and those studies show against no treatment a modest but felt to be clinically significant improvement in outcome. That's not your feeling.

DR. WHITE: I was making the comparison to 5-FU alone.

DR. KELSEN: Okay.

DR. DAVID JOHNSON: Rich, it might be worth doing a little historical review for purposes of this committee.

When you and I came on this committee initially several years ago, one of the very first things that we were asked to review was the utility of CPT-11 in this disease. There was a lengthy, detailed discussion about the efficacy of 5-FU versus 5-FU plus leucovorin in colon cancer. And randomized trials were presented, including SWOG data and others, which failed to really show a major survival advantage for the addition of leucovorin. Yet, the committee at that time, this committee, accepted, I recall very vividly, this issue -- Dr. Bunn was the Chair of this committee at the time -- that 5-FU/leucovorin was a standard. It didn't say the standard. It said a standard for the treatment of this disease.

Now, whether or not one can show a difference between 5-FU plus leucovorin versus 5-FU of any major substance I think is debatable and was debatable at that

time. Some members of the committee, as I recall, wondered why the committee accepted 5-FU/leucovorin as a standard when it had not been shown to be superior in survival to 5-FU. The answer ultimately boiled down to a difference in response rates that were perceived but not proved to be related to improvement of quality of life. If I can interject a little corporate memory into the discussion here, that's where we were at that time with that discussion.

In fairness, it seems to me -- I realize the committee has changed, and we can change our mind. We are free to do that, but as I recall vividly, that was the issue and it seems to me that it's still valid today, those discussions that we held almost 3 and a half years ago now.

DR. SCHILSKY: Thank you. We can maybe ask you to take on the official role of committee historian.

(Laughter.)

DR. DAVID JOHNSON: Well, in that regard, I actually had some comments then, if you wanted me to do that.

(Laughter.)

DR. SCHILSKY: This has not been rehearsed in advance, ladies and gentlemen.

(Laughter.)

DR. DAVID JOHNSON: No. Because I actually

think sometimes the corporate memory is helpful. I assume that's the reason why the FDA asks us to serve more than one meeting at a time, although I have to confess sometimes it seems like it's one meeting at a time.

But, for example, I was very interested in this elaborate analysis regarding the certainty, if you will, of the lower bounds of the 95 percent confidence interval. I appreciate the point that is being attempted to be made here, and this is by no means an effort to be flippant. But the reality is those two curves on which this analysis was done are so precisely the same that it seems to me that it's a lot of effort for not really a clinically relevant issue in my opinion.

Again, the corporate memory tells me that we have approved drugs, albeit maybe in an accelerated manner, with similar mechanisms of action with considerably less data than were presented in this randomized, I think well-conducted study. And it seems to me that that really is what we as a committee ought to focus on.

What did they do? They took a standard that we accepted once before in a well conducted study. I don't care if it was done in the U.S. candidly or in Canada. I noticed Canada was on both sides of this, so they need an identity check.

(Laughter.)

DR. DAVID JOHNSON: But the reality is this study was well done and I think proved the point that they set out to prove.

Now, the second issue. I agree with the points that were made. The study did not meet the endpoint that it was designed to do. But I think, as I see the sponsor's presentation, it's merely presented for supportive evidence, and you yourself pointed out the consistency of the data, in the UFT presentation. In fact, it's shockingly consistent.

DR. WHITE: Strikingly.

DR. DAVID JOHNSON: Well, I would say shockingly. I've never seen data this consistent from two studies like that. And I think that's very powerful evidence in my mind.

One, I think, last corporate memory issue that's worth making is related to -- and one other point that I wanted to bring out was the issue of the placebo, whether this is a placebo or not. I think the answer is clearly it is not a placebo, 5-FU/leucovorin, even if given poorly. You might argue it was a poor way of giving a standard treatment, or you might argue it was a good way if you're looking at it from a toxicity perspective. But I don't think that that impacts on the efficacy of the UFT, which I believe they have demonstrated at least is

equivalent to a standard way in this country of giving 5-FU/leucovorin, which we've previously accepted as a reasonably standard regimen. That's how I see these data personally.

DR. SCHILSKY: Thank you, David.

Dr. Raghavan.

DR. RAGHAVAN: I guess that I run the risk of being like some of my procedural colleagues which is often wrong, but never in doubt. I just am very perturbed by the presentation because it seems to me that it's totally missed the point.

One looks at the survival curves, and as my distinguished southern colleague pointed out, they are very, very similar. And one has just listened to an attempt to look at what might happen and if certain simulations occurred. It's sort of, really effectively, a historically controlled statistical analysis, and I think it's actually not very valuable.

But what I think I would really like to have heard the FDA do is concentrate more on what I think is the fundamental issue. There's an orally administered drug which has been designed to reduce the problems of having chemotherapy, and to me, treating a lot of patients, it's a no brainer. Patients like to take things by mouth rather than get stuck with a needle and to take them at home

rather than to come to a clinic.

So, I don't have a lot of interest in comparing 52 versus 53 versus 51 weeks and try to make sense of whether a benefit is lost when there is a large number of patients that are following identical survival curves.

But I'd be very interested, Dr. White, in your sense of the issues that we raised related to toxicity, which you kind of summarized just in one slide. Give us the FDA's gestalt. Does this make toxicity less? Does it make it easier for patients to deal with fluoropyrimidines?

You know, the whole story of fluoropyrimidines, corporate memory or not, is somewhat like rearranging the deck chairs on the Titanic. It's a small gain. We've recognized that. Dr. Johnson, Dr. Schilsky, and I were there 3 and a half years ago when we ground through whether 5-FU was good or bad and whether leucovorin added. But the reality is the community in time has accepted 5-FU/leucovorin as some form of standard.

So, the thing I'm really interested in knowing about this product is what is the patient benefit from the perception of the FDA? Is it easier to take? Do they live better lives? Is it better tolerated? Can we not assess it from the data presented?

DR. WHITE: Based on the quality of life assessment in study 11, there was no difference between the

two arms. So, the reduction of toxicity that's being claimed just didn't seem to result in improvement in quality of life.

DR. SCHILSKY: Dr. Margolin.

DR. MARGOLIN: I think that we need to be very careful how we interpret the information from the study about the quality of life which we actually didn't see presented but we had in some of the handouts -- and we haven't heard a statistical analysis of it either, which often breaks down its integrity -- versus the actual toxicities as measured by whatever toxicity scale was being used because in this study -- and I think somebody asked about this earlier and didn't get a full answer -- patients with this disease had a very short duration of treatment, a very short progression-free interval, and they were off therapy. The value of quality of life analysis, when patients are falling off as quickly as they are, has to be quite limited and I think needs to be looked at quite differently than the actual toxicities of treatment.

I think quality of life and the impact of an oral therapy versus a really relatively nontoxic IV chemotherapy are probably much more useful in a patient group that is benefiting over a much longer period of time, is being treated longer, or if it's adjuvant where everyone gets 6 months of therapy and then they go off, but

otherwise they're well.

DR. SCHILSKY: Dr. Krook.

DR. KROOK: A couple of comments and back to the quality of life issues. I am going to come back at Derek a little bit here, and maybe my statistician can help. But if I'm correct, these people will take 12 pills a day 28 days out of each 35 days, which is 336 pills in a cycle. I guess as an investigator I'm not sure that's easier than 5 days of 5-FU/leucovorin. Now, maybe I've been around long enough that I've passed out enough 5-FU/leucovorin, but it isn't that difficult. So, if it comes down to an issue of what's easiest and convenient to the patient, I guess I plead with the sponsor, if this is made available, that we do something about the number of pills. If I'm correct, it's 4 pills 3 times a day. So, I think that that's something that I come back to. I don't think taking that many pills is convenient.

Secondly, the quality of life scales that Dr. White or Dr. Johnson or Dr. Cohen -- I'm not sure who did them -- in the FDA document does show that at least that document is the same on both arms. And I have a little bit of trouble rationalizing out that there's less side effects when I look at these quality of life, and that when we look at all, if and and, they come down I think the two regimes in both studies are equal in quality of life. I don't

think there's a benefit of one over the other. And they appear to be similar in survival, however you look at it. After that, I agree with Derek, I think we're starting to pick it apart.

Perhaps Dr. White would like to comment on the quality of life at least being the same. That's what my question. There isn't a difference when you look at the approved scales.

DR. WHITE: Based on the claim in reduction in toxicity on UFT/leucovorin, I specifically looked to see whether that was going to translate into a quality of life improvement, and it wasn't there.

DR. KROOK: And I think 336 pills -- again, we can't ask that, but cost-wise certainly that's a problem. But somehow if this is available, I think that issue has to be dealt with.

DR. SCHILSKY: Just one other comment on the quality of life issues. Many of the reductions in toxicity were laboratory parameters, blood counts essentially. I don't know that one would anticipate that a reduction in a blood count nadir would necessarily have a quality of life impact on a patient. The number of febrile neutropenic events were different, but there were relatively few and they might not ultimately manifest themselves in a quality of life analysis. And one might argue that the reduction

in mucositis in the UFT arm was balanced by the increase in diarrhea in the UFT arm. So, maybe there's a plausible explanation for why there might not be an overall difference in quality of life, that there's just some tradeoff in toxicity. Some of the other toxicity reductions which the physician may appreciate as being potentially important may be, in a sense, unrecognizable to the patient.

I had one question for you, Dr. White. I wonder if you could help answer the question that you said Dr. Temple posed on that slide that you put in there having to do with compliance. So, was there information on compliance submitted in the NDA?

DR. WHITE: Yes.

DR. SCHILSKY: Did you look at it, and what's your assessment about compliance?

DR. WHITE: Well, it depends on your definition. And I made some comments on that in my review. Patients on UFT had to take the medicine for 28 consecutive days, and to be fair with regard to the 5-FU/leucovorin arm, there were about 39 patients, or 10 percent of the patients, on UFT/leucovorin who missed 6 or more days of the medication.

DR. SCHILSKY: Now, is that a compliance issue or is that a --

DR. WHITE: Well, I thought it was a compliance issue. I thought it was a compliance, that patients forgot, they missed. So, I looked at those patients in detail in terms of toxicity, and to my shock, it appears, at least with the graphs I provided, to coincide with the onset of toxicity.

DR. SCHILSKY: So, why were you shocked by that?

DR. WHITE: Because I thought it was just going to be a simple compliance, and at least based on what they were saying, that it was reduced toxicity, I gave them the benefit of the doubt.

DR. SCHILSKY: So, if I understand you correctly, you're saying that when patients missed doses, that it appeared that it was related to toxicity. So, it may have been either a protocol-specified dose modification or just a recommendation from the physician that they skip doses.

DR. WHITE: When patients missed 6 or more. And I used that as a cutoff because that was being fair relative to missing a day of 5-FU. What was the question again?

DR. SCHILSKY: I'm just trying to get your insight as to whether these missed doses were patients just being noncompliant as in not following instructions or they

were missing the doses because they were told to omit doses.

DR. WHITE: At least with regard to the first course of therapy -- and that's where I felt everything was equal and that's where I focused on -- it seemed to be due to toxicity, although it seemed that the patient was on drug a day or 2 more after the onset of grade 2 toxicity which was the cutoff when they should have come off treatment or when the weekly telephone call came.

DR. SCHILSKY: Ms. Forman.

MS. FORMAN: Just to ask the question a different way, is there any evidence as to patients who either forgot to take the medication or some other circumstances rather than the reaction to the medication? How many patients were in that category percentage-wise or numbers, whatever?

DR. WHITE: Yes. With regard to the first course, there were 95 patients who missed at least 1 day's worth of UFT. In terms of why those patients who missed less than 5 days of UFT, that hasn't been examined yet.

DR. SCHILSKY: Dr. Lippman.

DR. LIPPMAN: I agree with Dr. Johnson's assessments of the survival equivalence and his comments regarding the standards, but a lot of this seems to be the apparent discrepancies perhaps between issues of

convenience, quality of life, and toxicity grading.

Regarding compliance, again if you look at the table that was presented, the fact that 99 percent of the people took 80 percent or more of the medication seems pretty good, even given the number of pills.

Regarding the issue of whether there's clinically meaningful toxicity or we're just looking at grades -- because really there are impressive differences in toxicity grading. Again, I come back to looking at some of the correlates like the concomitant medication use, which seems to clearly support the clinical importance of these toxicity grades. Unless some of these antiemetics and so on are used prophylactically to a greater degree in one arm or the other -- and maybe there could be some comment -- if they're not being used prophylactically, this would seem to support the clinically meaningful differences in toxicity that were reported.

DR. WHITE: Let me just make a comment about the UFT compliance that you were talking about. When you look at the accessed database, there was, of course, compliance which only applied to UFT. I spent a lot of time trying to figure out what that exactly meant. I thought if I prescribed 28 days' worth of UFT and somebody took 80 percent, whatever that is, 23 out of 28 days, that's what that 80 percent meant. That's not the case. I

have a case report form.

What I believe happened is if a patient was prescribed 28 days, but if they only took it for 6 days but took only, say, 5 and a half days, it was the 6 divided into the 5 and a half and not 28, which would have brought it down to 17 percent.

So, those numbers that were presented relative to UFT compliance are inflated, and they don't match the dose intensity numbers that were included in the exact, same table.

DR. SCHILSKY: Dr. Raghavan.

DR. RAGHAVAN: Using the FDA tables, I think we still have a forest and trees problem, and I come back to the point because I think it's important, Dr. White. You said that the measured quality of life didn't show a difference, and I accept that. I think that the company goofed big time by not understanding the right indices of quality of life and how to apply them. Listening to Dr. Canetta, I think that they recognize that.

But if you look at the data that you've analyzed, we're looking at severe leukopenia less than 1 or 2 percent versus 19 or 12 percent, worse figures for neutropenia, equivalently different figures for severe stomatitis. Now, I defy any clinician or any patient to say that having a mouth fallout is a good thing.

Therefore, if you have severe stomatitis in 1 and 2 percent versus 19 and 16 percent, it seems to me a no brainer that quality of life is better in the people who don't get it.

So, therefore, I'm just really worried that the forest and trees issue here is that we're talking about small differences in survival where for metastatic disease the treatment is quite poor. We have what looked to me like poor quality of life official measures, sort of, if I could say, patient controlled measures. And I don't mean to demean those, but yet objective indices that go with poor quality of life that are vastly different.

So, Dr. White, I'm surprised that you haven't expressed concern over that discrepancy. It troubles me enormously because there are such big differences in the indices that I think make patients' lives worse.

I take Jim Krook's point that taking a lot of tablets is a bad thing. On the other hand, showing up to a cancer center week after week after week and getting stuck where sometimes you get stuck three or four times is no picnic either.

I'm just uneasy that, while we're getting very, very clever in looking at fine points, we're missing the big picture, which is that even though the company screwed it up, this looks like the medication actually causes less morbidity in a way that we're used to looking at

traditionally, and all the very clever indices of quality of life seem to be letting us down. I think this is going to come again and again at FDA. So, I think we probably ought to nail it down today.

DR. SCHILSKY: David.

DR. DAVID JOHNSON: It's perhaps repetitious to say it again, but again just as a clinician taking care of patients, patients complain of mucositis, patients complain of nausea, patients complain of being anxious, and these are all parameters that I see the UFT arm doing better.

Again, the concomitant therapies -- maybe that's a recording phenomenon; i.e., the company was very careful to record all those data for 5-FU/leucovorin and were more casual or less diligent, but I sort of doubt that that's the case. I think here that's good supportive evidence, as Dr. Lippman has said.

For those reasons, it seems to me again that they've shown that is what they set out to do. This is equivalent therapy. At worst, toxicity similar. As I see these data, the toxicity appears to be less.

In terms of the convenience issue, I think some patients will find pills more convenient and some will find injections more convenient. That's the way it is now for me with etoposide, and I'm glad I have that particular choice for patients. I see patients that live 250 miles

away from me and some that live a block away, and the trip to the clinic is easy for some and not for others. This gives some flexibility in the ability to treat those patients, it seems to me. That's the other "advantage" I see.

DR. SCHILSKY: We've been blending our discussion and questions. So, let me just bring us back for a moment to ask, does anyone have specific questions to the FDA regarding their presentation? Because we will have additional time for discussion.

Dr. Margolin.

DR. MARGOLIN: I guess it's just a reiteration of my original question that would have been to the FDA in the first place. I didn't get an answer. I know the FDA tries to be very rigorous, and generally when we recommend a new drug approval, it is with the requirement to show a clinical benefit either by survival or by some good surrogate for survival or quality of life.

In this study, it seems that even in the design of the phase III, the FDA agreed to use in the pivotal study equivalence as clearly defined for the new drug without defining what improvement in the tolerability or the quality of life or the toxicity profile would be sufficient to allow only equivalence to make this drug approvable.

And in the second trial, the supportive trial, the concept of progression-free survival as the endpoint we know is one that the FDA has been grappling with, although presumably that's an historical problem in that this study was agreed upon before the FDA started to revisit the value of progression-free survival.

DR. JUSTICE: Well, there would be no requirement to demonstrate -- I mean, if the committee votes for approval, you're voting that the survival is equivalent or non-inferior, whatever terms you want to use. You don't have to believe that it's less toxic to vote for approval.

Does that answer your question?

DR. MARGOLIN: No, because in previous meetings, it was always my impression that for a new drug to be approved, it had to be better than an existing drug.

DR. JUSTICE: No, that's not true.

DR. SCHILSKY: Dr. Blayney.

DR. BLAYNEY: In the discussions about quality of life and toxicity, et cetera, it sort of hinges on the fundamental question where they measured equivalently. I noticed in the UFT arm, a nurse or some study personnel at each site called the patient at least once a week. Was that done in the control arm?

And second, were the biochemical and

hematologic parameters measured equivalently in the control arm and the UFT arm?

DR. WHITE: The laboratory interventions were done the same, as far as I remember. I asked the company about whether the 5-FU/leucovorin arm was being called weekly, and based on what they told me, that was yes, that they were being called weekly.

DR. SCHILSKY: Okay. Any other questions for the FDA at this point?

DR. BLAYNEY: Excuse me, Rich. The other thing has to do with salvage or second-line treatment. The FDA analysis made a point about the U.S. versus non-U.S. sites in terms of the efficacy of the control arm. We were shown that in the 11 study 50 percent of the patients got some sort of salvage treatment. Do you know if there was a difference in the salvage therapy or the second-line therapy between the U.S. and non-U.S. sites?

DR. WHITE: We asked that question, and basically got the same numbers that you saw here. But Bristol-Myers Squibb said that they didn't investigate and weren't required to collect what regimen the patients were put on.

DR. BLAYNEY: But in terms of patients who received salvage therapy, was that subset analysis performed?

DR. WHITE: Oh, I didn't perform that subset analysis.

DR. SCHILSKY: I think we did see some data from the sponsor earlier about that point.

DR. BLAYNEY: But it was balanced in terms of treatment versus control arm but not U.S. sites versus non-U.S. sites, and in the FDA analysis, they made a point about the better performance of the control arm in the North American or U.S. sites. I wonder if that could be explained by availability of effective -- if you agree there is effective salvage or second-line therapy on survival.

DR. WHITE: What you've got in front of you is a draft review, so that may be something that we will go ahead and look into after the meeting.

DR. SCHILSKY: Before we go into a more general discussion, Karen Somers has another public statement to be read to the committee.

DR. TEMPLETON-SOMERS: This is a fax that has just been received today from the Hepatitis C Action & Advocacy Coalition. Actually I'm not going to read the whole thing. It came with a number of letters, and I'm just going to read the cover letter.

"To the FDA Advisory Committee for Oncology Drugs:

"We request that the following comments be read at the advisory committee meeting on September 16th for the consideration of Bristol-Myers Squibb's UFT, uracil/tegafur, fixed combination and leucovorin for the treatment of metastatic colorectal cancer.

"As a coalition of patients and patient advocates, we strongly oppose the approval of the two-drug combination with UFT/leucovorin if Bristol is allowed to market the drug solely in a fixed combination package under the brand name Orzel while the drugs are unavailable separately. This will lead in oncology to the same fiasco that now exists in hepatology with last year's unprecedented FDA approval of Schering-Plough's Rebetron combination therapy of Intron A, interferon alpha 2b, and Rebetol, ribavirin, bundled into a single package for the treatment of hepatitis C. Tegafur is currently not approved in the U.S., just as ribavirin was not approved in oral form before Rebetron approval. As a result of the approval of Rebetron, ribavirin is not available from Schering except in its fixed combination.

"There is no clinical reason for these oncology drugs to be packaged solely in combination. Should the advisory committee find this combination treatment safe and effective for approval, we urge you to approve them to be available separately and labeled appropriately for use in

combination. Such approval is the norm for all HIV antivirals that must be used in combination. The members of Bristol's team before you today are well aware of how their company has benefitted from HIV medications not being available only in bundled or combined forms. Bristol's popular medication, Zerit, d4T, is often used in combinations containing Glaxo-Wellcome's Epivir, 3TC. Glaxo markets Combivir, a single pill containing both 3TC and AZT, and other of its HIV antivirals. Yet, both AZT and 3TC are marketed separately at no higher price than when they are combined as Combivir. So, the physicians can individualize combination treatments, including combinations using Bristol's d4T.

"Bundling drugs together limits the ability of physicians to individualize treatment for patients when the dosage of one or both drugs must be altered from the fixed packaging. Amounts of one or both drugs are often not used, an enormous waste of scarce health care resources. Bundling also limits the use of appropriate and reasonable off-label combinations with one or both drugs as the HIV example illustrates.

"Bundling impedes research as well. Usually a competing drug company desires only one of the drugs of a bundled combination for research. Either the competitor must purchase the entire combination package and waste the

unwanted drug, or the competitor must submit its protocol to the company, revealing its strategy, something that most companies will not do and should not have to do. Then they must await the license holding company's decision whether or not to grant the request. The decision is not usually based on clinical research merit, but economics and market position of the license holder. Bundling, therefore, impedes the development of promising novel treatment combinations that would be economically unfavorable to the license holder of a desired drug.

"Far from any safety or efficacy concerns, the primary reason the company desires to bundle its products is to hold third party payors, patients, and physicians hostage by forcing them to purchase both drugs and use fixed amounts of the drugs whether or not they are actually needed. This scheme also allows the company to hide an inflated price for one or both drugs when separate sale of the drugs would make the unreasonableness of the prices transparent. Escalating drug prices are the single largest contributing factor to the rising health care costs in the U.S. today.

"Despite continued calls from the hepatitis C community, Schering-Plough selfishly refuses to sell the ribavirin in its combination kit separately. When Schering came before the FDA Antiviral Drug Advisory Committee in

May of '98, it cited convenience as well as safety and clinical concerns to defend its desired bundling practice, just as we are sure Bristol is doing today for its drug. The European Medicinal Evaluation Authority, in its review of Schering's application of interferon/ribavirin combination therapy for the European Union, saw through this rouse. On May 7, 199, the EMEA approved the combination only when the two drugs are marketed separately and labeled appropriately for combination use. Schering put ribavirin on the market in Europe separately as soon as it was allowed. Clearly any safety concerns that Schering may have had were far outweighed by the economic interest to get the drugs to market any way it could. We sadly suspect the same situation is occurring here.

"In the case of Schering's Rebetron, the FDA has expressed its willingness to unbundle the packaging of Rebetron and has written to Schering stating so. However, once it approved the bundled package, Pandora's box was opened and the FDA lacks the regulatory authority to compel Schering to separate its drugs once on the market. We urge you not to make the same mistake here.

"The American Medical Association's Council of Ethical and Judicial Affairs has publicly cited its concern over Schering's marketing practice. Congressmembers Christopher Smith, Frank Pallone, and Nancy Pelosi have

requested hearings on the matter. Next week members of the HAAC and other HCV patient advocates will be meeting with staff of the House Subcommittee on Health and Environment and with officials of the Federal Trade Commission to urge actions on this matter. In addition to the objections already cited, it is our view that bundling constitutes a form of tying under the Sherman Antitrust Act. Bundling is nothing more than forcing the sale of one product by tying it to the sale of another.

"Pharmaceutical manufacturers will argue either side of the bundling issue, depending on their individual economic advantage for the drugs in question. Regardless of the clinical results, if a company owns the drugs they want used in combination, it will argue the need to bundle the packaging, i.e., Orzel. If the combination requires use of a drug from a competitor, it will argue against it, i.e., Zerit. But the third party payors, researchers, physicians, and patients all lose every time if bundling is allowed to stand. Arguments of convenience, compliance, or dispensing errors have all been heard from Schering. Bristol will probably even tell you they can conveniently make a few different dosage kits supposedly to meet individual needs. Nonsense. These arguments pale in comparison to the economic and treatment options that are lost if bundling is allowed to continue. Physicians

working with their patients, not drug companies, should have the control and flexibility of deciding what is the best dosing for their individual patients. Individualization of treatment cannot be realistically achieved in a few fixed dosage combination drug kits.

"Bundling does not lead to greater safety or efficacy. On the contrary, it detracts from both. Attached to this letter, we have included a few testimonials from HCV patients to show how bundling has adversely affected them economically and therapeutically. We ask that you read these as well. We do not wish oncology patients to experience the pain that Rebetron has caused members of the hepatitis C community.

"We urge this committee to stop this bundling and tying scam here and now. We ask that you strongly urge the FDA to deny approval to Orzel or any future bundled drug combination products unless the drug company is also compelled to market the drug separately in addition to the bundled package."

This is from Brian Klein from the Hepatitis C Action & Advocacy Coalition, and it came along with five anonymous letters which in the interest of time and avoiding redundancy, I will not read them here. They will be available through the Freedom of Information Office next week if anyone would like to see them.

Thank you, and that's the end of our second open public hearing.

DR. CANETTA: Are we allowed to make a comment, a very brief comment?

DR. SCHILSKY: Perhaps you could just inform the committee about the plans for how the drug product would be marketed if it's approved.

DR. CANETTA: It's very simple. It's very short.

The NDA that you have being presented today is the NDA for UFT and leucovorin calcium tablets. Bristol plans to market the two things separate. Oral leucovorin is available on the market. Bristol has an NDA approved already for oral leucovorin that will be marketed separately, and I think diffuses the whole issue. We do not plan, though, to separate uracil for tegafur because there is a clinical reason not to do that.

DR. SCHILSKY: Thank you for that clarification.

Before we go into the questions, I'd like to just ask if there's any general discussion that the committee members would like to have, having now heard a thorough presentation of this application. Dr. Kelsen.

DR. KELSEN: At the present time, there are advances in the treatment of this disease that really are

important and they include drugs like irinotecan and oxaliplatin, but the data that we have right now, at least the preliminary data, is that both of those two agents are most effective when combined with fluorinated pyrimidines. So, it's highly unlikely that, at least in the immediate future, fluorinated pyrimidine therapy is going to be abandoned, and therefore, this is an important issue as to whether there's a more convenient and less toxic way of giving the same drug.

It's especially important to me because that fluorinated pyrimidine therapy remains the linchpin of curative therapy. We're not being asked to discuss curative treatment with this application today. It's for palliative treatment of patients with metastatic disease, but the key role of curing people still revolves around FU/leucovorin or some other fluorinated pyrimidine in one combination or another. CO6 may answer this question but we'll have to wait for that data.

This is more of a statement than a question. I'm unimpressed with the comparison that we just heard that UFT is a placebo or worse than a placebo. I don't think we ever actually got an answer to that table that we saw, although Dr. White might want to comment on it again during the discussion. But the placebo-controlled trials pretty regularly, although they're small in number, give a very

brief median survival of about a half a year, 5 to 6 months, with the one exception of the trial for totally asymptomatic patients, which was also inferior to UFT as historically controlled. Therefore, I think the statement that UFT is acting as a placebo is very difficult to support.

I think what we should really focus in on is what has been discussed now. Is this an equivalent agent? I think the agent has some activity. Fluorouracil leucovorin has modest activity and this drug has modest activity. Is this drug equivalent and easier to give and less toxic?

DR. SCHILSKY: Yes.

DR. BEHRMAN: I'd just like to address that because you're right. We're not asking you if this is a placebo. We're trying to ask you how much uncertainty are you willing to accept because we do prefer the term "non-inferiority." In other words, are you content or comfortable with the degree of inferiority that may be present? Obviously, the worst case scenario would be that the drug has no effect and, therefore, would be equivalent to a placebo, but I think the words are getting confused a little bit. We're not trying to ask you whether you believe it's a placebo or whether the added toxicity would make it worse than a placebo.

DR. KELSEN: Do you believe that it has no effect at all?

DR. BEHRMAN: Well, we're asking you the efficacy question. We spent a lot of time talking about quality of life and comparative toxicity, and that's really not what we're asking you. We're saying, given that the effect is small and the confidence interval is obviously not incredibly tight, are you comfortable that you're ruling out a significant -- decreasing the benefit significantly? That's what we're asking you, not whether we believe it's a placebo or whether we believe it's inferior, but are you comfortable that it's essentially giving the same effect, although we understand that the effect is not that substantial.

DR. SCHILSKY: So, we'll get to that specifically with, I think, the first question.

Any other general discussion anyone wishes to have? Dr. Krook?

DR. KROOK: Just the one question or comment of the U.S. versus the non-U.S. In Bob White's document which was there, there's a statement which I guess I thought was interesting, that in the U.S. it was organized through a principal investigator who I believe in the Minnesota terminology is now a provider with an M.D. degree, and in Europe it was by a sponsor, medical monitor. I don't know

if that has anything to do with it, but that question comes up. I think having been here the longest on this committee now, that question keeps coming up, U.S. versus non-U.S. I don't have an answer, but as a principal investigator in clinical research, I always go into a study saying I don't know the answer. Now, obviously if I'm being paid by someone, it may be different. It's a comment, Rich. Thank you.

DR. SCHILSKY: Other comments? Dr. Lamborn.

DR. LAMBORN: Just to the question of the U.S. versus the non-U.S., as we saw the analyses earlier where the question was asked whether the differences observed could be just due to chance, as distinct from being statistically significant, it's my impression that in fact those kinds of differences were potentially just chance phenomenon. I'm wondering if the FDA has done any analysis which would demonstrate other than that it is a chance phenomenon, including the potential that there would be an interaction, because I look at it and I say that it looks to me like it's just the luck of the draw. Is there any demonstration that it's other than chance from the analyses done by the FDA?

DR. WHITE: Well, the answer to that is no.

DR. SCHILSKY: Dr. Johnson.

DR. JOHN JOHNSON: Yes. I just wanted to

respond to Dr. Kelsen. He has spoken about best supportive care twice now this morning. In the slides that Dr. MacDonald used on page 2, he has a table there of three best supportive care studies. In the first one, there is a total of 163 patients, and the difference in median survival is 2 months, which is similar to the many studies that the FDA showed. The second study has a total of 40 patients, and it's mentioned that cisplatin was involved in that study. And the third study has a total of 21 patients. So, I don't think the FDA can give a lot of weight to studies that have a total of 40 patients and a total of 21 patients.

DR. KELSEN: I don't know if that's a question. I guess the Nordic trial, which is the trial that had asymptomatic patients in both arms, so the best population you could possibly have, had 183 patients in that trial.

DR. SCHILSKY: Any other general comments? Dr. Nerenstone?

DR. NERENSTONE: I sort of want to ask our statistician a question. In the study objectives for the trial 11, the first one was the equivalence of the two, and despite the very significant number of patients, the confidence interval was under the targeted .8 that they were looking for. It came in at .79.

The secondary objectives -- and you can say

it's close, but didn't quite meet it despite the very large number of patients. The secondary objectives included the assessment of tumor response, which was the same; time to progression, which actually favored the 5-FU arm in a statistically significant way; safety and quality of life, which were probably no difference.

How would you weight those in terms of primary endpoint and secondary endpoint when the one that's clearly statistically significant is in the opposite direction but is a secondary endpoint? Or is there an answer to that?

DR. LAMBORN: I'll have to think about it a little bit. I think that you always start with the biggest issue being survival. They put that as the primary endpoint. I think that one of the things we have to be careful of -- and it was addressed earlier -- is when you try to use a model and you sort of arbitrarily say, well, it has to be 80 percent as good as an absolute assurance, remember that that lower bound, especially since they used a two-tailed test, says that we're 97.5 percent sure that that's the worst it could be. Then you go back to what has been mentioned earlier. If you then look at the curves and you look at the superimposability, just remember that's the absolute sort of worst case. So, that's one piece of it to keep in mind.

I am in some ways more concerned that the time

to progression is in an opposite direction, and you usually would hope that while -- and somebody else again referred to the fact that there has been a lot of discussion about time to progression and the ability to identify it. And we have the problem that the assessment was done at different times, but the different times could conceivably be argued should have favored UFT.

But I would then turn it back to the nonstatisticians in the group to say how would you interpret that if what you're seeing is a similarity in overall survival. And I was, in fact, surprised that we didn't have more discussion of that earlier in the process. Response for a number of reasons I'm much less -- I think it's the general consensus that that's less of importance in this situation.

Does that help?

DR. NERENSTONE: Yes.

DR. SCHILSKY: I think maybe we should just go on with the questions. Ms. Forman?

MS. FORMAN: I have a question of Dr. Johnson. You had I think made a statement that said you have some patients that are 250 miles away from you and this might be a way to treat them because it is easier for them to get this treatment than travel to you. How would you foresee the kinds of things that you would normally have to do in

terms of their testing and following them and knowing where they are from the baseline right through the treatment to be sure that they are getting the best care, that they are not in jeopardy, that their levels of safety are monitored? How would you handle that? And any other doctor here who might be faced with that, I'd appreciate your response.

DR. DAVID JOHNSON: Well, unfortunately, not everyone lives within real close proximity of Nashville.

(Laughter.)

DR. DAVID JOHNSON: This is a problem irrespective of how one delivers the chemotherapy to the patient. It doesn't matter whether you give it to them intravenously or orally. It's a problem.

The question somewhat infers that if one gives oral therapy, one sends the patient out and says comes back and see me in a couple of months; whereas, if one gives intravenous therapy, one says, well, we'll be in close contact, we'll monitor you very carefully, et cetera.

I don't really foresee a lot of difference in terms of the level of concern that I have for the patient, and I would do the same thing for the patient who's taking an oral drug and lives 250 miles away as I do for a patient who gets intravenous drug and lives 250 miles away. We usually work with the patient's primary care physician in order to obtain laboratory data to monitor the patient when

that is appropriate to do and to also monitor the patient's progress. It's much more convenient again for a patient to drive down the street and get something done as opposed to driving 250 miles to get a CBC done, for example. So, I don't really see the fact that their taking an oral drug makes them less well monitored. In fact, perhaps quite the opposite. Maybe we will monitor them more intensely.

I can tell you that the way we handle it at our institution, which I suspect is true for everyone around this table, is that our clinical nurses, not our research nurses, but our clinical nurses are responsible for contacting those individuals to keep in touch with them to find out exactly what toxicities they may have experienced. And patients are educated before they leave, at any point during the course of their treatment, with specific indications to call us. In fact, we give them information sheets that very clearly spell out the reasons that they need to call irrespective of day, time, et cetera. So, I don't really see it being a whole lot different. I do see it being much more convenient though from the patient's perspective.

Again, you wouldn't know this, but I can tell you from the standpoint of the provider of care -- and I don't like the Minnesota approach to provider with M.D. -- but I've been a recipient with an M.D. too of chemotherapy,

and I can tell you right now -- and I took weekly chemotherapy that was injected -- if I had a choice again, if I ever have to do that again -- and I pray to God I do not have to -- and I have a choice between an oral and an injectable drug, I'll take an oral drug 100 percent of the time over an injectable drug.

DR. SCHILSKY: Scott?

DR. LIPPMAN: I guess I just wanted to follow up on the question I think that our statistician posed to us and no one really answered because I think we all know what the answer is but we should get it out since the FDA is asking us to address the efficacy question, and this issue of the significant difference in time to progression. There have been very large discussions and I don't necessarily think we have to have that now. It's maybe a useful marker in some cases, but in this case where you have a 9-day difference in time to progression, there are tremendous issues of ascertainment about when you actually check into that and get that data point. So, I think it's sort of the same issue of looking at the survival curves to try to find possible differences. They really are virtually identical.

DR. SCHILSKY: It is a small difference. The bias, though, is in favor of the control arm because there was less frequent evaluation by 1 week in the UFT arm. So,

the difference could actually be slightly greater than 9 days, but it's still going to be a small difference.

Yes.

DR. LAMBORN: Just to clarify, if I had just seen the 9-day difference, I wouldn't have been asking this at all. If you look at the curve, you see that there's sort of a sustained difference that becomes clear, moving beyond the median. So, it was really looking at the whole curve again rather than just looking at the median which led me to say at least I was surprised that somebody hadn't brought it up. That doesn't mean that I want to make a major additional issue of it, but just to clarify, it was not at the median that I was looking.

DR. SCHILSKY: If I can offer again some historical perspective. Typically we have always, in a sense, valued the survival endpoint as the absolute gold standard in evaluating new therapies. In fact, as you know, we had lengthy discussion at the June meeting about the role of time to progression as an endpoint in metastatic breast cancer, a slightly different situation, but the committee rejected time to progression as an appropriate endpoint in metastatic breast cancer. So, I think that here we have a large study with a clear ability to evaluate the survival endpoint easily, and we should, I think, focus on that a good deal.

Why don't we go on to the questions. Now, we have what I believe to be the longest preamble that I've yet sent to a question.

(Laughter.)

DR. SCHILSKY: So, the first eight pages of the questions represent a restatement essentially of the FDA's analysis of the data that Dr. White just reviewed with us. I think it's probably not going to be necessary, since we just had all this presented, for the committee to spend a great deal of time reading this through again. So, why don't we go directly to page 8 and the first question.

So, the question is, what percent of the survival effect of the control regimen would the committee be willing to lose with the UFT/leucovorin regimen and still call the UFT/leucovorin regimen equivalent to the control regimen?

Does anyone want to take a stab at that one? Dr. Margolin?

DR. MARGOLIN: I'll take a stab. I don't know if I have anything to lose. It's really more of a comment. I'm not going to give you my opinion on the percentage.

I think the most difficult issue here is really for us to sort of determine how we really think fluorinated pyrimidine based therapy impacts on patients with metastatic colorectal cancer and whether that needs to be

linked somehow with the response rate, which is very troublesomely low in both arms here in a very well executed study, and whether you really believe that somehow this therapy is helping a lot of people even though you can't measure that by objective responses. So, that's really just more of a comment.

I don't think that we can really come up with a percentage of the survival effect since we don't know what the survival effect is that we could be willing to lose and still call it equivalent. We know the survivals are equivalent, and I don't think anyone on the committee would argue about that.

DR. SCHILSKY: Well, I think that's what this question is actually addressing, is do we know that the survivals are equivalent, because the proposal is that the survival in the UFT arm could possibly be 20 percent worse. Now, we've heard it stated, I think very nicely, that that is probably the worst case scenario and that there's a high level of confidence that it's not likely to be any worse than that.

Perhaps one way of thinking about this question would be if in fact that were the case -- and we don't really know how likely that is that that would be the case, but if that were the case -- would we be comfortable in still accepting this therapy as equivalent in efficacy.

DR. DAVID JOHNSON: Yes.

DR. SCHILSKY: So, instead of answering this question with a percentage, maybe since the focal point of the study was the 80 percent level, we can just have some discussion as to whether people would feel comfortable with that level. Dr. Kelsen?

DR. KELSEN: Yes, I think that that's a reasonable way of looking at this, that if the very worst thing happened and that the outcome was a difference of a month or 2 months in a patient who has very advanced disease and the tradeoff, which is not stated here, but sort of implicit to me, is that it's less toxic and at least gives the doctor, as Dr. Johnson said, the option of offering a patient an other alternative, yes, I think that that's a very reasonable thing to accept.

DR. SCHILSKY: Dr. Raghavan.

DR. RAGHAVAN: Yes, I agree with David Kelsen's view. I think it's a contextual answer. If you're talking carboplatinum versus cisplatinum in testicular cancer where you're talking very high proportional cure versus somewhat less high proportional cure, you accept different figures from a situation where the management is palliative and you're looking at convenience. So, while I think the question as initially phrased is an odd one, I'd be happy to say 20 percent because 20 percent of a year in the

broader context is not an awful lot of time.

And I agree with David. I think the evidence that we've seen -- look at the survival curves. They're equivalent curves. And you can do any amount of statistical mumbo-jumbo to hypothesize what might happen on a Tuesday at 3 o'clock, but the reality is these are identical curves, and there's no evidence on the table to suggest that there is a real difference.

We spent a lot of time talking about what might happen in Europe and what might happen here, but it's all a hypothetical discussion. If you actually look at the data presented, there's a minuscule difference, and I'm sort of surprised we're spending so much time on it.

DR. SCHILSKY: Yes.

DR. BEHRMAN: The reason it was a concern to us is because it's not 20 percent of a year. It's 20 percent of the difference between best supportive care versus, and we feel there is less room for error there. So, that's why we're asking you.

DR. RAGHAVAN: I do understand that, but I guess I'm looking at a more global picture. Dr. Johnson is someone who should always be listened to carefully. I hate to say it in his presence.

(Laughter.)

DR. RAGHAVAN: Both John Johnson and Dave

Johnson, but in this case Dave Johnson. What he said is right. We've got to be consistent in the committee, and the reality of the situation is we have an unhappy situation with the conventional treatment.

David Kelsen made the point that even with really quite exciting new drugs that are there for gastrointestinal malignancies, fluoropyrimidines are not going to go away, and I think he's right. So, therefore, having a convenient fluoropyrimidine is important, and even though the company have tried very hard to mask the convenience with the assays they've used, it seems to me that it emerges time and again. So, therefore, I'm not too worried.

Even if we accepted that the time to progression difference was 3 months, I think the big picture is what happens to patients, and time to progression is so evanescent that I don't think we're doing a bad thing if we let this drug through.

DR. SCHILSKY: Any other comments on this?

I think there is some consensus among the committee that 20 percent would be the answer to this question. I don't know that we need to actually vote on that. So, maybe we can just go on to the next question.

So, question 2, the results on the 5-FU/leucovorin control arms in study 11 and study 12

appear different. Can the better tumor response rate, time to progression, and survival on the 5-FU/leucovorin control arm in study 11 be explained by the 25 percent more dose intense FU/leucovorin control regimen used in study 11?

Comments on that. Dr. Kelsen.

DR. KELSEN: Well, I think the answer to that is yes, it could, but in fact the numbers that were shown for both 011 and 012 are well within the range of what's been reported by many trials, including the SWOG multi-arm trial and a half a dozen others, for this type of regimen. So, it's true it could be. On the other hand, that's 5-FU/leucovorin.

DR. SCHILSKY: Dr. Krook.

DR. KROOK: I would simply say yes, and I think there are other things that can do that as a reviewer.

DR. SCHILSKY: Other comments? Dr. Nerenstone.

DR. NERENSTONE: I would say that supporting the fact that it's related to dose, the toxicity profile likewise is affected, and that seems to imply that perhaps dose is something that may be part of the reason.

DR. SCHILSKY: So, I think the consensus answer there is yes, but there may be other factors as well that are more difficult to discern.

Question 3, part a. Does the more dose intense every 28 day control FU/leucovorin regimen used in study 11

have an effect on survival?

Dr. Kelsen.

DR. KELSEN: Yes, it does have an effect on survival, but this implies because it is more dose dense, that it has an effect on our survival than the less dose dense every 5 week regimen, the infusional 5-FU? There are large analyses that look at many different ways of giving 5-FU with many, many other drugs. We talked about the repeatedly this morning. I personally think the evidence is reasonably compelling that chemotherapy, including a fluorinated pyrimidine, is better than no chemotherapy or delayed chemotherapy, but the difference is modest.

DR. SCHILSKY: Maybe you can go on just to give us your thoughts on part b, which is if FU/leucovorin does have an effect on survival, what is the magnitude of that effect?

DR. KELSEN: Yes. Then I'm going to fall back on the best data that I know, which is the best supportive care trials, such as the Nordic study, which is an MLF regimen if I remember. It was a methotrexate, 5-FU, leucovorin I think. I can check that. And the magnitude of the difference in that study in asymptomatic patients was 9 months versus I think 14 months. So, it's somewhere in the range of 2 to 4 months, depending on what you look at, that if you start therapy immediately, you get an

improvement in median survival compared to if you either delay therapy since only 60 percent of the patients were treated or never treat the patient. And that's the closest I can come.

DR. SCHILSKY: Dr. Raghavan.

DR. RAGHAVAN: I have the sneaky feeling that the FDA are trying to get us to create a standard today that they can look at for the future because that's is kind of what the question is asking. Where does the 28-day control FU/LV fit into the big scheme of things? I think the truth is that that wasn't the mission that we had coming in, so it's very hard to answer the question as phrased. I'm not trying to be critical, but I just think that that wasn't the topic. The topic was how does a new drug compare to a standard approach. It happens there were two variants of the standard approach, and if you get out into the real world, there are 50 variants and they all give you a median survival and a long-term survival in metastatic disease that's very close, which is why we continue to argue whether 4 versus 5, 750, 350. After 20 years, we still don't really know exactly the right way to use them, and I don't think today's deliberations will get you to that point.

DR. SCHILSKY: I would just add from my own point of view that there are many trials, most of which

have been reviewed here this morning, comparing 5-FU/leucovorin against best supportive care, more trials comparing 5-FU/leucovorin to 5-FU. Some of those trials show a survival advantage for 5-FU/leucovorin, some do not. The meta-analysis that was performed does not show a survival advantage for 5-FU/leucovorin. Those trials that show a survival advantage, the survival advantage is typically in the range of 3 to 5 months. So, if you accept the notion that the preponderance of evidence is that there may be a survival advantage, it's going to be small. It's going to be in the range of a few months, and it's probably very difficult to estimate it any more precisely than that.

Why don't we go on then? Oh, we have a part c here. Pardon me. This is actually 12 questions in 5.

(Laughter.)

DR. SCHILSKY: Part c. If the every 28-day control FU/leucovorin regimen has a survival effect, does study 11 show the effect on survival of the UFT/leucovorin regimen is at least as good? So, that's the question. Is the survival with UFT/leucovorin in study 11 at least as good as the control regimen?

Dr. Krook.

DR. KROOK: I would say that my looking at the data, the answer should be yes.

DR. SCHILSKY: Other comments?

(No response.)

DR. SCHILSKY: Anyone who dissents from that point of view?

(No response.)

DR. SCHILSKY: I think at some point, we may ask for a show of hands on some of these questions. These seem to be more sort of consensus questions.

Question 4. Does the less dose intense every 35-day control FU/leucovorin regimen used in study 12 have an effect on survival?

Dr. Kelsen.

DR. KELSEN: I think my answers to 4a, b, and c would be similar to my answers to 3a, b, and c, based on the same data that we've talked about several times now, both randomized studies against a non-leucovorin containing 5-FU regimen or against no immediate treatment. So, my estimate would again be several months. It may be 3 months. It may be 4 months, something in there, for a.

What's the estimate of the survival effect as shown? And the evidence as I've described.

And lastly, I think that the survival curves are equivalent. So, the survival curves are equivalent.

DR. SCHILSKY: Any other comments there?

(No response.)

DR. SCHILSKY: Okay, let's continue.

I think we're getting the message across even without a formal vote.

Question 5. The UFT capsule is a fixed combination. The regulations require the contribution be shown for each active component of a fixed combination. The fixed combination regulation is important and the FDA would not waive it without a compelling reason. However, a waiver could be considered if the committee believes the UFT/leucovorin regimen is an important therapeutic advance compared to present therapy for patients with advanced metastatic colorectal cancer.

The FDA did not believe this requirement to show the contribution of uracil to the UFT capsule had been met and requested more information. Additional data on the contribution of uracil to the UFT capsule was recently submitted to this NDA, but the review of it has not yet been completed.

A, if the FDA concludes the contribution of uracil to UFT is adequately shown, is this NDA approvable? For this I will ask for a show of hands.

Does anyone want to make a first stab at answering that? Dr. Margolin?

DR. MARGOLIN: Actually I just want to ask a clarification question. I think the question means would this entire NDA meet the requirement for approvability.

Right? I mean, otherwise this is the entire vote on the entire drug. Right?

DR. BEHRMAN: I'm sorry. I don't understand.

DR. MARGOLIN: Well, does this question just refer to if the uracil data are okay, can we then go ahead and answer the next questions, or is this the entire --

DR. BEHRMAN: This is it.

DR. MARGOLIN: This is it.

DR. BEHRMAN: Yes.

DR. SCHILSKY: This is the big one.

(Laughter.)

DR. SCHILSKY: Dr. Nerenstone.

DR. NERENSTONE: I just have sort of a question to the FDA, and it might be a little unusual. I still am very uncomfortable about the difference between the U.S. results and the European results which I feel may, in fact, be significant. I know subgroup analysis -- you get nervous about doing that, but they are very large groups of patients and they were stratified by being U.S. or not U.S. If in fact this is approved, can we request that this table, showing the difference in the two groups, be included in the material that goes out? Because I think individual physicians have to make up their own minds to decide whether in any individual case a decrease in median survival of 3 and a half months may be important for their

patients to know.

DR. BEHRMAN: If it was the recommendation of the committee, we would certainly consider putting that in the labeling, yes, in the clinical trials section.

DR. SCHILSKY: Any comments about that? Dr. Margolin?

DR. MARGOLIN: I would argue against that unless we could find medical reason. I think it would be misleading and perhaps lead to some misinterpretation of data. I think you really do need to look at a study and not do the subgroups unless there is some really compelling biological or medical thing that explains it or unless the statistical difference is so great that you're forced to repeat the study or do something like that.

DR. SCHILSKY: Dr. Lamborn?

DR. LAMBORN: I'd also like to reiterate something that was said earlier, just a reminder that I think it could also be statistically misleading because even if we ignore the fact that this was a post hoc analysis, which is sort of where you're coming from when you say subgroup analysis, but even if it had been a preplanned analysis, the analysis says that these differences could simply be chance differences. Again, unless there's a medical reason, unless there's something systematic that was found that could explain it, we do know

that it could be just a chance phenomenon, and I would hate to see us make a major point of it in the labeling unless there's some other rationale.

DR. SCHILSKY: Other discussion?

(No response.)

DR. SCHILSKY: Okay, so back to the question. If the FDA concludes the contribution of uracil to UFT is adequately shown, is this NDA approvable? All those who would vote yes, raise your hand.

(A show of hands.)

DR. SCHILSKY: 12.

All those who vote no?

(No response.)

DR. SCHILSKY: Any abstentions?

(No response.)

DR. SCHILSKY: Part b. If the FDA concludes the contribution of uracil is not adequately shown, a waiver could be considered if the committee believes the UFT/leucovorin regimen is an important therapeutic advance compared to present therapy for patients with advanced metastatic colorectal cancer. Is the UFT/leucovorin regimen an important therapeutic advance compared to present therapy for patients with advanced metastatic colorectal cancer?

Any discussion on that? Dr. Krook?

DR. KROOK: My feeling on this is that, no, it's not an important therapeutic advance. It's using again a prodrug. At least it's not a therapeutic as I look at therapeutic. I would argue that this vote should be no.

DR. SCHILSKY: Other discussion, comments?

(No response.)

DR. SCHILSKY: So, why don't we vote it? Let me read it again. Is the UFT/leucovorin regimen an important therapeutic advance compared to present therapy for patients with advanced metastatic colorectal cancer? All who would vote yes, raise your hand.

(No response.)

DR. SCHILSKY: 0.

All who would vote no?

(A show of hands.)

DR. SCHILSKY: 8 no.

Abstentions?

DR. SCHILSKY: 4 abstentions.

So, since the majority is that it is not an important therapeutic advance, we don't have to answer the part about if so, in what respects.

That concludes this morning's session. We will take a break for lunch. Why don't we plan to reconvene at 1:15.

(Whereupon, at 12:10 p.m., the committee was

recessed, to reconvene at 1:15 p.m., this same day.)

AFTERNOON SESSION

(1:20 p.m.)

DR. SCHILSKY: Good afternoon. Welcome to the afternoon session of ODAC.

We do have at least a couple new people seated around the table, so I thought I would briefly ask that we go around and have another brief round of introductions. Dr. Raghavan?

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

DR. LAMBORN: Kathleen Lamborn, biostatistician, University of California, San Francisco.

DR. KELSEN: David Kelsen, medical oncologist, Memorial Sloan-Kettering.

MS. ZOOK-FISCHLER: Sandra Zook-Fischler, Patient Representative.

DR. MARGOLIN: Kim Margolin, medical oncology and hematology, City of Hope, California.

DR. LIPPMAN: Scott Lippman, medical oncologist, M.D. Anderson Cancer Center.

DR. SCHILSKY: Rich Schilsky, medical oncologist, University of Chicago.

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

DR. NERENSTONE: Stacy Nerenstone, medical

oncology, Hartford, Connecticut.

DR. DAVID JOHNSON: David Johnson, medical oncologist, Vanderbilt University.

DR. PELUSI: Jody Pelusi, nurse practitioner, Phoenix, Arizona, and the Consumer Rep.

DR. KROOK: Jim Krook, Duluth, Minnesota, medical oncologist.

DR. CORTAZAR: Patricia Cortazar, FDA.

DR. WILLIAMS: Grant Williams, FDA, medical team leader.

DR. BEITZ: Julie Beitz, acting Deputy Division Director.

DR. BEHRMAN: Rachel Behrman, Deputy Office Director.

DR. SCHILSKY: Thank you.

I should also announce that Bill Gradishar, who was to be here as an ODAC consultant, was unable to make the trip because of the weather. So, we will do our best to get by without Bill.

Let's go into the open public hearing. We have a number of -- oh, I'm sorry. Karen has a conflict of interest statement to read.

DR. TEMPLETON-SOMERS: Again. The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the

record to preclude even the appearance of such at this meeting.

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

Dr. Douglas Blayney is excluded from participating in today's discussion and vote concerning Evacet.

In addition, in accordance with 18 U.S.C. 208(b)(3), full waivers have been granted to Drs. William Gradishar, Kathleen Lamborn, and Stacy Nerenstone which permit them to participate in all official matters concerning Evacet.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, room 12A-30 of the Parklawn Building.

In addition, we would like to disclose for the record that Dr. David Johnson has an interest which does not constitute a financial interest within the meaning of 18 U.S.C. 208(a) but which could create the appearance of a conflict. The agency has determined, notwithstanding this

interest, that the interests of the government in his 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 fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. SCHILSKY: Thank you. We have a number of individuals who have requested an opportunity to make statements to the committee. So, I'll just take them in the order that they're listed here. The first is I guess just a letter to be read from Robert Erwin representing the Marti Nelson Cancer Center.

DR. TEMPLETON-SOMERS: "I am writing this letter in support of the application for approval of the liposomal doxorubicin formulation, Evacet, submitted by The Liposome Company. I represent the Marti Nelson Cancer Research Foundation, a nonprofit organization that works

with cancer patients and their physicians to assist in access to experimental therapies and enrollment in clinical trials. We have no financial interest in The Liposome Company, nor in any other company developing and marketing products for cancer treatment. Our short-term objective is to help people with cancer obtain improvements in both quantity and quality of life.

"My wife, Marti, died of breast cancer at the age of 40 and she suffered many of the adverse effects of cancer treatment, including cardiac toxicity. I know first hand the importance of finding drugs that will be more effective against breast cancer than those available today, but I also know the importance of improving the safety of the drugs we currently have. Safety in a chemotherapeutic is the difference between having the breath to sing a song, or not; the desire to eat a home-cooked meal, or not; the strength to climb a single flight of stairs, or not; or, in my wife, Marti's case, the strength to do the work she loved as a physician helping other people, or not.

"Given that over 40,000 U.S. women die of breast cancer each year, it is tragically clear that doxorubicin is not an ideal drug for the treatment of breast cancer. Nonetheless, it is still one of the most efficacious drugs available and can provide extended life to many women with disease. As all of you know,

doxorubicin causes both acute and chronic cardiac toxicity which can be life-threatening. After a cumulative dose of 500 milligrams per meter squared, 6 to 20 percent of patients will experience significant and irreversible cardiac toxicity. This risk increases with prior radiotherapy. Surviving breast cancer can be a very hollow victory at the cost of facing the day to day morbidity that results from chronic heart disease.

"Other adverse reactions, particularly mucositis, can limit a patient's ability to tolerate an optimally dose-intensive regimen. Reducing the factors that cause a poor quality of life during, and too frequently long after, chemotherapy is an important research priority. If this priority is adequately addressed, not only will the quality of life of cancer patients improve, but the probability of achieving optimal efficacy with current therapeutics will also increase.

"The development of newer generation antiemetics such as ondansetron and granisetron have significantly improved the quality of life experienced by most patients during chemotherapy with doxorubicin. The use of dexrazoxane with doxorubicin reduces cardiac toxicity, but at the cost of reduced doxorubicin efficacy. Although we have not seen data directly comparing Evacet to doxorubicin plus dexrazoxane, the data available suggest a

favorable comparison, given the full maintenance of efficacy with Evacet.

"Approval of Evacet will provide another important option to the woman facing breast cancer, an option that might prove to be the difference between survival with debilitating morbidity and survival with normal health and full vigor. The experience of the individual in the use of a pharmaceutical to combat a disease must never be lost in the coldness of the statistics. It is the individual people who matter the most, in medicine as in life.

"In addition, approval of Evacet will provide physicians with greater flexibility in treating patients who are at higher risk for cardiac toxicity; and, if additional studies support the initial results obtained to date, the potential to achieve greater efficacy through the use of this novel doxorubicin formulation. Although it is a small point, approval of this drug will also increase the competition in the oncologic drugs market leading ultimately to a better efficacy to price ratio.

"The Marti Nelson Cancer Research Foundation recommends the approval of Evacet for the treatment of metastatic breast cancer on the basis of its superior adverse effects profile with comparable efficacy to conventional doxorubicin.

"Respectfully submitted, Robert Erwin."

DR. SCHILSKY: Thank you.

Next is Michael Cohen. Would you please again state your name, affiliation, and whether you've received any financial support to be here?

DR. COHEN: Yes. My name is Michael from the Institute for Safe Medication Practices. It's a nonprofit organization and we work in cooperation with the United States Pharmacopeia in their medication error reporting program. We receive reports of medication errors and we publish them in various publications' journal columns, including the Oncology Times.

I have nothing to disclose with this company. However, they did, more than 12 months ago, donate some funding to ISMP. Other than that, there's nothing.

From time to time, we have had reports of mix-ups between doxorubicin products, the conventional doxorubicin and the doxorubicin liposomal injection product. Doxil is the brand name. And you know there is quite a dosing difference. Because of the mix-ups, the company that manufactures Doxil at one point actually did make a package label change where they have on the front label panel now a statement that this is a liposomal product and that it is not to be substituted. And there's a red band that goes across with that and it's very helpful

in preventing mix-ups.

We actually have had mix-ups between other conventional products and liposomal products as well, amphotericin in particular.

So, we have the conventional product and the liposomal product already on the market for doxorubicin. The dosing difference is dramatic. The liposomal product currently is at about 20 milligrams per meter squared per dose, and the conventional product, more in the area of 60 to 75 milligrams per meter squared per dose.

Now we have the Evacet product which is being discussed today. As many of you know, the dosing here is even higher than the conventional product, and so we at ISMP have a concern that the possibility certainly exists, since we have this history of mix-ups between the conventional and liposomal product in the past, that now we could have mix-ups between the two liposomal products. And the dosing difference here is so dramatic that it could actually lead to a patient injury.

We would like to recommend that, if this product is approved, that along with the product, perhaps some enhancements of the generic name of the current liposomal product be considered. However, the United States Pharmacopeia and the Food and Drug Administration, to my knowledge, is actually working now to look at the

nomenclature of liposomal products in general. I'm not sure how that would affect the current product or the product that is being discussed today.

I think there are some things that would be need to be done as far as preventing mix-ups between the two liposomal products in particular in this case. I think the major problem that we see is with the product that is already on the market because if the dose is accidentally given in the higher dose -- in other words, instead of 20 milligrams per meter squared, more like 75 or 100 milligrams per meter squared is accidentally given -- and this could occur at the physician prescribing level. This could occur at the nursing level. It could occur at the pharmacy dispensing level, which is where we see many of these accidents. There would be a disastrous result potentially.

So, we'd like to recommend to FDA that, first of all, of course the nomenclature issue be considered with USP's Nomenclature Committee.

But second -- and there is precedence for this -- we would like to see something done, in addition to what is already present on the Doxil container, to further warn about the dosing differences between these products. The precedent is with the amphotericin products now. After several accidents where the liposomal product was ordered

and the conventional product was dispensed in the higher liposomal amphotericin dose, the company was good enough to work with FDA and place a stop sign on the conventional amphotericin product which warns against using this without checking the dose appropriately. We would like to see something similar done with the Doxil product. But at the same time, we think that this is unusual and that some education needs to be done as well and other types of reminders.

Early on we would like to see even stickers prepared by the companies and ask pharmacists to actually affix these to the containers, anything that can be done to prevent the mix-ups because I'm sure that it will happen without taking proper action.

Finally, in the interest of full disclosure -- and I immediately recognized this and mentioned it to Dr. Templeton right afterwards my appearance this morning -- I mentioned that BMS does help to sponsor the ISMP medication safety alert. I should also mention that they have in the past helped to sponsor medication error prevention programs that ISMP has done.

Thank you very much.

DR. SCHILSKY: Next is Margaret Volpe representing the Y-ME National Breast Cancer Organization. Again, please for the record state your name, affiliation,

and whether you've received any financial support to be here.

MS. VOLPE: My name is Margaret Volpe. I'm the Y-ME D.C. liaison, and we've received no financial support to be here in any way.

Thank you for allowing us to submit the statement to the committee. I am here today on behalf of the Y-ME National Breast Cancer Organization to express our position regarding the potential approval of Evacet, liposomal doxorubicin, for the treatment of metastatic breast cancer.

Y-ME is the nation's premier source of support, education and information for women diagnosed with breast cancer, their families and communities. Y-ME was started by two women diagnosed with breast cancer 20 years ago and offers two national, 24-hour hot lines in English and in Spanish. In addition, Y-ME has 26 chapters nationwide, numerous publications in adult and teen workshops on the early detection of breast cancer.

Y-ME has no financial connection to The Liposome Company.

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 Evacet will help

provide these choices. Therefore, I speak on behalf of women living with metastatic breast cancer.

One of the most commonly used agents to combat breast cancer, doxorubicin, also carries a substantial risk of damage to the heart, cardiotoxicity. For this reason, physicians often must limit their use of this drug to suboptimal doses.

Based upon the clinical studies presented at ASCO, Evacet represents a safer alternative to conventional doxorubicin while still being as effective against the cancer. The availability of such a treatment would be an important step in our quest for safer chemotherapeutic agents.

Quality of life beyond chemotherapy is important. Effective and relatively safe advances towards this end should be an option for women with metastatic breast cancer.

Thank you.

DR. SCHILSKY: Thank you very much.

Next is Laura Meeker, and again please state your name, affiliation, and whether you've received any support to be here.

MS. MEEKER: Hi. My name is Laura Meeker. I'm a public servant. I represent myself. I was recruited by my oncologist to come and talk about my own personal

experiences with cancer and with treatment. I have no financial interests in anything related to this meeting and have received no financial support whatever from anyone.

I am a 6 and a half year survivor. I'm living with metastatic breast cancer. I've had way more than the optimal doses of Adriamycin in an attempt at the beginning of my diagnosis to wipe out the cancer. Unfortunately, that treatment had to be stopped without a total remission because I developed incredible cardiac toxicity. I had congestive heart failure and cardiomyopathy to the point where, although I'm a public servant and I've continued to work during this entire time, there was a year in my life when I finally got to the office, I would plan my trips to the ladies' room 50 yards down the hall. I could do about two of them a day. Everyone came to me. I could organize my thoughts and deliver good advice to my clients, but I was basically a vegetable body.

I participated in two years of cardiac rehab three to four times a week and returned to close to normal but not close to what I used to be. I was a scuba diver, an athletic person who loved hiking, and that has not been a part of my life recently, though I hope it will be.

In addition to that, I had CMF which did nothing. So, it was the Adriamycin part of this FAC that treated me successfully and I finally had taxotere which

put me into remission again. Unfortunately, it's back in my bones, but I'm real happy to be here with bone metastases. I can live with those.

I'm not a scientist or a medical person, but I am a person who has been impacted by regular Adriamycin, both very positively -- it made it possible for me to live to be here -- and by the side effects of aggressive treatment which made it harder for me to be here.

I'd love to answer any questions if anybody has any.

Thank you for the opportunity to be here.

DR. SCHILSKY: Thank you very much.

Finally, we have a statement submitted from Ellen Stovall from the National Coalition for Cancer Survivorship.

DR. TEMPLETON-SOMERS: "This is a statement in support of oral anticancer drugs.

"The undersigned organizations provide educational advocacy and other services to people with cancer, their families, and their caregivers. People with cancer are desperate to have access to new anticancer medicines, not only for the sake of more effective treatment, but also in support of better quality of life, including less toxic and more convenient modes of therapy. Most current anticancer drugs are accompanied by

potentially serious side effects and because they are administered intravenously, they require the involvement of a physician, nurse, or other cancer specialist. While careful monitoring of patients receiving any type of chemotherapy is an important factor, intravenous administration of drugs can, by itself, create a hardship for patients living in remote, rural areas not directly served by a cancer specialist.

"The availability of oral anticancer medications with improved toxicity profiles and efficacy at least equivalent to intravenous alternatives is an important step for cancer patients. If an oral compound under review by the Food and Drug Administration exhibits efficacy that is undiminished in comparison to the intravenous drug alternative, demonstration of reduced toxicity or other contributions to quality of life should be given great weight in the deliberations of reviewers. Aside from the benefits of reduced toxicity, quality of life for cancer patients can be enhanced and should be valued along with other improvements in care.

"Cancer is a highly individualized disease and the more treatment options available, the better, so long as neither safety nor efficacy is sacrificed. Moreover, patient convenience and quality of life are important considerations that should argue for the availability of

oral drug alternatives.

"We encourage the Food and Drug Administration to take these patient oriented concerns into account in its review of any oral anticancer medications proposed for marketing approval.

"The National Coalition for Cancer Survivorship, American Cancer Society, Cancer Care, Incorporated, Cancer Research Foundation of America, Cure for Lymphoma Foundation, Kidney Cancer Association, Oncology Nursing Society, and USTOO International."

DR. SCHILSKY: Thank you. Is there anyone else who wishes to make a statement to the committee?

(No response.)

DR. SCHILSKY: If not, we'll move directly to the sponsor's presentation. We are running a bit behind, but the sponsor will have the full hour available to them. So, Dr. Lee?

DR. LEE: Good afternoon, Dr. Schilsky and members of the advisory committee, Dr. Williams and members of the FDA review team. We're very pleased to be here today to present the data from the NDA for TLC D-99.

The indication that we're seeking today is for TLC D-99 for the first-line treatment of metastatic breast cancer in combination with cyclophosphamide.

The recommended dose with D-99 is at 60 to 75

milligrams per meter squared in combination with cyclophosphamide at 600 milligrams per meter squared administered every 3 weeks.

After my introduction, Dr. Andy Janoff from The Liposome Company will present a preclinical overview. Dr. Eric Winer from the Dana-Farber Institute will present the need for a less cardiotoxic anthracycline. We will then present an overview of the study designs for the three phase III studies. Dr. Jonathan Alexander from Danbury Hospital and Yale University will present the findings for the significance reduction in cardiotoxicity. We will then present the findings on the preservation of antitumor efficacy. Dr. Jerry Batist from McGill University will present the findings from the clinical safety profile. I will then return to provide a conclusion for the sponsor's presentation.

The following consultants covering areas of medical oncology, biostatistics, and cardiology are either participating in the TLC D-99 clinical program or have helped with the preparation of the NDA. Many of them are present with us today and they are available to answer questions.

The data presented today will demonstrate that TLC D-99 is safe and effective for the treatment of metastatic breast cancer. TLC D-99 provides clinical

benefits to breast cancer patients by improving upon the therapeutic index of doxorubicin. Doxorubicin remains a mainstay for the treatment of breast cancer. However, as we just heard from the public statements, doxorubicin is associated with well documented cardiotoxicity, a dose-limiting toxicity that could be permanently disabling or potentially fatal to patients who are undergoing doxorubicin treatment.

Our data will demonstrate that TLC D-99 is significantly less cardiotoxic than doxorubicin. TLC D-99 also has significantly less mucositis and diarrhea, acute toxicities which could interfere with the daily activities of patients who are undergoing doxorubicin after every cycle. Importantly, TLC D-99 delivers antitumor efficacy that is comparable to that of doxorubicin.

We will now begin our presentation with a preclinical overview by Dr. Andy Janoff.

DR. JANOFF: Dr. Lee, good afternoon. It's my job today to give you an overview of our preclinical program and provide you a framework in which to evaluate our clinical data, so I'd like to start, if I could, with the rationale for D-99, which is based on the well-known ability of liposomes to alter the biodistribution of drugs. With this in mind, we set out to design a system that would decrease doxorubicin's cardiotoxicity, decrease its GI

toxicity, but maintain antitumor efficacy.

Now, to create D-99, we created doxorubicin citrate complex which we anchor securely in the interior of 100 nanometer liposomes. We engineer these systems to persist in the circulation which limits the peak availability of doxorubicin to cardiac and GI tissue, but ensures effective delivery to tumor tissue. We don't pegylate D-99, so it doesn't persist in the circulation long enough to extravasate into dermal tissue which is a biodistribution well known to produce palmar-plantar erythrodysesthesia.

On the next slide you see after a single -- this is a 1.5 milligram per kilogram IV push in the dog. More D-99 relative to doxorubicin persists in the circulation. This is particularly true at early time points.

Now, in these studies, we used whole body autoradiography to map the biodistribution of both D-99 and doxorubicin, and the next slide you see that these lines are reversed, less D-99 relative to doxorubicin, is delivered to myocardial tissue. This diminished myocardial exposure to doxorubicin correlated with profoundly diminished cardiotoxicities preclinically as judged histologically, and this was predictive of our clinical data.

In a similar fashion, the diminished intestinal mucosal exposure to doxorubicin also correlated with diminished GI toxicities preclinically. Again, this was predictive of our clinical data.

Now, to look at the antitumor efficacy of D-99, we evaluated 5 murine tumors, and we found that in each case D-99 was at least as effective as doxorubicin.

We also had the opportunity to look at a human tumor xenograft and that data is on the next slide. This is a human mammary carcinoma, and as judged by tumor growth inhibition relative to control, D-99 was at least as effective as doxorubicin.

So, in conclusion, in our preclinical program, we were able to show that D-99 reduced the cardiotoxicity, reduced the GI toxicity of doxorubicin without impacting efficacy. And importantly, there was no evidence of PPE in any of our preclinical models, consistent with the fact that D-99 is not pegylated.

So, it was against this background with this data that the company made the decision to enter into clinical trials, and you'll hear that data set next in the hour or later on in the hour. But up next is Dr. Winer. He'll discuss the need for a less cardiotoxic anthracycline.

DR. WINER: Good afternoon. I just want to

spend about 4 or 5 minutes talking about the need for a less cardiotoxic anthracycline in the treatment of patients with metastatic breast cancer.

As everyone knows, doxorubicin is an important drug in the treatment of patients with breast cancer, but it is limited by its cardiac toxicity. Doxorubicin results in the generation of iron-mediated intracellular free radicals. These free radicals damage cardiac myocytes. Myocyte damage occurs with each and every dose. It's initially subclinical but ultimately leads to dose-dependent cardiac dysfunction.

Cardiac dysfunction is rare, although it occurs occasionally in patients who receive less than a cumulative dose of 300 milligrams per meter squared. Above this dose, it becomes much more prevalent. I think over the past few years we've learned that cardiotoxicity with anthracyclines probably occurs at somewhat lower doses than perhaps many of us thought 5 and 10 years ago.

These are data from a trial published by Dr. Swain and colleagues in the Journal of Clinical Oncology two years ago and demonstrate the cardiotoxicity with FAC chemotherapy in patients with metastatic breast cancer. In this slide, a cardiac event refers to either the development of CHF or a substantial fall in ejection fraction. As you can see, at approximately a cumulative

dose of 300 milligrams per meter squared, cardiac events become more common, becoming much more common after 400 to 450 milligrams per meter squared.

These are more recent data. This is a trial published by Chan and colleagues this past summer in the JCO and compared docetaxel and doxorubicin in patients with metastatic breast cancer. A total of 163 patients received doxorubicin in this trial. All patients had baseline determinations of their ejection fraction, a subsequent determination later in the course of the study, and the dose of doxorubicin was actually capped in the study at a little more than 500 milligrams per meter squared.

Despite that, there were 6 patients in the trial who developed clinical CHF. CHF developed in the range of 400 to 450 milligrams per meter squared and there were 3 patients who died of this toxicity. I think this just highlights the ongoing importance of this problem as we take care of patients with breast cancer.

Now, a less cardiotoxic anthracycline could potentially be beneficial to all women with metastatic breast cancer. I just want to touch for a minute upon a subpopulation, that is, women who have had prior exposure to anthracyclines in the adjuvant setting.

These are data lent to me by Jane Weeks at my own institution from the National Cancer Center Network

database and demonstrate the number of patients with stage I and stage II breast cancer who are presently receiving anthracycline containing regimens. As shown on this slide, at least within NCCN centers over the course of the past two years or so, 61 percent of patients with stage I breast cancer received an adjuvant anthracycline-containing regimen and over 85 percent of stage II breast cancer patients. Obviously, a lot of women in the early disease setting are receiving adjuvant anthracyclines.

Despite adjuvant therapy, at least some of these women will, unfortunately, ultimately develop metastatic disease, and anthracycline may be of benefit at least in some proportion of them. Unfortunately, if a woman has received adjuvant anthracycline therapy, it takes a very limited number of cycles before she reaches a cardiotoxic dose with doxorubicin. And the availability of a less cardiotoxic anthracycline both in this patient population and in the broader patient population potentially provides patients and physicians greater flexibility in making determinations of how long to continue therapy with somewhat less concern about cardiotoxicity.

There are other available means to reduce cardiotoxicity in patients with breast cancer who are receiving doxorubicin-based therapy.

Dexrazoxane is commercially available. It is approved for use in women who have received cumulative doses of doxorubicin greater than 300 milligrams per meter squared. It does, at least to a limited extent, add toxicity. It is another drug adding on to the regimen. In addition, there have been concerns about possible interference with efficacy.

In some centers, prolonged infusions of doxorubicin, such as 96-hour infusions, are used, and these have been shown to reduce cardiotoxicity with anthracyclines. Such infusions require a central catheter and a pump. The bottom line is that outside of a few very specialized centers that have used this kind of approach for a long time, this is not a commonly used practice, at least in the U.S.

Now, there are reasons to be even more concerned about cardiotoxicity with anthracyclines now than a few years ago. The trials with herceptin where it was demonstrated that the combination of doxorubicin and Herceptin resulted in a very unacceptable rate of cardiotoxicity highlight this point. In addition, we know that there are women who have been treated with prior doxorubicin and are now receiving Herceptin who developed cardiotoxicity as well. There are certain schedules when doxorubicin and paclitaxel have been combined where there

appears to be excess cardiotoxicity. And these are both areas -- and I would say particularly the area in terms of Herceptin -- where future trials are warranted, and in fact there are future trials that are now beginning to enroll patients looking at these combinations.

Finally, although in the adjuvant setting, cardiotoxicity is not a major problem when we cap doses of doxorubicin at 240 or 300 milligrams per meter squared, this is still a concern to physicians and a concern to patients. We really don't have long long-term data in terms of safety of doxorubicin in this setting, and ultimately a less cardiotoxic anthracycline has a real role in trials in the adjuvant setting.

So, having said that, I do believe there's a role for a less cardiotoxic anthracycline in patients with breast cancer. I believe there's a role for D-99 in the treatment of patients with breast cancer, and I say that as one who participated in these trials and as a clinician who does this on a daily basis.

Thanks. I want to turn this back over to Dr. Lee.

DR. LEE: Over 1,000 patients were treated in the TLC D-99 clinical program. 11 phase I/II studies were conducted, followed by 4 phase II studies in first-line metastatic breast cancer. The centerpiece of our

submission is three phase III randomized, comparative studies in the first-line treatment of metastatic breast cancer.

The four phase II trials conducted in the metastatic breast cancer patients showed a response rate ranging from 43 percent to 73 percent, clearly indicating a high level of antitumor activity. Results from these studies indicate that 60 to 75 milligrams per meter squared provides encouraging safety and efficacy results and, hence, form the basis for the dose regimen to be studied in the phase III program.

The objectives and primary endpoints for the phase III programs are to demonstrate that TLC D-99 significantly reduces cardiotoxicity while preserving the antitumor efficacy of doxorubicin.

Three randomized studies were conducted. Study 1 is our pivotal study conducted in combination regimens. Our pivotal trial demonstrates the significant reduction in cardiotoxicity, as well as the preservation of antitumor efficacy.

Each of these endpoints were reproduced in an independent study. Study 2 is a single agent regimen study that provides confirmatory evidence for the reduction in cardiotoxicity. Study 3 is another combination regimen study that provides confirmatory evidence for the

preservation of antitumor efficacy in combination regimens.

I will now provide an overview of the study designs for these three studies and then the data for the two primary endpoints will be presented in subsequent presentations.

Study 1 is a study comparing the combination of D-99 plus cyclophosphamide to equal doses of doxorubicin plus cyclophosphamide. Randomization was stratified by prior doxorubicin. Prior adjuvant doxorubicin was allowed up to a maximum of 300 milligrams per meter squared. Patients were to be treated every 3 weeks until disease progression or significant toxicity. No dose escalation was allowed in this study.

Patients could not have been treated for the metastatic disease with prior chemotherapy. Patients must have had bidimensionally measurable disease, ECOG performance status of 0 to 2, left ventricular ejection fraction at baseline greater than 50 percent, and no prior history of congestive heart failure.

The planned sample size for this study was 288 patients. This was based on an 80 percent power to rule out a one-sided difference of 15 percent in response rates. Three interim analyses were planned, but due to rapid enrollment into this study, only the first interim analysis was performed. The study enrolled the full sample size as

planned and the total number of patients was 297.

Study 2 is a study comparing single agent treatment of D-99 to the same dose of single agent doxorubicin. The study design was very similar to that in study 1 except that in this study dose escalation was allowed at an increment of 15 milligrams per meter squared up to a maximum of 105 milligrams per meter squared.

Eligibility criteria were identical to that in study 1.

As in study 1, the planned sample size was 288 patients with three planned interim analyses.

The stopping rules were defined according to the O'Brien-Fleming stopping rule, with an overall type 1 error of 0.05. It is important to note that this study was not prematurely stopped. Rather it was stopped per protocol. At the third interim analysis, the study had met both protocol-specified endpoints for early stopping. The interim analysis results were discussed with the FDA and the agency agreed that the protocol endpoints were met for early stopping and that it was up to the company to decide to stop enrollment. After the meeting with the agency, the sponsor stopped enrollment into the study as called for by the protocol. The final sample size was 224 patients.

The D-99 clinical program was international in scope. Study 3 compared the combination of D-99 plus

cyclophosphamide to equal doses of epirubicin plus cyclophosphamide.

The objective of this study was to demonstrate that antitumor efficacy at equal doses of these treatments was comparable.

In this study no prior anthracycline was allowed and patients were treated up to a maximum of 8 cycles.

With a maximum of 600 milligrams per meter squared, it was expected that there would be a low incidence of cardiotoxicity with both treatment arms. Therefore, cardiotoxicity is not an endpoint in this study.

Eligibility criteria were identical to that in study 1 except that no prior anthracycline was allowed.

As in the pivotal study, the sample size was 288 patients. No interim analysis was planned or conducted. This study was terminated because of resource considerations. The final sample size was 160 patients. The study was stopped without any knowledge of the study results. The integrity of the study was maintained and the outcome of this study was not biased by the early termination.

Dr. Jonathan Alexander will now present our findings on the reduction of cardiotoxicity, focusing on results from study 1 and the confirmatory evidence from

study 2. Dr. Alexander had reviewed the cardiotoxicity results from these two studies on a treatment blinded basis.

Thank you.

DR. ALEXANDER: Thank you, Dr. Lee. My name is Jonathan Alexander. I'm a clinical cardiologist at Danbury Hospital and Yale University. It is my distinct privilege to present the reduction in cardiotoxicity data for TLC D-99.

As described by Dr. Lee, two phase III trials were designed to determined if TLC D-99 was associated with less cardiotoxicity compared with conventional doxorubicin in the treatment of patients with metastatic breast cancer.

The primary endpoint in assessing cardiotoxicity in both trials was a reduction in the left ventricular ejection fraction, as determined by serial MUGA scans. Guidelines developed by myself and the Yale University Nuclear Cardiology Laboratory were used to monitor therapy. These have shown that a drop in ejection fraction can be a preclinical indicator for stopping doxorubicin in an attempt to reduce the severity of cardiotoxicity and limit the incidence of congestive heart failure.

Therapy was to be discontinued if the left ventricular ejection fraction fell by greater than or equal

to 10 ejection fraction units to a level less than normal or greater than or equal to 20 ejection fraction units within the normal range. If detected, therapy was to be discontinued.

Additionally, at each clinic visit, patients were carefully monitored for signs and symptoms of congestive heart failure, and again if detected, it would be stopped.

In study 2, the protocol initially required that endomyocardial biopsy be performed after patients had received a cumulative lifetime dose of 425 milligrams per meter squared of doxorubicin. A score of 2.5 or 3 on the Billingham scale, which I will define, required that treatment be discontinued. Approximately 1 year after initiation of this trial and after careful review of the data with the FDA, the protocol was amended to discontinue use of this invasive procedure.

All of the participating institutions were required to submit their MUGA studies for standardization to the core laboratory at Yale University with subsequent certification. All MUGA scans were read blinded to the patient's treatment. If the scans were felt to be technically inadequate, they were asked to be repeated. To minimize the risk of congestive heart failure, results were provided to the site prior to the next scheduled dose of

anthracycline therapy.

In studies 1 and 2, MUGA scans were to be performed at baseline, before the next cycle after exceeding 300 milligrams per meter squared, 400 milligrams per meter squared, before each dosing after 500 milligrams per meter squared, at the end of the study, and 3 months after termination of the study.

My role was to review records of all patients reported to have congestive heart failure and those whose left ventricular ejection fraction fell to a level of less than 30 percent. This value was chosen because the incidence of congestive heart failure rises significantly in these patients. Charts were reviewed carefully to see if criteria for congestive heart failure was met. Confirmatory evidence was also reviewed, including results of chest x-rays and echocardiograms.

In study 2, endomyocardial biopsies were read blinded to treatment by Dr. Margaret Billingham of Stanford University, who developed the pathologic scoring system used to assess doxorubicin-induced cardiac damage. Grade 2.5 is defined as 26 to 35 percent of involvement of the myocytes. These patients have a 10 to 25 percent risk of developing heart failure with an additional 100 milligrams per meter squared of anthracycline. A score of 3 defines a more diffuse cellular injury with greater than 35 percent

of myocytes affected. These patients have a greater than 25 percent risk of developing heart failure with any additional challenge of anthracycline.

In the initial phase of this study, both the biopsy and MUGA scans were obtained at a dose of 425 milligrams per meter squared of doxorubicin.

Study drug exposure in study 1 is depicted on this slide. Although all of the overall differences in drug exposure were not statistically significant, the range in the D-99 group was higher. In addition, more patients were treated with greater than or equal to 8 cycles of therapy.

The prevalence of recognized cardiac risk factors for cardiotoxicity was similar in both arms. These included older age, prior exposure to doxorubicin, cardiac irradiation, and prior cardiac disease. One-third of patients in both arms had one or more risk factors for cardiotoxicity, a finding similar to other patients treated with metastatic breast cancer. The patients with these risk factors form a subgroup at high risk for cardiotoxicity.

The relationship between the total cumulative dose of doxorubicin, the incidence of significant left ventricular ejection fraction change, and congestive heart failure is shown for the D-99 and doxorubicin group in this

slide. 21 percent of the patients receiving doxorubicin had protocol-defined cardiac toxicity compared with 6 percent in the D-99 arm. This occurred despite the higher cumulative doses of doxorubicin in the D-99 arm. In addition, there were 5 cases of congestive heart failure with doxorubicin, none with D-99.

It's important to note that the majority of the change in ejection fraction, as well as the congestive heart failure, occurred in a dosage range of between 300 and 500 milligrams per meter squared, a dosage range frequently used to treat patients with metastatic breast cancer.

The difference between the estimated median cumulative lifetime dose of doxorubicin at the first occurrence of protocol-defined cardiac toxicity was statistically significant, as shown on this Kaplan-Meier analysis with a p value of .0001.

The hazards ratio of 5 indicates that patients treated with doxorubicin were 5 times more likely to develop cardiac toxicity than those treated with D-99. Cardiac toxicity was first evident at between 300 and 400 milligrams per meter squared of doxorubicin where the curves begin to separate.

In single-agent study 2, both arms received a median of 4 cycles of therapy. There was a significantly

higher range in the D-99 group, and a significantly greater portion of patients were treated with greater than or equal to 8 cycles in the D-99 arm.

The prevalence of cardiac risk factors was again noted to be similar in both arms, as shown in study 1. Up to 50 percent of patients in this study had one or more cardiac risk factors for cardiotoxicity, again representing a high risk group.

A similar analysis comparing the two arms with regard to cumulative dose of doxorubicin, significant change in ejection fraction, and incidence of congestive heart failure is shown here for study 2. The difference between the 28 percent in the doxorubicin arm and 13 percent in the D-99 arm was statistically significant. 9 patients with doxorubicin had heart failure, only 2 with D-99. Cardiac toxicity tended to occur at higher cumulative doses of doxorubicin in the combination trial, which is a finding consistent with doxorubicin's labeling which cites an increased risk of cardiotoxicity when doxorubicin is given with cyclophosphamide.

As in study 1, a Kaplan-Meier analysis for the estimated median cumulative lifetime dose of doxorubicin at the first occurrence of cardiac toxicity was performed, and the difference between the two groups is statistically significant.

The hazards ratio of 3.7 indicates that patients receiving doxorubicin were over 3 and a half times more likely to develop cardiotoxicity compared with D-99, and in these curves, the separation is at about 450 milligrams per meter squared when cardiotoxicity was first seen.

Before amending the protocol to delete the requirement for endomyocardial biopsies, 36 patients, 19 receiving D-99 and 17 receiving doxorubicin, qualified for the procedure. 70 percent of the patients with doxorubicin had scores of 2.5 or greater in contrast with 5 in the D-99 arm. Importantly, none of the D-99 patients had grade 3 cardiac toxicity.

Thus, determined from either a functional standpoint using MUGA scans or with endomyocardial biopsies, it appears that D-99 is significantly less cardiotoxic compared with conventional doxorubicin. These two differing methodologies support the same conclusion.

A meta-analysis of the high risk group of patients, those with one or more cardiac risk factors, was performed. On this Kaplan-Meier analysis, the difference between the D-99 group and the doxorubicin group was statistically significant with a p value of .0001. In this high group of patients, those receiving doxorubicin were greater than 6 times more likely to develop cardiac

toxicity compared with D-99, using the hazards ratio.

In the third phase III trial comparing D-99 to epirubicin, cardiac toxicity was not a primary endpoint since it was anticipated that these anthracyclines would be relatively cardiac sparing when capped at a dose of 600 milligrams per meter squared. Indeed, as shown here, 12 percent of the patients with D-99, 10 percent with epirubicin, developed a significant change in ejection fraction as determined by echocardiography. No patient in either group developed congestive heart failure.

Hazards ratio on the corresponding 95 percent confidence limits for studies 1 and 2 are presented here. There's a highly statistically significant difference in cardiac toxicity with a p value of .0001 for study number 1 and .0002 for study number 2. The hazards ratios, indicated here between 3.7 and 5 again, indicate that patients treated with doxorubicin were 3.7 to 5 times more likely to develop cardiac toxicity than those treated with TLC D-99.

A review of the entire database of 542 patients with predominantly solid tumors who were treated with D-99 at a starting dose of less than 100 milligrams per meter squared was reviewed. 8 patients, or 1.5 percent, developed congestive heart failure. As shown here, it is estimated that the cumulative dose of TLC D-99 was

associated with a 5 percent risk of congestive heart failure with 780 milligrams per meter squared. With doxorubicin, it's estimated to occur at 400 milligrams per meter squared.

In conclusion, data from two randomized, well-controlled clinical trials reproducibly demonstrate that D-99 compared with the same dosing schedule of doxorubicin affords a significant reduction in cardiac toxicity as defined by functional criteria using MUGA scans, incidence of congestive heart failure, or by myocardial biopsy scoring.

Thank you for your attention.

Before I turn it over to Dr. Lee, I'd just like to take a moment. As a clinical cardiologist who interfaces with many of the patients who are at risk for cardiotoxicity or who develop it, the prospects of having a drug that will limit the cardiotoxicity is very exciting, undoubtedly resulting in a significant decrease in the medical burden to the patients, with less cardiac medications, less need to interface with cardiologists, reduced need for hospitalizations, and a significant reduction in the morbidity associated with this disease.

DR. LEE: I will now present the results for the antitumor efficacy of TLC D-99.

All three phase III studies were designed as a

non-inferiority study for the efficacy endpoints. Since we're comparing a test drug to standard known therapies, the primary goal is to ensure that there is no loss in antitumor efficacy. The protocol-defined primary efficacy endpoint is response rate, and the protocol-defined test of non-inferiority is a one-sided test to rule out a difference of 15 percent with a type 1 error of 0.05. This specification of the primary endpoint and the analysis criterion was agreed with the FDA at the end of phase II meeting and was specified in the protocol.

In my presentation, I will also present the more stringent criteria of the two-sided 95 percent confidence interval for the difference in response rates. The data will show that the response rates in all three studies met the criterion of 15 percent delta and also the more stringent criterion of 10 percent delta. The FDA analysis that you will see for the response rate is based on relative risk.

Other protocol-specified secondary endpoints include duration of response, time to progression, time to treatment failure, and overall survival. To evaluate non-inferiority, the lower one-sided 95 percent confidence limit of the hazards ratios for these parameters should be greater than .75 if significant reduction in cardiotoxicity is demonstrated, as in studies 1 and 2, and should be

greater than .80 if there is no difference in cardiotoxicity, as in study 3. In my presentation, I will once again present the more stringent two-sided 95 percent confidence limits.

Study 1 compares the combination treatment of D-99 plus cyclophosphamide to equivalent doses to doxorubicin and cyclophosphamide. The objective response rates in disease progression results presented here are based on the treatment blinded assessment by Dr. Joyce O'Shaughnessy. Objective response is defined by the WHO criteria lasting at least 6 weeks. Disease progression is defined as an increase of 25 percent in any lesion or the appearance of new lesions. Time to progression is defined as the documented disease progression, as defined here, or death within 6 months of last dose. This criterion and this definition of time to progression was agreed upon with the FDA review team.

Patients were well balanced with respect to baseline characteristics. 10 percent of the patients in each treatment group had received prior adjuvant doxorubicin. The objective response rates were 44 percent versus 43 percent. The p value to rule out the 15 percent delta was highly statistically significant and the results also fulfilled the criteria of no more than 10 percent delta as evidenced by the two-sided 95 percent confidence

limit. There was no difference in duration of response.

There was also no difference between the two treatment groups in time to progression. The hazards ratio that is presented here, as well as in all of the subsequent presentations, are expressed with D-99 as the denominator. A hazards ratio of 1 indicates that there is no difference between the two treatment groups and a hazard ratio of greater than 1 favors D-99. The hazards ratio shown here is 1.07. As you can see, the lower limit of the one-sided as well as the two-sided 95 percent confidence limit fulfilled the criteria for non-inferiority.

Time to treatment failure is a composite endpoint considering both the efficacy and the safety component of treatment. Treatment failure is defined as the first onset of progression, cardiotoxicity, or off study due to adverse events. As can be seen in this analysis, D-99 is associated with significantly longer time to progression. The p value is 0.04, and the hazards ratio is 1.32.

There was no difference between the two treatment groups in overall survival. Overall survival was 19 months for the D-99 treated patients versus 16 months for the doxorubicin treated patients. The hazards ratio is 1.04 and the lower limit of the one-sided confidence interval was .80.

Just as a note of information, the numbers that you will see in the survival analysis in the list of questions that were handed out by the FDA will be slightly different from the ones that you will see presented by me. The difference is because the FDA numbers were based on a previous older data set. All of the other parameters that you will see from both sides are based on the updated latest data sets which were submitted to the agency in April of this year.

Quality of life is always important to patients, particularly for women who have metastatic breast cancer. Quality of life information was collected in this study using two instruments. The patient's self-assessment of symptoms based on a 10 centimeter visual analog scale where patients were asked to rate the cancer related pain as well as the other kinds of related symptoms. Additionally, an EORTC quality of life questionnaire consisting of 30 questions was also administered.

There were no major differences emerging from the EORTC questionnaire, but there were some very interesting and consistent findings observed from the patients' self-assessment. There was pain reduction for both treatment groups during the course of treatment as evidenced during the first 5 cycles where more than 50 percent of the patients were still on study. The

difference between D-99 and doxorubicin was statistically significant at cycle 3 and 4 in favor of the D-99 treated patients. Furthermore, D-99 patients also reported significantly less other cancer related symptoms at cycles 2, 3, and 4.

A summary of the efficacy results for this pivotal trial is presented here. D-99 fulfilled the protocol-defined criteria of demonstrating non-inferiority, as well as the more stringent criteria of the two-sided tests. Importantly, it is interesting to note that all the hazards ratios for the time to event parameters were greater than 1 in favor of D-99 and there was a statistically significant difference in time to treatment failure in favor of D-99, a reflection of the comparable antitumor efficacy and improved safety profile for TLC D-99.

In summary, this pivotal trial demonstrates that the antitumor efficacy of D-99 plus cyclophosphamide is comparable to that of doxorubicin plus cyclophosphamide.

Study 2 compared single-agent treatment of D-99 to doxorubicin. The efficacy endpoints and defined analyses in this study are identical to that of the pivotal study 1. Objective response in disease progression were assessed on a treatment blinded basis by Dr. Joyce O'Shaughnessy.

The treatment groups were well balanced in baseline characteristics. The only notable difference is the higher proportion of patients in the D-99 treated group with a negative progesterone receptor status.

Response rate is identical between the two treatment groups, 26 percent in each arm. The results fulfilled the protocol-defined test to rule out a 15 percent delta and also the more stringent criteria to rule out a 10 percent delta. The lower limit of the 95 percent confidence interval was minus 9 percent. There was no difference between the two treatment groups in duration of response.

I would like to note that in the original protocol, the protocol assumed a response rate of 60 percent, which in retrospect was unrealistic for single agent treatment. This observed response rate in the 20 percent range was actually more in line with what is recently reported in the publications and in the literature, and the study still fulfilled the protocol-defined criterion of non-inferiority.

There was no difference between the two treatment groups in time to progression. The hazards ratio is .91 and the lower bound for the 95 percent confidence limit was .70.

There was also no difference in time to

treatment failure. The hazards ratio is 1.21, and the lower limit for the 95 percent confidence was .94.

There was a nonsignificant trend towards the difference between the two treatment groups in overall survival. The separation of the curves began at around 12 months after the start of treatment. The hazards ratio is .76, and the one-sided 95 percent confidence limit was .58.

The most appropriate analysis is the protocol-specified, protocol-defined analysis. We did conduct some exploratory analyses to try to understand the reason for the survival findings. Exploratory analyses were conducted including stratification factors, center effect, and covariate adjustments with prognostic factors. The result shows a spectrum of summary statistics with p values ranging from .06 to .19, suggesting that these summary statistics are sensitive to the models and factors included. We do recognize that these are all post hoc, unplanned analyses and are exploratory in nature.

We do not fully understand the reason for the difference in survival. However, there are a few important points that I would like to bring to your attention. There is no difference in survival during the first year between the two treatment groups. You may recall that the median duration of treatment in the study was 4 cycles, about 3 months of treatment. The timing at which the separation of