilsky.

DR. SCHILSKY: I would agree with that. I think actually that may be the only way we'll ever get the information that we would like to have in

order to answer Questions 3 and 4.

My sort of caveat though would be that I think a study in which time to progression is to be used for accelerated approval has to be exceptionally well conducted with all of the requirements that I tried to describe earlier with respect to the difficulties in doing these sorts of studies.

CHAIRPERSON DUTCHER: Have any of the accelerated approvals been -- as the Phase IV data came out, have any of them been reversed? Any of the accelerated approvals been reversed after Phase IV data came out?

DR. TEMPLE: No. The bulk of Phase IV data was fairly readily available. Actually I have to correct that. In one AIDS drug, but I forget which one, the indications changed on the basis of the results of the trial, although the drug didn't disappear because it still was effective, but not quite where it was thought to be effective.

In oncology, we've only had data on a couple, I guess, some of which you've seen and which tended to support the original approval.

CHAIRPERSON DUTCHER: So shall we vote on 5(a)?

DR. SWAIN: In this situation are you talking about a randomized clinical trial? Because you'd have to have that to look at it.

CHAIRPERSON DUTCHER: I think you're talking about a randomized clinical trial with very strict baseline data and follow-up data.

Okay. Is time to progression a sufficiently reliable surrogate only for accelerated approval with confirmation of effect on survival or other patient benefit required in Phase IV to qualify for regular approval?

All those who would vote yes?

(Show of hands.)

CHAIRPERSON DUTCHER: Eleven yes.

Is time -- is that how many we have? Twelve. Sorry. Twelve.

Is time to progression a sufficiently reliable surrogate to be the basis for unqualified regular approval?

All those who would vote no?

(Show of hands.)

CHAIRPERSON DUTCHER: Twelve.

In other case, what magnitude of effect on the median time to progression would be sufficient? And I presume we're talking specifically about metastatic breast cancer because I don't think this is necessarily applicable across the board.

Dr. Margolin?

DR. MARGOLIN: Well, if we're going to do that, I think we're going to have to define groups because, again, if you look --

CHAIRPERSON DUTCHER: Well, we're talking about first line. We're talking about initial treatment in metastatic.

DR. MARGOLIN: But traditionally in most cooperative group studies and even large Phase IIs and certainly what's presented to the FDA, patients with bone only disease have been excluded as not being measurable, and that's a very large, very important group of patients who might be appropriate for this new definition, but they have a very different behavior as well.

DR. SLEDGE: I personally don't think we can answer this question because I think the idea that we're going to be able to use time to progression solely by itself and, therefore, we're going to be able to define a magnitude solely by itself is important I just don't think is possible.

I mean if a patient's right leg falls off reproducibly when you give a drug and there's a three month time to progression, that's going to be different than a patient who has no symptoms from the drug in a three month time to progression.

I just don't think we can answer this question.

CHAIRPERSON DUTCHER: But isn't that the problem? That's the problem that's going to be the problem going forward, is that the variability, the nuances -- I mean, it's fine to say that this is a surrogate, but what are we going to use to say it's not a good enough surrogate?

DR. SWAIN: Well, you have to define it so you can plan your clinical trials. You have to make some kind of decision about what is an important

effect, such as a 50 percent increase in time to progression or --

DR. SLEDGE: Well, that's the difference between a statistically significant effect and a clinically significant effect. I mean statistically significant effects are very easy to define. Clinically significant effects are very difficult to define. We all know that.

So I don't think we should pretend that one is the other.

DR. OZOLS: And you just cannot unlink the magnitude of the effect with toxicity.

CHAIRPERSON DUTCHER: Dr. Temple.

DR. TEMPLE: Well, no one would try to do that, but for example, suppose you just think about a drug that's sort of like the other drugs that are out there, has the usual range of toxicity, not worse, not better. Does that help? Could you say anything further about that? I mean, if you had a lot of early deaths or something really leg falling off like, that would be understood to say that the usual couple of months wouldn't do, but is a few months, which is what

we see typically, okay if it's sort of like anthracycline or sort of like the others?

You may still not want to answer that, but --

DR. OZOLS: But would that have a drug be going for accelerated approval?

DR. TEMPLE: Well, sure. The context is they took standard first line therapy. They added this new drug to it which no one had done before, and they showed a three month improved time to progression.

The accelerated approval says that you're supposed to show that you offer some advantage over available therapy in a serious of life threatening disease so that they could come in with that.

CHAIRPERSON DUTCHER: So accelerated requires improvement over standard.

DR. TEMPLE: Yes. Has to be serious life threatening disease and has to add to available therapy. We're in the process of defining what available therapy means. We're inclined towards thinking it means therapy we've approved, but that's

still in the works.

CHAIRPERSON DUTCHER: Dr. Simon.

DR. SIMON: Well, for accelerated approval, you would have to believe that it will translate into a meaningful improvement in what your real endpoint would be here, would be survival, and I would be skeptical that a three month improvement in time to progression will translate into a detectable effect on survival.

So my own view would be I would be more comfortable with a six months or greater effect on time to progression.

DR. SWAIN: Well, I would disagree with that because most of the studies I reviewed and the drugs we've seen have not had a six month increase in time to progression. So then we basically are not going to approve any drugs unless something really is a home run.

So I think for me that magnitude is too great, and I would accept a 50 percent increase in time to progression. I wouldn't give it a specific number because I think it would depend where you'd

start.

Most of the time to progressions are about six months. So a 50 percent increase would be up to nine months, is the same thing as what you're saying.

CHAIRPERSON DUTCHER: Dr. Ozols?

DR. OZOLS: Yes, and there were two large trials in ovarian cancer which showed a time to progression difference of about four to five months, which led up to significantly longer times in overall survival and differences.

CHAIRPERSON DUTCHER: How do people feel about the 50 percent?

Dr. Margolin.

DR. MARGOLIN: Well, I think you're going to get different answers from everybody at the table, and if you poll them twice, you get two different answers. So I think the FDA, if they want us to vote on this, should give us three choices or something so we can narrow it down.

CHAIRPERSON DUTCHER: No?

If trials utilize time to -- wait a minute. Never mind. We don't need to do number

seven.

If trials utilize time to progress as the primary endpoint, they may not be adequately powered for survival. That was the argument we were talking about earlier. Should these trials be required to have sufficient power to detect a clinically realistic difference in survival?

Dr. Simon.

DR. SIMON: Of course. We're saying that time to progression is only something that we think may translate into survival, but we want to see whether there is a medically relevant effect on survival. So the trials should.

CHAIRPERSON DUTCHER: Dr. Nerenstone?

DR. NERENSTONE: No, I agree. My other question though is going to be, again, about quality of life. Are we going to insist that those are done and that those are done in a statistically significant way and that those are done as a primary endpoint and that the trial design is big enough and make sure that these are actually done as part of the application?

CHAIRPERSON DUTCHER: How do people feel

about that? Would you make it a requirement? Dr. Swain?

DR. SWAIN: My suggestion would be to make it as an alternative. If you can -- and we've talked so much about quality of life, and having been on the committee for four years, we usually don't come up with an answer. If it's more specific, such as a pain score, a weight change, or a performance status change, those probably would be preferable, but I would make it as an alternative and wouldn't make it as a requirement.

DR. SLEDGE: Again, remember that quality of life and survival are measuring qualitatively different endpoints. So, I mean, it's to a drug company's advantage to measure both in that if either is positive, presumably it would be a reason for approval.

CHAIRPERSON DUTCHER: Dr. Margolin?

DR. MARGOLIN: I think it's really essential that we build in very well designed and taking advantage of people who have made careers out of this, to build that into these trials and to do

them right and to have them be interpretable and to get out of this habit that we have every ODAC meeting of looking at the quality of life data and dismissing it as being inadequate.

That needs to change, and then we're going to get a lot of important information about whether quality of life issues do or don't correlate with some of these other things we're trying to use as surrogates.

MS. BEAMAN: One comment here. I really don't know that it should be listed as an alternative. If it's listed as an alternative at the end of a long form, it's not going to be done. It's not going to be done.

DR. SANTANA: In kind of response to that, Kim, I think there's two ways of addressing that. One is as a committee we discipline ourselves to request that data and to critically review it and just not dismiss it when it's not there or when it's unquestionable, or in parallel to that where we come down making it a major requirement for approval of these kinds of questions.

DR. MARGOLIN: Certainly. I mean, as members of the committee, we get what we're given at the end of the trial and the analysis, and obviously the sponsors need to take advantage of what's now becoming a very growing field of high quality research in this area, to do it right from the very start.

CHAIRPERSON DUTCHER: Dr. Simon.

DR. SIMON: Just as a point of information, I had requested of the FDA to have a meeting of this committee or those who were interested to try to discuss quality of life analyses, to try to -- because we have been unhappy with many of them, so that we could review the problems we see and so that they could develop recommendations for sponsors, so to make our job easier and maybe the sponsor's job more successful, but I don't know what the status of that is. I requested that about five months ago.

DR. SANTANA: I would second that comment.

CHAIRPERSON DUTCHER: Ms. Zook-Fischler.

MS. ZOOK-FISCHLER: Regarding that particular statement, I think that's wonderful, and I think it's really important to have the input of

advocates and patients on that.

The other thing, in terms of the particular question, I would like to see that qualification that quality of life be considered, and I think it's good that it's on the table, and it shouldn't get relegated to the back burner again.

CHAIRPERSON DUTCHER: Dr. Temple.

DR. TEMPLE: I'm occasionally allowed to go to quality of life meetings --

(Laughter.)

DR. TEMPLE: -- even though I'm not in the business, and it's an extremely formidable problem. For starters, quality of life by the people who defined it initially has three elements, one physical, one social, and one psychiatric, and it's very hard, and there are very few examples of where treatments have affected the last two, perhaps because it takes longer to reintegrate into the community or something like that, whatever the reasons.

So in trying to figure out what improvement you'd like to see, you really have to specify those things very well and pay attention to

it.

Part of the problem is what Dr. Sledge pointed out. You're not likely to get physical improvement as a result of treatment if you're not physically impaired. So you can't really expect a great deal unless the people are already impaired.

So there's huge problems. We take the point that how to do it better and how to do it is of great interest, and we have an internal working group that Julie Beitz is part of, but it's a really hard problem, and you realize that as soon as you go to meetings among the people who are absolutely in the business. It's a very hard area.

CHAIRPERSON DUTCHER: But the negative use of that type of data could be that if you have a new agent combined with standard therapy and the quality of life is even worse than the standard therapy, even though the outcome may be better, then that's really going to be a point for discussion.

DR. TEMPLE: Well, again, the question is whether you get a better answer by doing quality of life survey than you do by looking at the accumulation

of horrible symptoms. That's the constant debate here that goes on.

And we've urged people to look for and add tumor related symptoms as the sort of thing an anti-tumor agent might actually do with very little success in getting anybody to do it or getting any success on it, for what that's worth.

DR. BEITZ: Yeah, I think what we've heard is the difficulties in assessing quality of life in the short term in patients who are refractory and progressing, and what might actually be more pertinent to what some of the patient advocates are speaking about is quality of life in survivors or patients who are out from treatment but may have long term side effects from the treatments they did receive, and perhaps that's something that needs to be focused on.

But it doesn't necessarily help you with a specific drug approval.

DR. SLEDGE: Here though we're talking about first line metastatic breast cancer, right?

DR. BEITZ: Yes.

DR. SLEDGE: I mean, the truth of the

matter is that many patients with front line metastatic breast cancer are relatively asymptomatic. So while I think it's certainly imminently important and reasonable to actively encourage drug companies to do good quality quality of life studies, the simple truth is that for the studies that we currently do, most of the time those studies are not going to show a difference in quality of life because they are biased a priori against quality of life studies.

DR. BEITZ: I completely agree with you.

DR. SLEDGE: So mandating that for all of these studies, frankly, is not going to help us a great deal.

DR. MARGOLIN: But that's just talking about the quality of life for patients with respect to their cancer symptoms. The other half of this at least is the difference between, you know, the new or the investigational treatment versus the comparator, and is it worse. If it's worse, is it worth being worse for if there's a benefit in whatever endpoint, other endpoint we decide is important?

DR. SLEDGE: The problem is we have to my

knowledge exactly one study which is the one I did that's actually looked at that question for a new drug, and it didn't show any difference between the three arms in quality of life. I mean none whatsoever.

I mean, believe me. I'm a strong believer in quality of life studies. Personally I think we should do them on all of our randomized trials, but I guess the question gets back here. If quality of life survey shows no difference but we see a difference in overall survival, do we really believe that we're not going to approve a drug?

DR. NERENSTONE: I think it's just the opposite, that if we see a significant detriment in quality of life that carries out through the eight months of median survival with the new drug, even though time to progression is delayed a month or two, is that drug really worthwhile approving to add to our armamentarium?

And even if we do approve it, shouldn't that be something that has to be publicized for the physicians who are going to use it and to the

patients?

So I think this is in response to patient advocates who are saying we understand that these drugs may improve survival by two months, but at what cost over standard or other treatment? Yes, it may be worth it to some, but we don't have that information in any kind of way that we can really inform our patients when we're making these decisions.

DR. SLEDGE: I think our differences here are small, but you know, if you say there's going to be a significant detriment due to the drug, presumably it's going to be due to toxicity, and in truth, we are reasonably good at picking those up.

So I don't think there's a major disagreement here. I mean, my guess is that if there's a significant detriment in quality of life, it's going to be due to the fact that patients had horrible Grade 4 mucositis or something like that. I suspect we will pick that up.

CHAIRPERSON DUTCHER: Dr. Justice.

DR. JUSTICE: In response to Dr. Simon's comment, I'd just like to confirm the committee is

willing to add another sixth meeting this year.

(Laughter.)

DR. SIMON: Well, actually when I proposed it was when there was going to be a closed session morning meeting in conjunction with another meeting, and so that was if it could be scheduled in that kind of a context, I think it would be best.

DR. SCHILSKY: And if I could just reaffirm, I guess, my own believe of the importance of having broad representation from the patient community at that meeting, one of my concerns is that we all have a different view of what quality of life means, and I'm not even sure that we all utilize the term the same way. In fact, I suspect we all utilize it differently.

And I suspect that the people who do quality of life for a living utilize the term very differently from the way patients utilize it.

So I think if we have such a meeting we have to involve the patients because if the goal is to have a good quality of life for our patients, we need to fully understand what they mean by quality of life.

CHAIRPERSON DUTCHER: Okay. Back to Question 8. Do we all agree with Dr. Simon's "of course"? Do we need to vote that it should be powered for survival evaluation at a later date?

PARTICIPANTS: Yes.

CHAIRPERSON DUTCHER: And then we added onto that issues related to quality of life, and you heard the comments. So that that needs to be added into that subsequent evaluation.

Question 9, do you want us to do that? Yes.

Recently the FDA received a proposal to include patients for initial treatment of metastatic breast cancer and patients for second line treatment of metastatic breast cancer in the same randomized controlled trial combining the two groups for analysis to obtain marketing approval for initial treatment of metastatic breast cancer.

Okay. So one study, one randomized trial, but patients for initial treatment or second line treatment, but the marketing approval would be for first line treatment.

Are initial treatment and second line treatment of metastatic breast cancer sufficiently similar that they can be considered in a single indication?

DR. SLEDGE: Actually, can I ask a question here? Is this a case where we're talking about sequential versus combination therapy or is this a case where we're actually talking about truly different drugs, different regimens?

DR. JOHNSON: Truly different regimens.

DR. SLEDGE: So we're not talking about adria to taxol, taxol to adria versus A plus T?

DR. JOHNSON: No, just standard two regimens. And we had one request to do this, and now we have a second pharmaceutical company that wants to do this. We really need to get an answer to this.

DR. KROOK: Both in breast, John?

DR. JOHNSON: Yes.

DR. MARGOLIN: I guess I'll take a little stab. I think this has to be somewhat study by study and case by case, and I think it's pretty clear what is being referred to here is what we're going to

discuss this afternoon, I guess, right? I don't know that we could vote in a general way to always say yes or no to this question.

CHAIRPERSON DUTCHER: Dr. Swain?

DR. SWAIN: I think that the patients getting treatment second line are going to have a worse time to progression, a worse survival. If anything it will put the results in the opposite direction. So I have no problem with this at all if the investigators want to do this. I don't see any problem. It's going to dilute your positive effect.

DR. WILLIAMS: Jan, if I could ask a clarifying question, there may be first line therapies that are thought to have some special value that you wouldn't want to lose, and that wouldn't necessarily translate to the second line setting.

So are you worried that some value that might be added in first line setting might be diluted by including second line patients? For instance, if you thought that was a doxorubicin advantage in first line therapy, would you miss it by including patients in second line therapy?

For instance, if you're comparing the new drug 2-doxorubicin in first line therapy and you were going to, let's say, show equivalence, would you be concerned that if you included it in your control arm, both first and second line patients, that equivalence comparison would not -- could not be considered valid because the first line patients might be the only ones showing the advantage?

CHAIRPERSON DUTCHER: Dr. Simon?

DR. SIMON: Oh, I think I agree with Dr. Margolin. We couldn't make any general conclusions, but I think in general it's -- I mean, I think in some cases at least it's going to be problematic because, for one thing, you may have the events dominated by the second line patients since their time to progression and survival will be shorter, and so you'll have the problem of knowing whether the conclusions really apply to the first line patients or not.

And certainly in an equivalence type of trial, it'll be very complicated because interpreting the trial will depend upon how effective the active

control is, and that may be very different for second line as for first line, if you had any data from either of them.

So I think you also have the issue of measuring the size of the benefit relative to the toxicity of the therapy, and that difference will be different probably for the second line versus the first line.

So I think it's going to raise all kinds of complications in terms of interpreting the trial.

DR. SWAIN: Rich, what if you powered the study so that you would have enough first line patients in there to get an evaluation, if you had a substrata, you know, you stratified for first or second line? Then you should have enough to really look at the results.

DR. SIMON: I think things are clearer if you just view them as two separate studies and you size them both to get answers.

CHAIRPERSON DUTCHER: Comments? Dr. Margolin.

DR. MARGOLIN: Well, I would agree

strongly that if you prestratify -- there's two purposes of stratification. One is just the balance between the factors, and then you don't look back. You don't think of it as two separate groups for analysis.

But the other would be sufficiently stratified patients to do two separate studies, and then you might as well just do two separate studies.

DR. SIMON: Interim monitoring will be a problem if it's one study. You may get the study stopped when you don't have the answer for the other strata.

CHAIRPERSON DUTCHER: Dr. Temple.

DR. TEMPLE: That wouldn't be the first case where one part of a study was stopped and the rest was allowed to continue. I mean, you could do it if you wanted to.

What's the difference between a study with two strata where you just happen to use the same facility but really are treating them as completely independent, separate conclusions? Is that troublesome compared to -- I mean, I guess I can't see

what the difference is if they're definitely completely separate for analysis purposes.

DR. SIMON: It just makes it clear that they are when they're two different protocols. It raises an ambiguity when they're not.

CHAIRPERSON DUTCHER: All right. We do this not infrequently in Phase 2 leukemia studies, for example, where you have multiple subgroups that have different prognostic factors just to see what the effect of the drug is.

Enough?

All right. Thank you all very much. We're going to try to start on time at two o'clock. We'll be back this afternoon to talk about epirubicin.

(Whereupon, at 1:08 p.m., the meeting was recessed for lunch, to reconvene at 2:00 p.m., the same day.)

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

(2:04 p.m.)

DR. TEMPLETON-SOMERS: Hello. We'd like to start with a few announcements from Dr. Justice and Dr. Temple over there, who may not quite be ready. You're on.

DR. JUSTICE: Sorry. It's with some regret that we are losing or at least four of our members are going off the committee, and we'd like to recognize their dedication and service that they provided on numerous occasions at numerous meetings, and we have both a letter from Dr. Henney, which I'll read.

It says, "I would like to express my deepest appreciation for your efforts and guidance during your term as a member of the Oncologic Drugs Advisory Committee. The success of this committee's work reinforces our conviction that responsible regulation of consumer products depends greatly on the participation and advice of the non-governmental health community.

"In recognition of your distinguished

service to the Food and Drug Administration, I am pleased to present to you the enclosed certificate."

And I think what I'll do is just acknowledge the members who are retiring, and then I'll walk around and give you your certificates.

The first one is for Dr. Robert Ozols, and we thank you very much for your four years of service.

The next is for Jim Krook, who has probably attended more telecons. with us than anybody else, and for that we're grateful, and can't thank you enough for that.

DR. KROOK: Thank you.

DR. JUSTICE: And the next one is for Ms. Carolyn Beaman, whose done an outstanding job as our consumer nominated representative, and we appreciate your help.

And finally, or last but not least is for Dr. Janice Dutcher, who has been our chair for what, the last three years and I think has done an outstanding job, and we're very grateful, and Dr. Temple will have another gift after I give these out.

(Laughter.)

DR. TEMPLE: Thank you very much.

(Applause.)

DR. TEMPLE: What I have is a special award. It's the first time it's been given, as far as I know, and it comes from the Office of Special Health Issue, OSHI, which is our office that deals with consumers and patients and has been heavily responsible for helping get people to talk at meetings and for getting participants, patient participants, at these meetings.

Anyway, this is an award to Dr. Dutcher again. So you can do more than just leave it turns out.

(Laughter.)

DR. TEMPLE: And the plaque says, "In recognition of your thoughtful and consistent support of FDA initiatives to incorporate the views of cancer patients and cancer patient advocates into the deliberations of the Food and Drug Administration's Oncologic Drug Advisory Committee."

And I think everyone notices your receptivity and positive attitude toward these things,

and so that's what this award is for. It's the first, as far as I know the only, and we are very pleased.

I should add that you've been a terrific chair also.

CHAIRPERSON DUTCHER: Thank you very much. Thank you.

(Applause.)

CHAIRPERSON DUTCHER: Okay. We have to read a few more comments about conflict of interest.

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

Based on the submitted agenda 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 Drs. Kim Margolin, Victor Santana, Stacy Nerenstone, Robert Ozols, David Johnson, and Ms. Sandra 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.

In addition, we would like to disclose for the record that Drs. Richard Schilsky and Robert Ozols have interests which do not constitute financial interest 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 in their participation outweighs the concern that the integrity of the agency's programs and operations may be questioned.

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

will be noted for the record.

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

Thank you.

CHAIRPERSON DUTCHER: All right. I think with that we will -- oh, we have open public hearing. Are we doing that before?

Okay. We have two people who have asked to speak, and we have copies of their addresses. The first is Karin Noss of Y-Me.

And just to remind you, please identify yourself, your organization, and any financial assistance in coming to the meeting.

MS. NOSS: As Dr. Dutcher said, I'm Karin Noss from Y-Me.

I'd like to thank you for allowing us to submit this statement to the committee.

Y-Me National Breast Cancer Organization is a nonprofit patient organization whose mission is to decrease the impact of breast cancer, create and

increase breast cancer awareness, and insure through information empowerment and peer support no one faces breast cancer alone.

We are here today to support the approval of the drug Ellence, epirubicin hydrochloride injection, which was developed by Pharmacia and Upjohn. In general, Y-Me believes that women and men diagnosed with breast cancer should have access to as many treatment options as possible.

Doctors and patients should have choices. We believe the approval of epirubicin will help provide those choices.

Clinical trials with epirubicin and anthracycline antibiotic, in combination with other chemotherapy drugs, have shown it to be effective in the adjuvant setting with early stage node positive women and women with metastatic disease.

The common side effects are similar to those of other members of the anthracycline family of drugs: transient nausea, vomiting, low white blood cell counts, and temporary hair loss.

The rarer but serious side effects of

cardiotoxicity to leukemia are also present.

We have been asked why we support the approval of a drug that is similar to a drug doxorubicin hydrochloride that is already available. There are many cases of drugs belonging to the same class being approved. The assumption is that the patients may respond differently to drugs of the same class.

There may also be price differences that could benefit patients. So we return to our basic belief that patients and their doctors should have as many treatment choices open to them as possible.

We urge you to approve epirubicin as a drug to be used in the treatment of breast cancer.

Thank you.

CHAIRPERSON DUTCHER: Thank you.

The next speaker is Nancy Davenport-Ennis, Patient Advocate Foundation. Is this someone different, same organization?

MS. BORWHAT: Yes. Yes, I'm Margaret Borwhat with the Patient Advocate Foundation speaking on behalf of Nancy Davenport-Ennis and members of our

executive board for the Patient Advocate Foundation.

We did not receive any compensation to be here today. We have received a small educational grant from Pharmacia and Upjohn in 1998.

To the honorable members of the advisory board, thank you for the opportunity to express our support of the approval of epirubicin hydrochloride for injection for use as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection or primary breast cancer, Stage II and III.

Our support is based on our review of published data reported from European clinical trials and on the fact that this drug has now completed trials in the United States with positive results. It is our position that both the safety and efficacy of the drug has been established through its long term use in European markets, including 80 countries throughout the world.

Additionally, it is our position that epirubicin delivers fewer side effects, such as nausea, vomiting, stomatitis, bone marrow toxicity,

and congestive heart failure.

In reviewing data from Spanish, Italian, German, New Zealand, and French studies published throughout the late '80s and early '90s, there were fundamental positions affirmed in each of these studies, including the following.

The drug may be administered alone or in combination with other agents both to patients with early breast cancer and those with metastatic disease. Epirubicin is an analog of doxorubicin with a similar activity, but less toxicity.

Quote, patients with metastatic breast cancer are incurable. Remissions with long survival can be adduced by chemotherapy in 50 to 80 percent, with ten to 20 percent complete remissions. However, recurrence is unavoidable. Therefore, the strategy of therapy in breast cancer must include two aspects: first, prolongation of overall survival by multiple remissions with regimes that are not cross-resistance and, secondly, conservation of quality of life by minimization of therapy condition side effects.

Epirubicin exhibits the same high

activity, but lower side effects compared with the parent compound, end of quote, from epirubicin results in breast cancer, Oncologic, 1986, August 9th.

Remission rates include 33 percent and 313 patients studied in a German study of 1986. Forty-two, point, eight percent remission with a median duration of 6.3 months in the Italian study reported in Tumori, 1993, February '82. Sixty-one percent overall response rate with ten complete and seven partial responses with 63 percent of the patients having no side effects as reported in Tumori, 1992, October 31st.

The incidence of clinical congestive heart failure, approximately 20 percent observed in the Milan and Copenhagen trial, suggest a potential limitation on the long term administration of this combination.

Quote, limiting the cumulative dose of doxorubicin, adding cardioprotectors and substitution less cardiotoxics and anthracyclines, that is, epirubicin, represent investigational efforts to minimize cardiac toxicity, end of quote, as suggested

in M.D. Anderson's study of 1997, reported in "Optimal Dosing of Paclitaxel and Doxorubicin in Metastatic Breast Cancer."

The position of the Patient Advocate Foundation is that precautions must be initiated to insure patient safety as it relates to the potential cardiac side effects from prolonged exposure to epirubicin.

The widespread successful use of this product in European markets suggests that the availability of this product to American patients insure that patients may have access to successful European protocols that include epirubicin, while reducing toxicity and its inherent side effects.

In surveying each of our scientific board members, the comments repeatedly urged the availability of epirubicin in America, citing reduced toxicity, less than doxorubicin, and therefore, reduced side effects while insuring enhanced remission rates both in those patients receiving single agents, epirubicin, and combination therapies with epirubicin.

We strongly urge FDA approval of

epirubicin, as yet an additional agent to be used in the war on breast cancer.

Thank you.

CHAIRPERSON DUTCHER: Thank you very much.

We will now proceed with the sponsor's presentation. Dr. Miller.

DR. MILLER: Thank you. Thank you.

Good afternoon. My name is Langdon Miller, and I'm here representing oncology drug development at Pharmacia and Upjohn.

We would like to share with you today important efficacy and safety information regarding the use of epirubicin for the therapy of breast cancer. The data we will describe are presented in support of obtaining FDA approval of epirubicin as a component of adjuvant therapy for early breast cancer and as an option for the treatment of metastatic disease.

Within the presentation today, we would like to provide you with background information regarding the regulatory history and worldwide use of epirubicin, as well as to describe the pharmacology of

the drug.

Thereafter, we will provide the results of clinical trials of epirubicin based adjuvant therapy in patients with early breast cancer.

We also plan to summarize data from clinical trials of epirubicin used in patients with advanced disease.

Finally, after providing overall conclusions, we would be pleased to address any questions that you may have. Personnel from Pharmacia and Upjohn, as well as investigators who conducted the trials, are here to assist in responding to your queries.

Now, epirubicin is currently registered in over 80 countries worldwide, having gained its first approval in France in 1982 for the therapy of breast cancer, and having been registered in most countries since 1984. Approvals were based on use of single agent starting doses of 60 to 90 milligrams per meter squared or on starting doses of 50 to 75 milligrams per meter squared when epirubicin was given as a component of combination chemotherapy.

A U.S. NDA was submitted in 1984 requesting approval of epirubicin at these same starting doses as therapy for advanced breast cancer. The NDA was not approved due to the small sample sizes and limited survival documentation that were available at that time.

For business reasons, the decision was made not to pursue the NDA further.

This situation has substantially changed since the U.S. NDA in 1984. Epirubicin has been extensively studied. The focus of these trials has often been on its application in breast cancer, but epirubicin clearly has a broad spectrum of activity in other tumor types.

As a consequence, epirubicin has been the subject of over 2,000 publications and has been given to literally millions of patients worldwide. Based on drug use estimates, hundreds of thousands of patients currently receive epirubicin treatment each year.

This means that the short and long term efficacy and safety of epirubicin have now been thoroughly characterized through controlled clinical

trials and Pharmacia's and Upjohn's surveillance programs involving large numbers of patients over very protracted periods of time.

Epirubicin hydrochloride is a synthetic derivative of donorubicin, the prototypic anthracycline. As shown in the accompanying structural diagram, it is different from doxorubicin because it has reorientation of a hydroxyl group in the four prime position of the davnosamine ring.

Although the precise mechanism of action of the anthracyclines is not fully known, it appears that epirubicin may have several cytotoxic effects, including DNA intercalation, topoisomerase II inhibition, helicase inhibition, and also free radical formation.

The activity of the drug appears to be almost exclusively due to epirubicin itself. Epirubicin metabolites are relatively noncytotoxic.

Now, epirubicin is a unique anthracycline, and its structure has definite pharmacologic implications. Epirubicin has a lower PKA and is more lipophilic so that it can penetrate cells more readily

than doxorubicin.

In addition, the equatorial orientation of the hydroxyl group allows the glucuronidation of epirubicin and may be responsible for the higher clearance and the faster terminal elimination of epirubicin than that of doxorubicin, as is shown in the graph to the left on this slide.

Epirubicin's pharmacologic profile allows escalation of the starting doses. This has made it possible to redefine the maximum tolerated dose, resulting in starting doses of epirubicin that were higher than those originally approved outside of the United States. Starting doses can be safely escalated up to 180 milligrams per meter squared.

Literature reviews of tumor response rates have suggested that higher epirubicin starting doses are associated with higher objective response rates in patients with advanced breast cancer.

Based on these types of analyses, Pharmacia and Upjohn began a clinical development program that was aimed at increasing the epirubicin starting doses in patients with selected neoplasms,

including breast cancer.

Seven major Phase III, well controlled clinical trials that resulted from this developmental program formed the basis for epirubicin approval as both adjuvant therapy and as therapy for advanced breast cancer. In node positive early breast cancer, three trials have been conducted. These studies demonstrate that epirubicin based CEF produces significantly longer relapse free survival and overall survival than a standard regimen of CMF; that epirubicin demonstrates a dose response effect; and that it prolongs the disease free interval when added to tamoxifen therapy in postmenopausal patients.

In advanced breast cancer, four studies that closely parallel the design of the adjuvant trials document that dose escalated epirubicin based therapy improves response rate and the duration of tumor control in patients with locally advanced or metastatic breast cancer.

Now, you might well wonder why these seven studies were selected as the basis for approval, given the large number of clinical trials that have