FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

SIXTY-THIRD MEETING

OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE

8:01 a.m.

Friday, September 17, 1999

Kennedy Ballroom
Holiday Inn
8777 Georgia Avenue
Silver Spring, Maryland

ATTENDEES

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ATTENDEES (Continued)

COMMITTEE MEMBERS: (Continued)

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ATTENDEES (Continued)

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MASSIMO CARDINALI, M.D.
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JAMES O'LEARY, M.D.
JAY SIEGEL, M.D.
ROBERT TEMPLE, M.D.
GRANT WILLIAMS, M.D.

ATTENDEES (Continued)

ON BEHALF OF BRISTOL-MYERS SQUIBB:

DON BERRY, PH.D.
RENZO CANETTA, M.D.
CRAIG HENDERSON, M.D.
LARRY NORTON, M.D.
DAVID TUCK, M.D.

ON BEHALF OF HOFFMANN-LA ROCHE, INC.:

ANTONIO BUZAID, M.D.
LONI da SILVA
SAM GIVENS, PH.D.
PROFESSOR JEAN-JOCK GROB
LEON HOOFTMAN, M.D.
MAURIZIO RAMISIO, PH.D.
ELIZABETH WASSNER, PHARM.D.

ALSO PRESENT:

MARGARET VOLPE
MARISSA WEISS, M.D.

C O N T E N T S - MORNING SESSION

NDA 20-262/S-033, TAXOL (paclitaxel) Injection
BRISTOL-MYERS SQUIBB COMPANY
Indicated for the Adjuvant Treatment of
Node-Positive Breast Cancer
Administered Sequentially to Standard Combination Therapy

C O N T E N T S - AFTERNOON SESSION

BLA 97-1001, ROFERON-A
HOFFMANN-LA ROCHE INC.
Indicated for Use as Adjuvant Treatment of
Surgically Resected Malignant Melanoma
Without Clinical Evidence of Nodal Disease,
AJCC stage II (Breslow thickness greater than 1.5 mm, N0)

P R O C E E D I N G S

(8:01 a.m.)

DR. NERENSTONE: Good morning. I'd like to thank everybody for coming and starting on time.

I'd like to start with going around the table and introducing the committee members. If we could start with Dr. Krook.

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

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

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

DR. PELUSI: Jody Pelusi, oncology nurse practitioner in Phoenix, Arizona.

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

DR. BLAYNEY: Doug Blayney, medical oncologist, Pomona, California.

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

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

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

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

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

DR. O'LEARY: James O'Leary, medical reviewer at the FDA.

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

DR. JUSTICE: Bob Justice, acting Division Director, FDA.

DR. NERENSTONE: Thank you.

Dr. Somers will now read the conflict of interest statement.

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

Based on the submitted agenda for the meeting and all financial interests reported by the 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. Richard Schilsky and Dr. Richard Simon are excluded from participating in today's discussion and vote concerning Taxol.

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

Further, Dr. Kim Margolin has been granted a limited waiver which permits her to participate in the committee's discussion of Taxol without voting privileges.

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. Scott Lippman 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 a conflict. The agency has determined, notwithstanding his 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. Therefore, Dr. Lippman may participate fully in today's discussion and vote concerning Taxol.

Further, because of Dr. James Krook's and Dr.

David Johnson's past interests involving Taxol, the agency has determined, notwithstanding their interests, 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. Therefore, Dr. Krook and Dr. Johnson will be permitted to participate in today's discussion of Taxol without voting privileges.

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.

I'd also like to remind people that Dr. Gradishar was not able to travel to this meeting because of the weather. Thank you.

DR. NERENSTONE: We are now going to open the public hearing part of the meeting. We have one speaker who has been asked, Margaret Volpe of the Y-ME National Breast Cancer Organization. Ms. Volpe?

MS. VOLPE: Good morning. My name is Margaret Volpe from Y-ME National Breast Cancer Organization, and I have no financial connections with Bristol-Myers Squibb.

Thank you for allowing us to submit this 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 Taxol injection for the adjuvant treatment of node-positive breast cancer administered sequentially to standard combination therapy.

Y-ME National Breast Cancer Organization is a nonprofit patient advocate organization whose mission is to decrease the impact of breast cancer, create and increase treatment awareness, and ensure, through information, empowerment, and peer support, no one faces breast cancer alone. We have 26 chapters nationwide, numerous publications, and several outstanding public education programs. Y-ME has no financial connection to Bristol-Myers Squibb Company.

The addition of Taxol to the adjuvant treatment of node-positive women after standard chemotherapy, doxorubicin and cyclophosphamide, represents a major advancement in the treatment of breast cancer. The results of the CALGB study 9344 showed that the addition of Taxol increased overall survival and disease-free survival rates.

Y-ME believes that women and men diagnosed with breast cancer should have access to as many treatment options as possible. We believe the approval of Taxol in the adjuvant setting will add a valuable option.

Thank you.

DR. NERENSTONE: Thank you very much.

Are there other public speakers at this time?

(No response.)

DR. NERENSTONE: If not, then we'll continue with the sponsor presentation.

DR. TUCK: Thank you. Good morning. I'm David Tuck from clinical oncology at Bristol-Myers Squibb.

We plan to present this morning the data from the supplemental new drug application for the use of Taxol for adjuvant treatment of node-positive breast cancer.

The initial presentation this morning will be by Dr. Larry Norton, who will discuss current approaches to adjuvant therapy for breast cancer. He will be followed by Dr. Craig Henderson, who will present the results from the pivotal study Intergroup 0148. Following this, Dr. Renzo Canetta from Bristol-Myers Squibb will present some concluding remarks, and then we will accept questions.

First of all, I would like to welcome our external consultants today. All of them had to make extraordinary travel arrangements to get here today, and we

appreciate that. But I would like to mention in particular the heroic efforts that Dr. Don Berry made to get here from Houston, driving in all night last night, at least the last leg, and arriving just a little while ago.

Dr. Stephen George, the Director of the CALGB Statistical Center, also participated in the preparation of the NDA but was not available today.

Dr. Craig Henderson was the study chair for the pivotal study.

And Dr. Larry Norton is the Chair of the CALGB Breast Committee.

The activity of Taxol is well established in a variety of settings with metastatic disease for breast cancer. Early in the development, Taxol was shown to have high response rates in metastatic breast cancer in phase II trials, including heavily pretreated patients and patients who had failed anthracycline therapy.

In 1994, a large randomized study led to the initial approval by the FDA of Taxol for the second-line treatment of metastatic disease using a dose of 175 milligrams per meter squared over 3 hours.

In 1998, based on a large randomized trial, Herceptin was approved to be used in combination with Taxol using a dose of 175 milligrams per meter squared over 3 hours for the first-line treatment of HER2 positive

metastatic breast cancer.

The pivotal trial, which is going to be presented today, is an intergroup trial, INT-0148, which looked at both doxorubicin dose escalation as well as the addition of Taxol versus no further therapy as part of the cyclophosphamide/doxorubicin adjuvant chemotherapy regimen for node-positive breast cancer.

The coordinating group was the CALGB, and most of the major cooperative groups in the U.S. participated, including the Eastern Cooperative Oncology Group, the North Central Cancer Treatment Group, and the Southwest Oncology Group.

A total of 3,170 patients were accrued between May 1994 and April 1997. This pivotal study then is the largest randomized trial of chemotherapy in the adjuvant treatment of breast cancer that has ever been submitted to the FDA.

As you will hear today, the results of this study show that Taxol, given with standard dosage following standard chemotherapy, demonstrates significant advantages in disease-free and overall survival.

The safety profile in this setting is consistent with the large experience accumulated with this approved dose and schedule.

Therefore, we propose the following indication:

Taxol administered sequential to standard combination chemotherapy is indicated for the adjuvant treatment of node-positive breast cancer.

Now I'd like to have Larry Norton discuss adjuvant chemotherapy.

DR. NORTON: Thank you. Good morning. My job is to sort of introduce the topic by giving some background and by showing some context. In this regard, I'd like to start off with the next slide which describes sort of the basic core kernel of knowledge of what we know at the present time about the adjuvant chemotherapy of breast cancer.

We know for sure that adjuvant chemotherapy improves disease-free and overall survival. We know that the use of multiple agents, so-called polychemotherapy, is superior in this regard to the use of a single agent, monochemotherapy. We know that multiple cycles of administration is superior to a single exposure. This is largely a single perioperative exposure in some very early trials. We know that there are no major advantages to durations of therapy exceeding 3 months, and we know that the anthracycline combinations are slightly better than CMF, which is probably the world's most studied regimen, that the anthracycline combinations are somewhat superior.

Now, how do we know all this? We know this

clearly from individual large studies, but also from the worldwide overview that's being conducted based in Oxford, England every five years. This activity, with which you're all familiar, puts together all of the investigators in the world who have done randomized trials, published and unpublished, for the treatment of breast cancer, as well as other therapeutic approaches in early disease.

Presented here is just a basic summary of some of the key points for prolonged polychemotherapy, meaning more than one cycle and involving more than one drug, on reducing the annual odds of recurrence and death. One of the really key things from this worldwide activity is not only putting together the world's experience, but also the way that the efficacy of therapy is expressed as a reduction in the annual odds of an event.

For example, if you look at the CMF combination versus no chemotherapy with over 8,000 randomized patients throughout the world, there's a reduction in the annual odds of recurrence by 24 percent. That's very statistically significant, as shown here in yellow, with this being the standard deviation. So, 2 standard deviations would be the borderline for significance.

Death is reduced by 14 percent per year.

Chemotherapy. This plus stands for additional agents, such as vincristine and prednisone and other such

agents, compared to no such therapy, is in the same ball park of efficacy showing no real advantage.

Nevertheless, anthracycline combinations versus CMF with almost 7,000 patients randomized shows an incremental benefit for the doxorubicin or other anthracyclines of 12 percent in recurrence and an additional decrement in the annual odds of death by 11 percent.

A very important observation is that longer regimens versus shorter regimens of various trials involving 6,000 patients, that there's no statistically significant difference between the longer versus the shorter regimens.

Now, how does this translate to the familiar time to event curves? In this case we're doing the event being recurrence. If you take a simulated example shown here in yellow of no therapy being applied in the adjuvant setting for a patient with very poor risk breast cancer, relapsing at an average rate of 15 percent per year, you can see that the curve goes down by about 15 percent with each year, and at the end of 10 years, you're left with 20 percent of patients free of disease.

CMF, if it reduces that 15 percent by 24 percent, leaves you a residual risk of recurrence of 11.4 percent per year, and that graphs out as this magenta

curve.

AC involving an anthracycline reduces that 11.4 percent by 12 percent, leaving 10 percent. So, the light blue line is 10 percent less each year than the year immediately preceding it and that this is the overall benefit.

So, this is how reductions in the annual odds translates to time to event curves. We should keep this in mind as Craig in a few minutes presents the data for the use of paclitaxel in the adjuvant setting.

Now, we know a few other things which are very relevant to planning research and analyzing research. We know from CALGB study 8541 that looked at three different dose levels of chemotherapy, that Adriamycin doses, doxorubicin doses, less than 40 milligrams per meter squared are inferior to the now standard dose of 60 milligrams per meter squared. This study did not go above 60 milligrams per meter squared.

We know from the NSABP study B-22, that cyclophosphamide doses greater than 600 milligrams per meter squared are not superior, rendering this dose now the standard in wide use.

And we know from the worldwide overview that chemotherapy seems more effective in estrogen receptor negative than estrogen receptor positive disease. And I

say "seems" because the tests for interactions are somewhat complicated and don't always reach statistical significance, but there certainly is a trend in that direction.

I'll show you what we mean by that. If you look at the impact of polychemotherapy versus no polychemotherapy in young patients under 50, the impact in patients with estrogen receptor disease is larger than the impact in patients with estrogen receptor positive disease. In fact, it's large enough in terms of survival that it's statistically significant here, but in the ER positive subset, it's not statistically significant.

For patients who are older, 50 and older, again the same thing is seen. The impact in ER negative disease is greater than in ER positive disease, and again for survival, the impact is significant here, but you don't even see a significant impact on survival for ER positive disease in the older age group.

Now, building upon this data set, where can we go to improve? These are some of the possibilities for where we can go, and these were certainly in consideration in the design of the intergroup study that we're presenting to you today.

One is, can you do better escalating the dose of the anthracycline? The previous CALGB study stopped at

60 milligrams per meter squared.

Is there any advantage to integrating new agents such as other chemotherapy drugs or biological agents?

And if we are going to integrate them, how should we do so? What is the best way to apply them in a drug schedule? I will show you in a few minutes a consideration of one approach which is called dose density or dose dense sequential therapy.

But first, if we are going to integrate a new chemotherapeutic agent, which one should we use?

Well, the four that have recently been approved for the treatment of advanced breast cancer are shown here. The first one, of course, was paclitaxel, docetaxel to following, capecitabine recently, and this not being a chemotherapy drug, this is the monoclonal antibody directed to the extracellular domain of HER2.

Well, of these, this was the one that was clearly available and had clearly demonstrated attractive features at the time that the study was designed in 1991-1992. So, the data we'll present to you today involves the use of paclitaxel, but I will show a little later how other agents are integrated into this overall treatment approach.

Why paclitaxel? It's active as first chemotherapy for stage IV disease with response rates

approaching 60 percent in two very carefully done phase II studies and now universally corroborated in hundreds of trials throughout the world.

It's also active after extensive prior chemotherapy, including patients whose disease is refractory to anthracycline. It's not just regression and regrowth, but flat-out failure of anthracycline response if their response is to paclitaxel, and overall after extensive prior disease, response rates as high as 30 percent are seen at the NCI, at Memorial Sloan-Kettering Cancer Center, and now worldwide in multiple corroborating studies. So, it seems like a very reasonable drug to use, especially after standard therapy that may involve an anthracycline.

Now, this demonstrates a simulation of a tumor that's growing in a curvilinear fashion on a semi-logarithmic plot, the so-called Gumpertzian curve, and then responding to various doses of therapy with regression and regrowth, as you see. Leaving cells behind, even a small number of cells, one can get rapid regrowth, replenishment, and eventually recurrence at about 10 to the 11th cells and death at about 10 to the 12th cells.

Well, one concept that certainly has appealed to many people to try to improve upon this is just to escalate the dose of the chemotherapy, and that's shown on

the next click where each dose of drug is higher. You get more regression with each dose of therapy, but as you can see, there's a very interesting biological phenomenon, which is that as the tumor gets smaller, it regrows more quickly, and that eventual regrowth is such that the eventual outcome in terms of relapse-free and overall survival can be extremely modest. This can actually explain a great deal of data that we're seeing lately in terms of the use of very high doses of chemotherapy purely on a kinetic basis.

Now, there is one other approach that makes sense and actually from a mathematical modeling view is more rigorous, and that's shown on the next slide. The next slide shows the standard dose intensity we're using as a comparison, but I'll show you here with this simulation that we're giving the same dose of drugs, but just pulling them closer together in time. This is termed dose density. You can see it's the same dose of drug, the same efficacy with the first cycle. The second cycle is more efficacious because it's given sooner when the tumor is smaller and so on, and in this simulation, you actually get eradication with four doses of exactly the same chemotherapy, just done more closely together in time.

Now, how does this relate to the current study? That's shown on the next simulation where you have two sub-

lines growing, one responsive to one therapy, one responsive only to the other. It's certainly seems to be a rational, intuitive thing to come in with the other dose of drug here because the tumor cells are growing. But you can see, when you do that, you are actually spreading the doses far apart of both the red treatment for the red cells and the white treatment for the white cells, so the dose density is very poor for both treatment plans. As a consequence of which, both sub-lines are actually grossly sub-adequately treated.

This can be overcome -- next simulation, please -- by giving all of this therapy first in a dose dense fashion, as we showed in earlier simulations, allowing this tumor to grow but then coming in with dose dense therapy for these tumor cells and therefore, because it's dose dense, causing eradication of the subpopulation. This simulation, therefore, shows how sequential therapy is actually a form of dose dense therapy.

Well, this was actually tested prospectively by Bonadonna, Buzzoni, and colleagues in a trial in stage II breast cancer patients with 4 or more involved axillary lymph nodes, involving doxorubicin sequentially with CMF or the alternation of CMF with doxorubicin, a carefully designed trial where the doses are exactly the same, the time between therapy is exactly the same, duration the

same. Everything is the same except that this is sequential, as shown in my second simulation, and this is alternating, as shown in the first.

As predicted by the model, there is superiority in both relapse-free survival and in overall survival by the use of the sequential Adriamycin followed by CMF versus the alternation of the two treatment plans.

Well, the CALGB, in preparation for applying this concept in the stage II setting, first did a pilot study that was presented by George Demetri at ASCO in '97 in node-positive breast cancer patients. It was a very large size pilot involving 172 patients with node-positive stage II or IIIa disease. It involved an escalated dose of cyclophosphamide -- this is before the B-22 data became available -- involving G-CSF for actually 5 cycles with doxorubicin at 75 milligrams per meter squared. This was obviously a very aggressive treatment program. Following this, patients received 4 cycles of paclitaxel at 175 milligrams per meter squared as a 3-hour infusion every 3 weeks for 4 doses.

Of the 172 patients, 145 reached the paclitaxel stage, and of those, about 90 percent were able to complete the paclitaxel. During that period, the only major toxicities were the grade IV neutropenia in a quarter of the patients, grade IV thrombocytopenia in 4 percent of the

patients, all short-lived toxicities from which the patients recovered very rapidly with no sequelae.

As a consequence of this, this was regarded as a pilot, and the intergroup study that we'll present to you today was designed according to this model. It's shown here and Craig Henderson will show it to you again shortly. The cyclophosphamide dose was reduced because of data to 600 milligrams per meter squared. That's the cyclophosphamide dose. The doxorubicin dose was -- patients were randomized between 60, 75 or 90 milligrams per meter squared, this requiring G-CSF, to test the concept of dose escalation of the anthracycline. Then patients were either crossed over or not to paclitaxel at standard dosage and sequence. Patients with hormone responsive disease, starting with estrogen responsive and then changed by amendment to progesterone receptor positive, received tamoxifen for 5 years thereafter.

Well, that trial obviously is going to be presented to you in a great deal of detail. I just want to close by showing the relationship between that trial and other trials that were started before the results of this trial were available and afterward, just to put it into global context of where the American cooperative groups are going.

NSABP started their study called B-28 in a

comparable group of patients. They started accruing to this trial about 16 months or so after we started accruing to the intergroup study that we'll present as the pivotal trial today.

Another major difference between that trial and the trial we'll present today is that the dose of paclitaxel is higher. It's 225 milligrams per meter squared. The trial has an endpoint of survival, so that it will require a longer follow-up to give results. Concomitant tamoxifen was used for hormone receptor positive disease for 5 years, and the eligibility was very broad, involving all patients with hormone receptor positive disease or patients who are over age 50 regardless of hormone receptor status, meaning that a much larger percentage of the patients received tamoxifen. Because this study was started later, because it has a survival endpoint, it has finished accruing, but no data is available. No analysis has been done, and we do not have any information about this trial at the present time.

CALGB, upon closure of the study, the pivotal trial study, opened this study which also now has closed to full patient accrual which took the regimen that I've just presented to you from our study and compared it with three others. One of the other trials that was done using dose dense sequential therapy was done at Memorial Sloan-

Kettering by Cliff Hudis, et al. involving doxorubicin, followed by paclitaxel, followed by cyclophosphamide, so-called ATC. Everything was given every 2 weeks to maximized dose density by the use of G-CSF permitting that manipulation. So, the intergroup CALGB trial involved this regimen and the same regimen given every 2 weeks to see if that dose density makes a difference, and this regimen also given every 2 weeks the standard way and every 3 weeks without the G-CSF, so you have a two-by-two factorial design. A very rapidly accruing trial, but much too early. No data has been provided on this study at the present time.

Also before the results from the pivotal trial, this study was initiated as an intergroup study coordinated by SWOG in patients with 4 to 9 positive lymph nodes, stage II or IIIa breast cancer, using the ATC regimen in actually augmented doses, as was originally done by Hudis, et al., and comparing it to an induction with AC, followed by high dose chemotherapy requiring hematopoietic stem cell support, STAMP I or STAMP V. This study is about halfway completed with its accrual and continues to accrue well.

Lastly in this category is a trial that's about to be coordinated for the intergroup by ECOG that takes the same regimen as is in the pivotal trial, AC followed by paclitaxel, and also randomizes patients to three other

possibilities: paclitaxel done weekly, which is actually more dose dense, a variety of paclitaxel, and docetaxel done every 3 weeks and weekly. So, there will be a comparison of schedule here, as well as comparison of different taxanes.

Now, the last, of course, important thing to keep in mind is that the integration of biological agents has long been considered a real possibility for improving prognosis, and the biological agent we have to work with, because of approval, is of course trastuzumab, or Herceptin, the anti-HER2 antibody.

Based on the data that led to approval of Taxol with Herceptin, that integration into the adjuvant setting is being conducted by a number of trials. The NSABP trial will involve HER2 positive disease, use the same design as the pivotal trial that's being presented today, but add Herceptin during and after chemotherapy for these patients who have HER2 positive disease in a randomized fashion.

The North Central Cancer Treatment Group will be coordinating an intergroup study that has some other features, the same basic crossover design involving paclitaxel alone, paclitaxel alone followed by Herceptin, or paclitaxel with Herceptin followed by Herceptin, asking the same basic questions but also asking the question is the simultaneous exposure to Herceptin an important feature

of this particular regimen or not.

Lastly the CALGB has designed a two-by-two-by-two factorial experiment in stage IIIb, or locally inoperable breast cancer, of AC followed by the weekly paclitaxel that the North Central Group will be coordinating, with surgery and radiotherapy to follow, with three randomizations of the Zinecard or not during AC to minimize cardiac effects to show, we hope, that the dexrazoxane does not impede the doxorubicin efficacy in this setting, Herceptin or not during the paclitaxel, and then Herceptin or not to complete a year after the paclitaxel. So, all the critical questions will be addressed in this particular trial.

Hence, this approach, the sequential dose dense approach, has some real advantages. In the study we're presenting to you, it integrates paclitaxel, which is active as a single agent and active post anthracycline. We'll be showing you data that it significantly augments the efficacy of chemotherapy in the adjuvant setting.

It does so in a way that actually minimizes incremental toxicity, and as we all know, the combination of taxanes with anthracyclines can have considerable incremental toxicity. And we'll demonstrate to you that we can minimize, truly minimize, that incremental toxicity by the sequential approach.

And the sequential approach also allows the integration of biological therapies such as Herceptin, as I've just presented to you.

Thank you very much.

The next speaker will be Craig Henderson, who chaired the pivotal trial, and he will be presenting the data on this trial to you.

DR. HENDERSON: Thank you. Good morning. It's always a pleasure to be able to present and discuss with this group.

This is an intergroup study addressing two questions, a Taxol and doxorubicin question. It was led by the Cancer and Leukemia Group B and involved substantial participation as well by ECOG, SWOG, and the North Central Group.

The study rationale has really been presented I think quite nicely by Larry. Just to remind you, based on everything we know, the dose response for doxorubicin may be steep. Cyclophosphamide, obviously, had been ruled out, and so we concentrated on doxorubicin dose escalation.

We know that Taxol and doxorubicin are not cross-resistant from a number of studies. So, Taxol was a logical drug to add here.

Finally, sequential use of AC and Taxol allowed us to evaluate two separate questions, that is, the

doxorubicin dose and a promising new drug.

Our study objectives then were quite simple: to assess the effects of three doxorubicin doses, 60, 75, and 90, in combination with a fixed dose of cyclophosphamide; and to assess the effects of sequential addition of Taxol following cyclophosphamide.

Now, we very consciously tried to make this a large, simple trial in many ways, which I think is increasingly more important. The number of patients that you accrue and having a large trial is probably more important than fine definitions, and in addition to that, it means that when you finish, the results are going to be applicable to a broad population of patients.

So, this included all patients who had operable breast cancer where you could remove the entire tumor with clear margins. Patients had to be node-positive. Treatment had to start within 84 days from the last surgery, whether that was lumpectomy or node dissection. No non-surgical treatment was allowed, and they had to have normal liver function.

It was a three-by-two design, asking first in three arms either 60, 75, or 90 per meter squared of doxorubicin the doxorubicin dose question, and in one of two arms the Taxol versus no Taxol. We gave 4 cycles every 3 weeks of the cyclo/adria and we gave 4 cycles every 3

weeks of the Taxol. Again, cyclophosphamide remained constant. Patients on the highest dose of doxorubicin received G-CSF routinely, while patients on the other two arms received G-CSF in accordance with the label for G-CSF in the product insert. Patients on the 75 and 90 per meter squared dose received doxorubicin on day 1 and day 2, that is, split because of our concerns of cardiotoxicity, while these patients received it as a bolus in the usual fashion. When Taxol was given, 175 milligrams per meter squared over 3 hours was administered based on the fact that this is the approved dose and is the most commonly used dose in the community at the present time.

So, study design. Three-by-two with stratification based on nodal groups only, 1 to 3, 4 to 9, and 10-plus.

Tamoxifen was given for 5 years for all patients that were ER positive, and regardless of the arm to which the patient was randomized, tamoxifen was begun on week 24 so that tamoxifen duration or the duration of exposure did not become a confounding factor.

Radiation therapy, however, was given immediately after the completion of chemotherapy, so that in the patients randomized to cyclo/adria, that would be after 3 months; for those randomized to cyclo/adria plus Taxol, that would be 6 months.

We powered the study to detect the effect of Taxol, the effect of doxorubicin dose, and the interaction between Taxol and doxorubicin dose.

Our median disease-free survival for our power calculations was assumed to be 6 years without Taxol.

Our power was 95 percent to detect a 25 percent decrease in the hazard rate from the addition of Taxol.

Based on these assumptions, we planned to accrue 3,000 patients over 3 years, and we assumed that we would have 1,800 occurrences 4 years thereafter.

The randomization was central. Data management was conducted by the Cancer and Leukemia Group B using its standard procedures.

There was an independent data safety monitoring board. They were the only ones who saw the data. In fact, as the PI in the study, the first indication I even had of the trends that were happening in this study were 6 weeks before the data were presented at ASCO. They did an interim safety analysis every 6 months. They did analyses of disease-free survival after 450, 900, 1,350, and a planned 1,800 events. So, we've completed this analysis and had dramatic effects that the data safety monitoring board felt justified for publication.

3,170 patients were accrued. However, between giving informed consent and the time when they received the

first dose of treatment, a certain number of patients dropped out, leaving 3,121 who received at least their first course of therapy. Usual policy in the Cancer and Leukemia Group B is to omit these patients from the analysis. So, everything you will see now is based on the 3,121 patients who were randomized and treated. We do not have data and did not follow up the patients who elected to drop out of the study.

Accrual was from May 1st, 1994 to April 15th, 1997. So, we accomplished the accrual goals in slightly less than the planned 3 years.

We had a preplanned interim analysis based on 450 events, so it was actually done at 453 events. And the data safety monitoring board decided that the results were such that it was important to release them to the public and that patients who were participating in it, making future decisions, deserved to know the results of these analyses in March of 1998.

And in May of 1998, we presented them to ASCO, and at that time had a 22 percent reduction in risk recurrence and a 26 percent reduction in mortality.

Now, it was after that that we began a collaboration with Bristol-Myers Squibb for the first time. They were not involved in the design or management of this trial at any point before that. The interactions between

BMS were with the National Cancer Institute, but not directly with the Cancer and Leukemia Group B.

In October of 1998, BMS and the CALGB had a pre-sNDA meeting with the FDA. It was decided to update the trial and have a larger database, and that was conducted in December of 1998. And the sNDA submission was in April of 1999.

Now, just to give you some sense of the differences between the first presentation and ASCO, May 1998, and at the time of the sNDA, the median follow-up at the first presentation was 20 months; for the data that you're looking at today, 30 months.

Number of events for disease-free survival: 453 in the first analysis; 624 today.

For overall survival, the number of events: 200 at the time of ASCO; 342 today.

Just to put this in perspective, in 1979 a National Cancer Institute consensus conference decided that it was appropriate to recommend adjuvant chemotherapy to all premenopausal node-positive women, and at that point, the number of events in these two categories from all trials worldwide was less than half of what was available at the time of the ASCO meeting. I state that to underscore the power of this very large trial.

The pretreatment characteristics are well

balanced between the two arms in all subsets.

You will notice particularly that about two-thirds of the women are premenopausal, which I think is understandable in a study of chemotherapy of this intensity.

The number of women who had 1 to 3 positive and 4 to 9 positive nodes, however, is about the same. The 10 positive node group is somewhat smaller, reflecting the fact that this is less prevalent in this society as a rule; that is, among breast cancer patients, having more than 10 positive nodes is not that common in the United States.

Secondly, patients who were enrolled in this trial had to be offered participation in a randomized trial evaluating high dose chemotherapy in bone marrow first, and if they declined that, then they could participate in this trial.

About two-thirds of the patients were treated with a modified radical mastectomy.

About two-thirds of the patients were receptor positive.

Now, among all the patients who were enrolled and started on course number 1, you can see that there is no significant difference between those randomized to AC and those randomized to AC plus Taxol in terms of dropout over these first 4 courses. So, approximately 3 to 4

percent of patients in the two arms dropped out over their first 4 courses of AC.

Now, among the patients who then went on and had been all previously randomized to Taxol, there were 4 percent who said, look it, I've had enough and decided not to go on as they had been previously randomized. So, we have 92 percent of all the patients randomized to AC plus Taxol who started on course number 1 of Taxol and there's a 7 percent dropout rate during those 4 courses of Taxol.

This shows you now the disease-free survival differences between AC, shown in white, and AC plus Taxol, shown in yellow. You'll notice that at the 1-year point, almost all of the patients who had been randomized had reached that point and had a year of follow-up. At the time of even the initial analysis, all patients were a year from randomization and at least 6 months from the completion of chemotherapy.

You can see that even at 3 years of follow-up, the number of patients at risk exceeds 600, which is considerably more than most randomized trials in the adjuvant setting in the past.

We see that these differences are highly significant, based on a multivariate Cox model. This is the model that was used. It shows, first of all, the comparison of Taxol with no Taxol and the risk ratio is .78

or a 22 percent reduction, highly significant.

On the other hand, when we look at doxorubicin dose, for example, comparing 60 with 90, we see no advantage from adding dose.

We see that there is a twofold increased risk if you had 10 positive nodes instead of 1. There's an increased risk, which is statistically significant for patients with larger tumors than with smaller tumors. However, there is no difference in patients who are pre- and post-menopausal in terms of disease-free survival.

Finally, patients who were receptor negative had about a two-and-a-half-fold increase in risk compared to those who were receptor positive.

If we look at the same data now for overall survival, shown here in white is the AC. Shown in yellow again, AC plus Taxol. Highly significant in our Cox model, and this shows you the model Taxol versus no Taxol, a 26 percent reduction in risk. Highly significant. No evidence of effect of doxorubicin dose. Again, positive nodes, tumor size show an increased risk. Estrogen receptor negative, increased risk. Here we also see an increased risk of dying -- this is dying of any cause now -- among the post-menopausal compared to the pre-menopausal, which isn't surprising considering that it's an older population.

Now, just to look at the two different times that we analyzed the data, we see that the results are identical. At the time of ASCO, a 22 percent and 26 percent reduction in risk of recurrence and mortality; at the present time, 22 and 26 percent.

Now, we saw no evidence of a dose effect whatsoever for doxorubicin. This shows you the three curves for disease-free survival, the white being the 60, the yellow being the 75, and the blue being the 90 per meter squared, and also for overall survival. You see no evidence of effect.

Further, we could show that individually, for example, the effects of adding Taxol to 60 milligrams per meter squared of doxorubicin are greater than the effects of giving 90 per meter squared of doxorubicin alone, which is only one part of the evaluation showing no evidence of an interaction between doxorubicin dose and paclitaxel addition.

Now, we did a number of subset analyses. These were not necessarily planned subset analyses and are confounded, obviously, by multiple comparisons, but I think most physicians and I would imagine most of the ODAC panel would be interested in seeing these, so we've summarized them here.

I think the take-home points are, first of all,

that we saw a similar effect in almost all of the subsets we looked at, certainly the node-positive groups where there is no significant difference in the effect of adding paclitaxel in these groups, tumor size, and interestingly in terms of menopausal status.

Secondly, the size of the effect is quite substantial in all cases, ranging from 20 to 25 percent.

Now, the one exception to that are in patients who have receptor positive versus receptor negative tumors. This was not a planned subset analysis and it's not one that has traditionally been done either by the Cancer and Leukemia Group B or, until very recently, by any groups. The overview data that you saw from Larry Norton is a first that they have actually looked at that.

We looked at this a little bit further and here we can show you the disease-free survival hazard ratios by receptor status. So, here is the hazard ratio with 95 percent confidence intervals for the entire study. So, we're at about 78 percent there, or 0.78.

Now, we look at the same thing, but just for those patients who are receptor positive and for those patients who are receptor negative. You can see that there is a greater effect. Even though the confidence intervals overlap here quite substantially, there appears to be a greater effect in the patients who were receptor negative

compared to those who were receptor positive.

We can see the same thing in terms of overall survival. The overall survival of the group as a whole with the hazard ratio here being .74, as I showed you earlier, with the effects in the receptor positive and in the receptor negative patients. Again, considerable overlap but the appearance of a greater advantage in the receptor negative patients.

Now, to summarize then what I have just gone over in terms of efficacy, we conclude the following. The addition of Taxol following standard combination chemotherapy in patients with node-positive breast cancer reduces the risk of recurrence by 22 percent and reduces the risk of death by 26 percent. And if you do that in terms of annual odds of recurrence, you come up with exactly the same number.

There is no evidence of a dose response to doxorubicin for doses above 60 per meter squared.

There is no evidence of an interaction between doxorubicin dose and Taxol.

And the benefits of Taxol in various subsets, including the receptor subsets, are consistent with the effects of chemotherapy in the worldwide overview.

Now, to turn to safety, the first thing it's important to understand about safety is that this study was

designed to intensely evaluate the first 325 patients. We concentrated on those patients because we did not feel, in the design of this study, that it was necessary to collect extensive safety data on cyclophosphamide, doxorubicin, and paclitaxel, drugs in which there are already huge safety databases. On the other hand, we were escalating the doxorubicin dose, quite substantially and we wanted to make sure that we monitored that very carefully.

So, the first 325 patients we obtained CBCs, for example, twice weekly. We required safety information on all types of toxicity, and we collected and put in our database anything that was grade 2 or above. These 325 patients were appropriately distributed among the major participants, so they weren't all from the CALGB. In other words, we had the same number from CALGB, ECOG, SWOG, and a slightly smaller number reflecting a smaller group from the North Central.

Now, our original plan, or at least the original plan that I had in my mind and a number of the people on the Breast Committee, was to only report ADRs after collection of these data very intensely and very carefully. However, as happens oftentimes with groups, there was a continuing discussion of whether we should stop all collection of data and get only ADRs, which we did by default for 1,815 patients, or whether we should collect

more information mainly because of issues regarding presentation of the data and so on.

So, we made an amendment to the protocol here as a consensus among the different points of view, and for the last 981 patients, we collected grade 4 and 5 hematologic toxicity and we collected grade 3 and above non-hematologic toxicity routinely.

Now, some investigators, having started with the intense reporting, continued to submit that even though it wasn't required by the protocol in the interim.

The take-home point is these are the data that are going to be most precise and represent the most careful monitoring for safety and those are the ones that I will emphasize. I will show you all of the patients together as well in separate columns as we go along.

First of all, grade 3-4 hematologic toxicity. Patients randomized either to AC or AC plus Taxol in the early population. First of all, you see that there is no difference in the overall hematologic toxicity in these two arms.

Secondly, you see that, as you would expect with the very intense therapy, that you have a high incidence of leukopenia and granulocytopenia. We'll talk about the degree to which this occurred in just the Taxol part in a few moments.

You see that the numbers in the total population are smaller, but again, you see no difference when you look at the total population in the hematologic toxicity in patients randomized to AC or randomized to AC plus Taxol.

Sequelae to hematologic toxicity, that is, infection, fever, hemorrhage. The requirement for platelet transfusions, requirement for red blood cell transfusions is also not significantly different. There's an appearance of a significant difference here, for example, in the incidence of infection, but among the 14 percent of patients randomized to AC plus Taxol who had infection, which constitutes 23 patients, 21 of the 23 patients had the infections while they were receiving the AC, not while they were receiving the Taxol. So, only 2 out of these 23 patients had an additional infection as a result of Taxol directly.

And the same thing is true for patients with fever. There were 4 patients, or 3 percent, who had fever that was grade 3 or grade 4, and all of them on the AC therapy.

We looked at a variety of non-hematologic toxicities, first of all, cardiovascular, neuromotor, alopecia, nausea and vomiting, diarrhea, stomatitis, and abnormalities of liver or renal function. We see no

significant differences either in the early population or overall among patients randomized to AC or those randomized to AC plus Taxol.

The greatest difference is in stomatitis. Again, that's greater actually in the patients randomized to AC only rather than those randomized to AC plus Taxol.

Now, we looked very specifically at non-hematologic toxicities that are commonly associated with Taxol: neurosensory, neuropathies, arthralgia, myalgias, or hypersensitivity reactions. It's not surprising, since these are associated with Taxol, that there is a higher incidence among the patients randomized to the Taxol arm in the study than there are to the AC. However, the total percentage of grade 3-grade 4 toxicities in these three categories is relatively modest.

Other adverse events. Hospitalization, no difference. Late cardiac disease, no difference. This is being monitored on every follow-up form and has been consistently. So, this applies to the entire population of patients.

Secondary malignancies occurred in 2 percent of the patients. No difference in AC and AC plus Taxol. The incidence is about what we would expect to see in most adjuvant therapy trials, and also as with most trials, about half of all the second malignancies are second breast

cancers.

Now, looking specifically at toxicities that occur while patients were receiving Taxol, again looking first at the hematologic toxicities, grade 3 and grade 4, early population here and the total population here, we see that 17 percent of the patients had a grade 3/grade 4 leukopenia while getting Taxol; 46 percent had grade 3/grade 4 granulocytopenia. As previously, thrombocytopenia and anemia are fairly uncommon with Taxol therapy.

The sequelae, infection, fever, hemorrhage, requirement for platelet and blood transfusions occurred in 1 percent or less of the population.

We look at non-hematologic toxicity, again specifically during Taxol therapy, the same group that I showed you before, and you can see again it occurs very infrequently, at most 1 percent of the patients.

Finally, we look at non-hematologic toxicity for those things that are known to be associated with paclitaxel and are unique to that drug, neurosensory, arthralgia, myalgia, and hypersensitivity. This is only while now the patients are getting Taxol and the numbers are very similar to what you saw before.

Finally, you remember that at the beginning of the presentation I showed you the dropout rate over the

course of therapy. What were the reasons why patients dropped out?

First of all, why did patients drop out of AC? First of all, the patients here who were randomized to AC and the patients here who were randomized to AC plus Taxol, but these two columns represent the dropout from AC itself. First of all, 95 to 96 percent of patients completed all 4 courses, as I've shown you before.

2 percent of the patients on each arm requested that they drop out for one reason or another. That's not specified on the case report forms. 1 percent of the patients, again the same in both arms, because of specific toxicities, and then a small number because of disease progression or a mixed category.

Now, we had 1 patient here who died within 30 days of having gotten a dose of chemotherapy, so still on active dose. That particular patient was on the AC only arm and that patient had respiratory failure and cardiac failure which was assessed to be due to neoplastic process.

Now, among these 1,570 patients randomized to AC plus T and got AC, you remember I showed you earlier that only 1,449 of those patients went on to receive paclitaxel. Now, of this group, 92 percent completed treatment. The reason for not completing it, 1 percent patient request, 6 percent because of toxicity, a small

number for disease progression and other, and there were 2 patient deaths within 30 days of a chemotherapy regimen. One had a hypersensitivity reaction as a cause of death, and one patient had a brain infarction with subsequent sepsis.

So, in conclusion, we believe that we've shown that the benefit of adding Taxol to standard anthracycline-containing therapy is similar to adding chemotherapy to surgery. The basis of saying is that when you look -- and you saw the numbers earlier from Dr. Norton -- at chemotherapy versus nil, you see a reduction in the odds of death or reduction in the annual odds of recurrence that are about the same as we have shown here in adding paclitaxel to doxorubicin.

The robustness of the results of this large study is supported by the consistency of the treatment outcomes in the two points of analysis, that is, first a presentation at ASCO in 1998 and the presentation today.

And finally, the addition of a single agent Taxol to standard combination chemotherapy is very well tolerated compared to most things that we do as medical oncologists today.

I thank you for your attention.

DR. CANETTA: Thank you, Craig.

I will just offer a very few concluding remarks

to wrap up our presentation.

We believe that the data that we have shown actually follow in the footsteps of what we have found out about the effects of Taxol in breast cancer and I think it is comforting to see that as you move to earlier stages of disease, the magnitude of the benefit increases. The pivotal study, whose results you've seen presented, is the largest trial that's ever been submitted to this agency for the approval of a new chemotherapeutic agent in node-positive breast carcinoma.

The comparison of Taxol versus no further therapy does demonstrate there is a significant effect, a significant benefit in the two important endpoints in the setting of the disease, disease-free survival and overall survival.

I'd like to point out that when you look at the subset analysis, multiplicity of analysis, but one data is very, very comforting and very reassuring. No matter what subset you look at, there is always a positive effect of Taxol, and that is very, very solid evidence that it is the drug that is exerting an effect.

Finally, although Taxol is a cytotoxic agent, I think that what we have seen in terms of the safety profile, even in this setting, is very, very consistent with what had been seen with exactly the same dosages of

Taxol that have been approved for a long time in the treatment of this disease and in treatment of other diseases.

Therefore, we do propose that Taxol administered sequential to standard combination therapy be indicated for the treatment of node-positive breast cancer.

And the dosage and schedule that we recommend is the classical standard dosage of 175 milligrams per square meter given intravenously over 3 hours every 3 weeks for 4 courses, as you have seen.

I'd be glad to take questions from the committee.

DR. NERENSTONE: Thank you very much.

We're going to open up now for questions from the committee to the sponsor. I would like to take the Chair's prerogative for just a moment and ask two points of clarification.

One, on the patients who died on the Taxol, one had a septic related death. Can you tell me what the dose of doxorubicin that patient had received prior to the Taxol?

DR. CANETTA: We need to check that.

DR. NERENSTONE: While you're looking at that, the second question is really sort of a clarification of the toxicity slides. When Dr. Henderson reviewed the

toxicity data, especially of the grade 3 and 4 toxicities, his numbers were early population and then a percentage for the total population. But in fact, aren't those numbers incorrect because you didn't have data on 1,800 patients in the middle group who did not have recording of grade 3 and 4 toxicity. They only had reporting of ADRs.

DR. CANETTA: I think I can address that. The early population, as Dr. Henderson said, is the one that has been intensely monitored, and that's very obvious when you look at granulocytopenia. Twice a week counts result in 90 percent incidence of grade 3 or 4 granulocytopenia in the early population. The late population, every patient was included in the denominator, but you need to remember that all the serious adverse events have been reported even after the early population. So, when you look at severe toxicity, of course, you have a slight underestimate, but I think it's very reassuring that for clinically important toxicities -- and you have the infection example -- the incidence is actually the same whether you monitor intensively or whether you don't monitor intensively.

DR. NERENSTONE: Okay.

DR. CANETTA: For that patient, Dr. Tuck will give you some details.

DR. TUCK: That patient was on the high dose of doxorubicin, 90 milligrams.

DR. NERENSTONE: Other questions? Dr. Blayney.

DR. BLAYNEY: You didn't specify as part of the trial protocol what premedications were used with paclitaxel. Could you review that? And as part of your proposed labeling, do you propose a premedication regimen with paclitaxel?

DR. CANETTA: Yes. During the Taxol phase, the standard three class of agents premedication was administered with a steroid, H1 and H2 blocker. We do maintain that in this proposed dosage we will retain the same type of premedication.

DR. BLAYNEY: Did the patient who died of -- it was reported as an anaphylactic event receive the premedication?

DR. CANETTA: Yes. That patient did receive premedication. It is very unfortunate, but severe hypersensitivity reaction can still occur despite premedication in a very, very small percentage of patients.

DR. BLAYNEY: Are there other medicines that you would caution physicians to avoid as part of the paclitaxel administration? For instance, trastuzumab or Herceptin?

DR. CANETTA: I think it's important to point out that there is nothing special about this patient population vis-a-vis the pharmacologic behavior of Taxol.

So, all the type of cautions that are already attached in the current package insert for Taxol for this dosage and schedule of Taxol will be maintained. So, whatever we say that refers to Taxol for metastatic disease will also refer to this population.

We are not in the possession of data of the use of Taxol and Herceptin in combination in the adjuvant setting, and we cannot refer, at least in our package insert, so we've been told by the agency, to the Herceptin data. So, I think patients and care providers will have to be directed to the Herceptin package insert.

DR. BLAYNEY: Thank you.

DR. NERENSTONE: Dr. Raghavan?

DR. RAGHAVAN: I have two questions. I guess Dr. Henderson drew out the issue of receptor positive disease and showed that there was a reduction, but probably the least significant level of reduction. I'm just interested just to confirm that the randomization was not stratified for receptor status.

And secondly, the group with 10 nodes positive disease seemed also to be one with a relatively small impact, and the question on that relates to does Dr. Henderson feel the study was well powered to identify clearly the level of difference in that context.

So, the questions are receptor positivity. Was

the stratification included for receptors? Second question, lymph node 10 plus. Were there enough cases to have a strong feeling of where that fits into the scheme of things?

DR. CANETTA: I'll let Dr. Henderson answer.

DR. HENDERSON: First of all, there was no stratification based on receptor status.

Secondly, when you read over the statistical section -- and I very carefully checked this, writing the paper -- there is no mention even of the possibility of doing that subset analysis. That was an unplanned subset analysis and even the overview data that we've shown you weren't out at that point. This idea of doing subset analyses in receptor positive patients is something that really has popped up in the last couple years, maybe even in the last year, year and a half, and not something that was done before that.

The second question had to do with the power within the group that has more than 10 positive nodes. The way I look at this is to ask the statisticians to say can you tell me that there is a significant difference, using a regression model, in these three groups, even though it would appear that way just by eyeballing it. And the answer has come back repeatedly no. There is not evidence of a significant difference.

Now, I believe that that's because of the difference in the power in the first two groups, 1 to 3 and 4 to 9, versus the 10 group. But using a test for trend, for example, you do not see a significant difference.

DR. NERENSTONE: Dr. Lippman.

DR. LIPPMAN: Yes, I really had a related question to Dr. Raghavan's regarding the subset analyses, because this will come up again I guess in the FDA presentation. I'd like some thoughts from your statisticians perhaps on the issue of subset analyses because, particularly if you look at overall survival in the two different receptor groups, it's 17 percent reduction in the positive group and 29 percent, so still substantial in both groups. It wasn't a prespecified subset analysis, and I guess from Dr. Henderson's presentation, it has never been done in a prespecified way in any large phase III adjuvant study. When you look at the graph and the confidence overlaps on the overall survival between the two, it's pretty large. So, how strong is that particular subset analysis for clinical recommendations to patients?

DR. CANETTA: Dr. Don Berry will address this.

DR. BERRY: Subset analyses are problematic, as you know. This was unplanned. Is the result strong? Is the result real? I don't know. I don't think anybody can

say. I think that it is a subset analysis and that there is no difference between the two. It may turn out, as we go down the line, that other studies show that there is a relationship and that's one of the reasons we announced the study when we did is so people could look at this question. I don't think it's very strong.

DR. LAMBORN: While you're up there, could I just ask a clarification? The actual test for a difference or for an interaction was non-significant or what was the p value? I recognize that it is a subset analysis. We don't have the information about the potential difference.

DR. BERRY: It actually was significant at the time of the ASCO presentation in terms of disease-free survival. It is not significant now. Am I correct in that statement? The test for interaction using a Cox model in which receptor status and Taxol is included in the interaction term. I don't believe that it is significant now, but it was at the time of ASCO.

DR. NERENSTONE: Dr. Williams, did you have a question?

DR. WILLIAMS: I do have a question regarding Dr. Henderson's statement about looking at subgroups on receptor status. Somewhat different but extremely closely related is looking at the effect of chemotherapy in patients who have received tamoxifen. Obviously, that's

the very same group we're talking about here, not just their receptor status, but the fact that all patients were supposed to receive tamoxifen. Certainly it looks like in the overview that was addressed specifically, and I would imagine that goes back some years. Whether or not you do it within a trial is another question, but clearly it was specifically addressed as a concept that there might or might not be an effect in this group.

DR. CANETTA: We have a few slides to show and Dr. Henderson will present.

DR. HENDERSON: First of all, we didn't show you the data separately, actually prepared slides, for the overview data ER and tamoxifen. The reason we didn't show them to you -- and I don't know whether we have them here. We can -- is that my feeling was that when you look at the overview data, the interaction is stronger for ER than it is for tamoxifen.

Now, if you look at the four groups, because the way the overview is set up, it's under 50 and over 50. You don't have the whole population put together, as I'll underscore in just a minute. That's the way the data were shown to you.

For example, the tests for interaction on all but one of the subsets for ER are negative. Only one of them is positive.

DR. WILLIAMS: Could you clarify what you mean by that?

DR. HENDERSON: Well, if you do a formal test for interaction so that you say is there an interaction between the effects of therapy and the presence or absence of an estrogen receptor or the effects of therapy and the presence or absence of tamoxifen, the formal tests for interaction are negative.

As you know, that's not a very strong or very robust statistical test to use and some people aren't enthusiastic about it at all, but nonetheless, that was done as a formal evaluation and led people like Richard Peto to say we don't see a significant difference in those two populations.

Let me just show you briefly. First of all, these are the results using the Kaplan-Meier estimates for AC and AC plus Taxol disease-free at 1 year, 2 years, and 3 years. This is for the entire population.

The point that we're going to make is that it's important to look at your patients at risk and look at the confidence intervals around the estimates in the receptor positive patients at each of these points. This is for the entire population of patients, but if you look at just the receptor positive subset, you'll see that as we get further out, the confidence intervals around any differences grow

larger at each point.

The take-home point then is that our ability to use just a single point, such as 3 years, which was put into the questions and the summary of the questions, is probably inappropriate. You want to look at the growing effects, and you can see a difference with fairly tight intervals of about 1 percent at 1 year in the ER positive patients in absolute difference in disease-free survival and about 2 percent at 2 years. At 3 years you see a smaller effect, but with very, very wide confidence intervals.

DR. TEMPLE: Is that for the whole population, Craig?

DR. HENDERSON: Pardon.

DR. TEMPLE: That's for the whole population. Right?

DR. HENDERSON: Yes. No. This is for the whole population. The slide I wanted up here -- we just made a mistake. Sorry about that -- was patients who were receptor positive. And maybe they'll get that up for you in a moment.

DR. WILLIAMS: So, where would be the appropriate -- I mean, in a normal adjuvant trial, we would have enough data that we would have a 5-year survival and that would be probably a fairly appropriate place to look.

This is just as close to the plateau as one can get with these data, which are somewhat premature. If you want an estimate for women of what's going to be the case based on these data, you have to pick some point other than a hazard ratio which has little meaning.

DR. HENDERSON: Why you think a hazard ratio has little meaning?

DR. WILLIAMS: Because there's an absolute risk of death from breast cancer in particular women, and that absolute risk times the relative change in that risk is your benefit. A 20 percent benefit, if there's a 1 percent risk to start with, doesn't mean much.

So, these women obviously have much less risk of recurrence, and that relative risk, regardless of how confident you are of it, overall means less in that setting.

DR. HENDERSON: I would take a slightly different point of view. First of all, in terms of using hazards or, as we have done in the last 15 years in the breast cancer literature, using reductions in odds of death or reductions in odds of recurrence, the annual reduction in odds of death or the annual reduction in odds of recurrence have been constant across all the subgroups that we've looked at carefully with one exception well established, that is, between ER and tamoxifen. So, when

you use tamoxifen, the reduction in odds is much greater in receptor positive than receptor negative patients.

We're working hard on that question to say is that true for HER2 positive patients, but I would say that's still a point of great controversy and we certainly haven't looked at it yet in the adjuvant setting with any statistical power.

Now, we have a third possible interaction where the reduction in odds is different. That's a hypothesis, hypothesis generated in part by this trial, that maybe there is an interaction between chemotherapy and receptor status that is a qualitative rather than a pure quantitative interaction.

Now, when you accept those three, now you go back to all the other subsets. Until proven otherwise by careful prospective trials, it is reasonable to take the reduction in annual odds, which is almost always, I'd say, very, very close to the difference in hazard. In other words, 1 minus the hazard rate is going to be very close, within a percentage or two, in almost all cases to the reduction in odds.

Now, for a doctor practicing, what I usually encourage doctors to do is say calculate what the risk is to your patient. You have to consider these qualitative interactions, but for all other subsets, take your estimate

of 10-year mortality and multiply that by the reduction in annual odds. That's doable because what we have seen in almost all studies that are done is the reduction in annual odds is constant. In fact, if you look at the longest trials we have, the ovarian ablation trials which go back to 1948, you can show that the reduction in odds is constant up through 25 years at almost all time points. So, what is going to be dependent is what are going to be the effects within or the risks within that particular group.

So, I would say that for the overall analysis, I certainly wouldn't call these premature data when you have this much statistical power, but for the subset certainly these would be early data.

DR. WILLIAMS: Your statement that you expect the same proportional reduction in these groups -- didn't the overview show a different proportional reduction like 19 percent for the 50- to 59-year group that received tamoxifen versus a higher percent, around 30 percent, for the groups overall? So, the proportional reduction in recurrence was not estimated to be the same for patients who had received tamoxifen versus the other patients studied.

DR. HENDERSON: That's a good point. I probably should put that into a fourth category. We have a

tendency, and have for some time, to a priori divide our patients into pre- and post-menopausal. So, that's a very well taken point. And the effects in older and younger women of chemotherapy are clearly different. For tamoxifen they're not clearly different.

DR. WILLIAMS: That's not older and younger. This is the patients who had received tamoxifen, those trials, plus or minus chemo versus the other patients. It wasn't specifically an age factor, and that's exactly the question we have here, the patients who received tamoxifen versus those who didn't.

DR. TEMPLE: You don't show tamoxifen yes or no. Actually the data look even more different when you do.

DR. HENDERSON: I'll show you those data right now. Okay? So, let's go back one slide.

This was the slide I wanted first. This is just now looking at disease-free survival for the receptor positive subset for the 3 years follow-up. The point that I was trying to make and describe to you before were the differences in the confidence intervals around a 3-year figure, for example, compared to either a 1 or a 2-year figure, just emphasizing follow-up is important, the duration and the number of patients at risk.

Next slide please.

DR. TEMPLE: Craig, before you leave that, we're familiar with the treacheries of subset analyses. Okay? We know that. This is a little striking, though. Two-thirds of the patients randomized seem to have not much going on and all of the good action is in one-third.

So, I guess one question you need to address is, when does something that you didn't plan overwhelm you so much, look so strong that you should believe it anyway? Some people would say the answer is never, and I always quote Salim Yusef and all that. We all do that.

But still, that's the question here. This is two-thirds of the population. It's not some little subset that emerged, and it can be defined either by receptor status or by the use of another tamoxifen. Concomitant therapy is the sort of subset one does look at. That's not pulled out of left field exactly.

DR. HENDERSON: Let me address that question, but let me finish the first one, which is just looking at the hazard risk for the two populations, the receptors which I showed you a moment ago, these again. Disease-free survival. These are the data that I showed you for disease-free survival.

Next, overall survival.

Next, this is now for tamoxifen, disease-free survival. This is the overall estimate. This is now the

patients who did not get tamoxifen and those who did get tamoxifen. Looking at this as receptor positive/tamoxifen or receptor negative/tamoxifen and so on is not very informative because the number of patients in these subsets, other than the two major ones, get down to 125 patients to 150 patients at risk. So, we don't think that that's very meaningful. So, this is disease-free survival.

Next, overall survival again for the group as a whole and then the two subsets where you see wide overlaps for the tamoxifen, just as you did for the receptor.

Now, next slide please. This is getting now to more directly addressing your question. This is the effects of adjuvant chemotherapy in estrogen receptor positive patients from the overview. Now, again as I've told you, we have to look at younger women and older women separately because that's the way the data are available to us. Again, we see this same difference -- this is younger women -- in the effects of therapy in the receptor positive versus receptor negative. Among older women, it's even more marked, but again an overlap in the confidence intervals.

Next, please. And the effects now in terms of reduction in annual odds of death. Again, you can see that when you look at the younger women -- and you're looking now at adjuvant chemotherapy, over 1,000 women now in this

subset -- you see that for the receptor positive patients, there in fact is not a statistically significant survival benefit from adjuvant chemotherapy either in the receptor positive women under age 50 or the receptor positive patients over age 50, while it's in the group who are receptor negative in which you see significant survival advantages. Again, you see this same pattern of difference.

Next slide, please. Now, for this particular study, I think it's too early to make a firm conclusion because in the receptor positive subset, there appears to be a smaller benefit, but the relative effects are quite similar to what you see in the overview. And we believe that as time goes on and we have more events, particularly in this particular subset, the picture will become clearer.

So, now coming back to your direct question, when do you decide on the basis of a subset analysis, even if it's very large, that you are not going to give therapy to that particular group or that you're going to change therapy on the basis of an unplanned subset analysis? I would go so far as to say that thus far I've been resistant to doing that consistently across the board in all cases. It seems to me that what you do is a subset analysis. You generate a hypothesis and then you go out and test it.

The best example in my experience is in the

issue of HER2. Should we use HER2 to select patients for therapy? Our first subset analysis, which we published a few years ago, showed a p value which was way out there. I don't remember. .001 or .0001. And then our subsequent analysis wasn't quite as clear. When we look at all of the data, it's still being sorted out with results that are not totally consistent. Is this due to doxorubicin? Is it due to dose?

There were people who were prepared to argue on the basis of that first study, which is a very large study, 1,800 patients in the entire study randomized -- or 1,500. I've forgotten the number that were in the HER2 subset, but it was about 600 I think. So, it was a very large subset analysis. There were people who were saying we should declare a change in therapy at that time, others who said let's wait. I personally was in that latter group and I would be in that latter group here as well. I think that the issue here is probably not an issue of Taxol. This is an issue of chemotherapy and probably applies across the board.

But I've been writing for a number of years on the issues of chemotherapy in older and younger women and some of these issues whether we should give chemotherapy at all. The way I usually present this is to say your first question is, is chemotherapy appropriate in a particular

patient? And then your second question is, if it's appropriate, then what is the marginal advantage of going from CMF to cyclo/adria, of cyclo/adria to cyclo/adria plus Taxol? Then what is the marginal increase in toxicity? And then asking the patient whether that's worth it to that patient. So, to me that's the thinking that you go through, but you wouldn't jump to the end of that process and say, I'm going to not give Taxol for this particular group of patients, but I would give cyclo/adria to that group of patients. I don't think that that's the appropriate sequence for thinking out the problem as a clinician.

Does that answer the question you're asking, in other words, when and why?

DR. WILLIAMS: I hate to keep going here. This is not our usual format. But this is the most central point for us.

I want to ask Dr. Berry, who mentioned the point about the interaction. I do remember now where I read that and it was in your study report that there was interaction either with tamoxifen or the estrogen receptor. So, I would imagine it holds up for these data, and if it was really present at ASCO, that means that there was a very strong interaction almost certainly at two times because you had less data then. If it was positive then

with less data, that means that the effect was even stronger.

DR. BERRY: Yes. I want to correct something that I said to Dr. Lamborn.

By the way, I'm responsible for this subset analysis. I plead guilty to that. It's difficult for me not to look at these things, and my attitude was similar to Dr. Temple's. I must say over time I've been moved in the other direction.

This is the disease-free survival, Cox regression, and you see the usual covariates, number of positive nodes, et cetera, menopausal status, not significant. This was the issue that Dr. Lamborn raised. The interaction between Taxol and ER status is statistically significant but barely, and the next slide shows the corresponding thing for survival and it's not statistically significant.

At the time, Dr. Williams, of ASCO, indeed it was more highly significant than this.

And Dr. Temple is right. We don't have the corresponding Cox regressions for interaction with tamoxifen, but there is a somewhat stronger, although not incredibly stronger, interaction with tamoxifen.

I would like to address something else that Dr. Williams raised. Could I have the next slide? This is the

hazards over time, and this is a compelling picture for me. There are three curves on here. One is the AC plus Taxol. Another is the AC alone, and the third curve, the one that extends out here -- and I can't tell the difference between these two colors and I guess it doesn't make any difference. But this one is our previous study, CALGB 8541. These are hazards, which means that one calculates the number of recurrences in a given time period, divided by the number at risk in that time period. So, it's like an actuarial comparison.

What that means is that these comparisons at 3 months and 9 months are really independent. The set of occurrences in this time period is different from this, is different from this, and you see that the benefit -- the hazard ratio that we're talking about is averaged over this entire time period. You see the benefit of Taxol occurs early, and these are like four or five independent analyses. They're all in favor of Taxol.

The point I want to make here is that the benefit of chemotherapy -- and it's not just in this study, but in every study in node-positive breast cancer -- occurs early. After 3 or 5 years, there is essentially no benefit. The overview looks exactly like this, and the hazard for node-positive disease returns to the hazard for node-negative disease. If you were node-positive 5 years

ago when you had breast cancer and you're still alive and disease-free now, you're essentially like you were node negative at diagnosis.

So, I think it's compelling that the benefit is in the early time period. It's exactly where we would expect the benefit to be for a chemotherapy.

DR. NERENSTONE: Dr. Lippman?

DR. LIPPMAN: As a non-statistician, I tend to have a very negative view of subset analyses because, first of all, this is a secondary analysis and a subset analysis. When you look at the subset table, the changes over time, although under disease-free survival there's a bigger difference in receptor status, they come together under overall survival, and there are much bigger differences, for instance, when you subset out the nodal groups. So, I think in terms of planning patient management on this, this is why I raise this, whether we're confident about an unplanned, secondary, subset analysis.

DR. CANETTA: I would tend to agree with Dr. Lippman's statement. I think that in this subset analysis story, what again it is important to keep in mind -- and we're all aware of the vagaries of subset analyses, we're all aware of the problems of multiple analyses. But one consistent thing that has happened in this subset analysis is that no matter what subset you look at and no matter

what endpoint you look at, because this is true for both disease-free survival and for overall survival, every single analysis comes with a direction in favor of the use of Taxol. And that is consistent with what Dr. Berry was talking about.

DR. NERENSTONE: Dr. Lamborn?

DR. LAMBORN: I'd like to ask one question about the subset analysis. Sometimes things will happen over the course of the trial where you have new information, and therefore, while it is a subset analysis, there is a medical logic to why you're looking at it, where perhaps you didn't originally plan it. What I thought I have heard is that there has now been a large evaluation of adjuvant chemotherapy which said that the risk reduction would be expected to be substantially less in the node-positive. So, in a sense, this is not one of a whole set of cases. So, I just wanted to make sure I understood what it was we were saying.

DR. CANETTA: Dr. Norton or Dr. Henderson? Can we give a chance to both of them?

DR. HENDERSON: If it had happened the way you described --

DR. LAMBORN: Excuse me. ER positive.

DR. HENDERSON: There are two possible scenarios here. One scenario is that the committee of

investigators or the CALGB breast group said, look it, this is becoming an important question and turned to our statistical group and said, let's look at it because the hypothesis has been generated. Now let's look at it in our data. That's one scenario. That kind of a scenario implies what you were suggesting. There are other people that have generated a hypothesis. People are beginning to think about it and now going forward.

The other hypothesis is you've got somebody sitting there saying, well, let me just look at the data and see what happens in this group and happens in this group and happens in this group. As you know, the probability of getting a false positive result in subsets when you do that approaches 50 percent. So, that's why we usually don't do that.

Now, which scenario applies to what we showed you? The latter, not the former. The first time that I had ever seen these data, had ever thought about it and so on was when the data were sent to me after the data safety monitoring committee released the data. It had not been something that had been discussed or planned or anything prior to that. So, it was not something where the scientists and the physicians involved in the study generated and said, let's ask this question, but rather an individual looking at it privately came to that conclusion.

So, that's why I describe it as a hypothesis generating subset analysis rather than a test of the question.

DR. NORTON: Could I just clarify this again just to sort of emphasize it again? Because I think there's a danger here that there's a lot of people who potentially could really benefit from Taxol who may not end up getting it depending upon what this committee does, and I think it would be a very bad thing if that happens. The reason I'm saying that is because let's just look at these curves again in this thing.

These are overall because there are a lot of patients here. You subdivide it. You get wider confidence limits. Of course, that's always going to happen. And you see that the effect by ER negative/ER positive, that this is now subdivided and there's a little bit less effect in ER positive and a little bit better effect in ER negative, and they average out to an overall effect. This is for disease-free survival.

Overall survival, same thing. They subdivide out. The real issue here -- I mean, the median points here, the central point of effect is still good. It's just that the confidence limits widen out, and that's why we see this. And the confidence limits widen out because we're dealing with a subset analysis here.

Next slide, same thing. It moves in a positive

direction, but wider subset analysis.

Next slide. This is by overall survival by tamoxifen use, the same basic thing.

Next slide. The point I want to make is if you look at the whole worldwide overview, you're dealing with much larger numbers. Obviously, these get further away from the 0 line, the no effect line, because you're looking at chemotherapy versus nothing. Before we were looking for Taxol adding to AC, which is already good treatment. So, the magnitude of the effect is going to be somewhat reduced. But it's the same basic direction. The reason why these are impressive is because the larger numbers involved bring the confidence limits down and so it pulls it away from the line of no effect.

Next slide, please. In fact, when we start to do this with more reasonable comparisons, this is the effect on subsets by age in the overview, you see that basically you do, indeed, come to conclusions that the impact of therapy on the ER positive group, whether they're older or they're younger, starts to even get into that category. They start to actually get into this no effect kind of group.

Now, universally worldwide, we're giving chemotherapy to ER and PR positive patients that are pre-menopausal and post-menopausal. If this number were not

7,000 but this number were 70,000 or 100,000, then the confidence limits would shrink down and the patients would clearly be receiving benefit. There's absolutely no doubt about this. Because we're dealing with a trial that's a huge trial of over 3,000 patients, but it's not 20,000 patients, with the exact, same magnitude of the effects here, that we could be misled into denying patients therapy that could be lifesaving for them. And I think that we really have to be aware of this as a potential danger. It's really not a matter of subset type things. It's a matter of when you subset, you have a smaller number of patients and you have wider confidence limits.

There are very good kinetic reasons why the effects are so. ER positive disease grows more slowly. The effect of chemotherapy may be less because it's growing more slowly, as is universally seen in all models we've looked at. But also, it takes longer to see a benefit because it takes longer for patients to relapse. So, for very good kinetic and logical reasons we get these basic effects, exactly the same effects we see for chemotherapy universally in all of our experience as summarized in the worldwide overview.

DR. NERENSTONE: Dr. Johnson, did you have a question?

DR. JOHNSON: Yes, I had a couple and it had

nothing to do with subset analysis --

(Laughter.)

DR. JOHNSON: -- although I'm thinking about asking one now.

(Laughter.)

DR. JOHNSON: I had two questions. One had to do with the cardiac toxicity which seemed shockingly low to me, especially in light of yesterday's presentation where we saw a lot of data about the use of single agent doxorubicin. I guess it matters how one assesses the cardiac toxicity in order to make that determination.

So, it wasn't very clear to me how that was done in this trial, even in that first 300 patients. Were they required to receive MUGA scans, for example, and if so, on what basis and how frequent?

As a corollary to that, do we know what the late developing cardiac toxicity might be in an individual who receives AC followed by Taxol? We know, I think, a lot about giving the two together, but what about the sequential use of these?

DR. CANETTA: For the cardiac toxicity, can we show that?

While the data are being sorted out, let me make a statement concerning your last question, the sequential effect. The monitoring of this trial continues

and continues for late cardiac effects and for secondary neoplasm, as you know. Very recently in August, we filed the 120-day safety update, which is mandated by law, to this NDA. I can tell you that there was no difference again between the incidence of cardiac effects occurring late in patients who received AC as compared to patients who received AC followed by Taxol. By the same token, there was no difference in the incidence of secondary malignancies even with the 120-day safety update.

Here is the data. This is the data for the cardiac toxicity during the period of follow-up. As you can see, we decided to display this by doxorubicin dose, given the fact that there was the 60, the 75, and the 90 milligrams per square meter dosage. There seems to be a certain increase of cardiac toxicity that is not really related to Taxol but appears to be more related to the dosage with Adriamycin administered. That's not surprising.

DR. HENDERSON: I think the important thing, comparing yesterday and today, is the fact that the maximum dose of doxorubicin, cumulative dose in the study is 360 per meter squared. As you know, you don't really see a lot before you get to that point.

The second this is that when you're randomizing 3,170 patients and you multiply that by the cost of the

MUGAs, if you're obtaining them on a regular basis, the costs are astronomical. We didn't feel that the costs justified the kind of intense monitoring that took place in the study you heard yesterday or, for example, in the Zinecard preparations. So, we had a baseline MUGA on all the patients. We require that every single follow-up form provide information on whether there have been any cardiac events of any type since the last follow-up form. So, unlike some of the data where it's hit and miss, this is one of the things that has been monitored on every follow-up form from day 1.

I was just checking the exact day. I think it's 5 years, but there is a required MUGA, as part of the long-term follow-up, and we felt that it was more important to look at this for all patients at the same point in time, but some time out. As you know, cardiotoxicities often do not manifest early and particularly not in an adjuvant setting. It becomes more manifest particularly when the patients relapse and undergo the extra stress to the heart and the various things that affect it.

So, I think that given 360 per meter squared is your maximum dose and given the fact that we're not intensely looking for things, that this is probably very reasonable to what a practicing oncologist would see.

DR. CANETTA: If we can show the slide, let me

back my statement with the actual numbers. This is the 120-day safety update. As you can see, these are percentages, and there is no difference between the two treatment arms. This is consistent with what was presented in the NDA.

DR. JOHNSON: Now, what does cardiac function mean?

DR. CANETTA: This is left ventricular ejection fraction as contained in the follow-up form.

DR. JOHNSON: Is that statistically different?

DR. CANETTA: It's a reduction of the LVEF.

DR. JOHNSON: I don't understand. So, 40 patients in the AC had a reduction versus 56. Nearly 50 percent more? Is that what you're saying?

DR. TUCK: Because of the way the data was reported, it's not possible to give, for instance, a breakdown of the not specified. This could include a variety of different kinds of --

DR. JOHNSON: No. I'm looking at cardiac function there. It says cardiac function, 40 under AC, 56 under ACT, total 96. I think those two add up.

DR. TUCK: It's not statistically significant according to the statisticians.

DR. JOHNSON: Just in response to Dr. Henderson's comment from yesterday. Actually the data

yesterday showed -- and I agree that clinically we don't see much in the way of cardiac toxicity, but in that intensely monitored group, actually the largest number of events, as it were, occurred between 300 and 399 milligrams per meter squared of doxorubicin of left ventricular ejection fraction decline, which if that in turn is a marker or a surrogate endpoint I guess for subsequent cardiac problems, it might be interesting to know in that first 300 patients. I like the idea of doing the late follow-up, though. I think that's critical.

The second question I have, though -- and actually Dr. Norton addressed this in his overview, and I'm appreciative of what he had to say about the number of cycles, but I want to go back and ask this question very specifically. That is, is the difference here Taxol, or is the difference here cycles of therapy? And if it's the difference in therapy, I would sort of like the impression of the two breast cancer experts on their thoughts about this.

DR. CANETTA: Dr. Norton will give you the answer.

DR. NORTON: We thought about this very hard, and I think you don't know for any individual patient obviously if you're eradicating all, let's say, the AC sensitive cells with 4 or if you need 5 cycles. There

probably is some small percentage of patients that would benefit from a little bit more of a monotherapy, but it's probably going to be very small. Obviously, we thought about this very intensively both in the design of the analysis and the study.

If you look at the worldwide overview, this splits it down by -- these are all the longer versus shorter regimens, and these are the regimens that were longer than shorter ones, but the shorter ones are at least 6 months, and the more relevant ones are longer versus regimens that are less than 6 months, especially these last four which are basically 6 cycles versus 3 cycles of something, three of them with CMF and one of them with epirubicin. As you can see overall there, if there is an effect at all of duration, it's in the 7 percent reduction range with a standard deviation of 4, which doesn't meet statistical significance. Even if you look at the most relevant ones, you can see that the confidence limits really overlap the no-effect curve for longer versus shorter. This one actually goes in the other direction. These may go in a direction, but it's a very, very slight effect.

This particular study with longer follow-up was recently reported, and the confidence limits just barely shrunk down to make it. This is the only one. It's an

outlier effect, and it took a long follow-up to basically see the effect. So, there may be an effect of duration, but it's a very slight effect and it doesn't come close to the magnitude of the effect we're seeing in this trial.

The next, by the way, just shows the exact, same thing. This next slide just shows for mortality. In mortality the points I was making are made even more clearly.

DR. JOHNSON: Now I'm going to try to expand on this just a little bit, and the statisticians may come to my rescue here because I'm going to ask sort of a statistical question I think. How confident can we be of these data that this is not simply a duration effect? In other words, you've just shown us a 7 percent difference, and the magnitude of the difference here I see is quite large, in the 25 percent range. In other words, do those two confidence intervals overlap or are they really separate --

DR. NORTON: Well, in the overview it's 7 percent for recurrence-free survival, less for overall survival. Neither of them reach statistical significance. Here we're talking about 22 percent and 26 percent reduction in death rate, both very statistically significant and early on. Obviously we have a very large trial and a large number of patients giving us great power,

so that's why we're seeing it early on. But these are the 7 percent and less than 7 percent, not statistically significant, with 15-year follow-up. You see? So, if we're seeing these kinds of magnitudes this early, you can imagine how good it's going to look in 15 years. So, I think it's really very clear we're seeing something very different here than any kind of subtle duration effect.

DR. NERENSTONE: Our time is running a bit short. Drs. Temple, Lamborn, Raghavan, and Blayney all have questions. Dr. Temple?

DR. TEMPLE: When you showed the subset analyses for the overall population, one of the things that was, I guess, impressive was that whatever the number of nodes, tumor size, et cetera, the hazard ratios were all the same. Did you happen to do that for the tamoxifen treated and for the no-tamoxifen groups? I'm absolutely sure I know what the answer is -- I mean, I know what the result of that is going to be, but each subset is going to show nothing on the tamoxifen treated patients. Right?

DR. CANETTA: I think actually Dr. Henderson already showed that. We can show it again, the hazard ratio bar graphs by tamoxifen treatment.

DR. TEMPLE: For each of the node subsets and tumor size subsets, things like that.

I'm making the point that to achieve a hazard

ratio of approximately 1, you're going to have to have the same effect in all of the subsets that were impressive before because they all showed the effect. It's just that there's a consistent finding. What to make of it is a tough question. Do you understand the analysis --

DR. CANETTA: Yes. We'll try to pull out the data, if we can.

DR. BERRY: I don't understand the question, Dr. Temple. Are you saying that if you restrict to those who were treated with tamoxifen, what do you get? If you restrict to those who were not, what do you get? Are you saying if you look within 1 to 3 nodes, do you get the same effect for tamoxifen interaction?

DR. TEMPLE: Yes. One of the things that's always impressive in a large database is that you look at all the reasonable subsets and you find the same effect in all of them. That was done for the entire population.

My guess is if you do that, dividing the population up into the tamoxifen treated and the non-tamoxifen treated, or receptor positive/non-receptor positive, you will see the same phenomenon. The subsets will all look terrific for the receptor negative ones and the subsets will all look like nothing for the receptor positive ones or the tamoxifen treated patients.

DR. BERRY: Yes, you are absolutely correct in

what you say. If you look at 1 to 3 positive nodes, 4-plus positive nodes, and you look at the potential interaction with tamoxifen, it's essentially the same in both.

And the effect of Taxol is the same in both. In fact, it's essentially statistically significant in both of those groups.

DR. NORTON: These are the actual data that we pulled up because we analyzed. This is the overall effect, which is good, narrow confidence limits. The one thing that moves up here is -- and this is the one. This is the ER positive or hormone receptor positive getting tamoxifen. It moves up. The others are down. This even could be a statistical fluke outlier, frankly, because the others move in the direction. But even here, even in this subset, the midpoint is still below the 0 line.

Remember, we're talking about subsets of subsets, 129 patients, 800 patients, 150 patients. So, when you start to get subsets of subsets, you're going to get variable data.

DR. TEMPLE: I didn't mean the very small ones. It's just the observation you made before, that when you break it down by receptor status, it looks different. It looks even more different actually when you break it down by whether or not they were treated with tamoxifen because in the small subset of receptor positive people who weren't

treated with tamoxifen, Taxol looked okay again.

DR. NORTON: Yes, but it's a subset of a subset, and who knows what to make of this. This was all unplanned. Patients were not randomized to tamoxifen. It's hard to know what to make of that.

DR. WILLIAMS: Before you leave that slide, I don't think that's a random subset, though. That is the group that would benefit from tamoxifen. The others wouldn't. So, it's not at all illogical that if the tamoxifen effect was competing for the chemotherapy effect, that that group alone would show it.

DR. NORTON: Yes. Obviously you would see it in that effect, and it would be a lesser effect. But we're dealing now with 1,900 patients. We're not dealing with 190,000 patients. You know what I mean? It's not a matter of direction. It's exactly as the overview. It's a matter of the confidence limits and it's a question of how far you want to drive it. But it's entirely consistent with our whole worldwide experience over 15-20 years.

DR. TEMPLE: That's been said multiple times.

The idea that there's a difference between the groups in the overview is one thing. You're talking here about hazard ratios that are very close to 1.

One thing that Dr. Berry may want to comment on -- it has come up several times -- that patients were not

stratified by receptor status. What I always learned is that when you're talking about a characteristic that's very common in a large study, such as receptor status or something like that, it's a pretty fair assumption that patients were randomly assigned to treatments whether they were receptor negative or positive. You're talking about 2,000 patients and 1,000 patients. That is not likely to be a problem. There are plenty of other problems in interpretation, but that doesn't seem like it would be one of them.

DR. BERRY: Yes, I absolutely agree.

DR. NERENSTONE: Dr. Lamborn.

DR. LAMBORN: I'd like to go to a whole different topic, which is the issue of how do you interpret the p values in this environment and the issue that came up of the fact that there was a decision to announce the results early, that the results have to be interpreted in the context of interim analyses, and there's obviously the recognition that if you look at the data multiple times, that you have an inflation of the p value.

I would like to get a sense from the thinking of the group that made the decision to make the announcement early. As I understand it, there was a change from the original stopping rule planned and the announcements were made early. So, I'd just like a

discussion of that and the implications of that for our ability to evaluate how strong this data is.

DR. CANETTA: The data safety monitoring board of the CALGB proceeded with this decision. I'd like Dr. Berry to discuss it. I just want to make the point that Bristol-Myers Squibb was not part of the DSMB and appropriately so.

DR. BERRY: This is to discuss a bit about the DSMB deliberations. I can't tell you what the DSMB deliberations were in closed session because I was not there. I was not on the DSMB. I reported to the DSMB, and so I can tell you what my deliberations were.

I was the person who drove from Charlotte in the wee, small hours of the morning and lost sleep over this study. That is not the first time I've lost sleep over this study. I lived with it in the days when I was the only one who knew the results. We presented to the DSMB blinded results by three arms. They did not know that the three best performing arms were the Taxol arms, and I lost sufficient sleep that I wanted them to share my grief and I unblinded them in the early days of the study, December 1996 -- not early days, but after 2,000 patients, when patient accrual was continuing. My question to myself and the DSMB is, is it reasonable to continue with accrual of this study in view of the results?

So, I'll address to some extent Dr. Lamborn's questions about significance testing, adjusting for interim analyses, announcing early versus early stopping, the factorial design and early monitoring, the receptor status interactions we've talked about, potential for treatment crossovers, predicted probabilities and power calculations versus ethics.

At the time that we announced the results of the study, all patients had completed therapy. In fact, the last patient was entered on April 15th of 1997, a year before we announced the results.

The predicted probabilities of positive significance results after 1,800 events were considered, and delayed announcement might have denied some women the potential benefit of receiving Taxol. That was a critical issue.

The O'Brien-Fleming -- this was based on four analyses including the final analysis at 1,800 events. Of course, it wouldn't be a final analysis. We'll continue to monitor this study -- indicates a p value of .000007. It's extremely conservative, and we did not reach it. So, strictly speaking, the results at that time were not statistically significant, even though the nominal p value, the actual p value if we ignore interim analyses, was .007.

O'Brien-Fleming boundaries were proposed for

early stopping. This is not a question of early stopping. We had stopped the study. There was no accrual of the study. The question was should we announce the results early or not.

There was no consideration in the protocol to adjust for a significance level for the factorial design. That was my fault and so, strictly speaking, we couldn't obey what the protocol told us to do.

The predictive probabilities -- and this was very important to the DSMB I'm led to believe -- of a statistically significant result, if we went to the 1,800 events in May of 1998 for Taxol versus no Taxol, the probability of statistical significance was 93 percent. At the current time with 624 events, it's 99 percent; that is, if we were to continue and monitor it to 1,800 events, it's very likely we'd get statistical significance.

DR. LAMBORN: Could you just clarify under what assumption?

DR. BERRY: Yes. This is a Bayesian calculation assuming a non-informative prior.

This is related to Dr. Williams' question about 1 year, 2 years, et cetera. The data are essentially in at 1 year. There is a highly statistically significant difference at 1 year, and so if we were to go 30 years from now, this observation is essentially the same now as it

will be then, and this is about a 40 percent reduction in disease-free survival. And similarly, about a 45 percent reduction in death.

This is a picture I showed you before, and in this region we have essentially complete data. So, these results are not going to change even if we were to follow up longer.

One further question about this subset thing. I didn't mention it. One of the reasons for announcing the results was precisely so that laboratories could address this question of Taxol versus tamoxifen or Taxol versus hormone receptor status, and that is being done. To my knowledge, the only extant explanation, to address one of Dr. Lamborn's earlier questions, biologically for the relationship is HER2 nu and estrogen receptor status. There's a negative relationship between the two. HER2 nu is known to affect Taxol. There are some people who publish results showing sensitivity, some showing resistance. If indeed there's sensitivity, then this might explain some of the interaction, but it cannot explain all of the interaction.

DR. NERENSTONE: Dr. Raghavan? Dr. Blayney.

DR. BLAYNEY: On page 20 of your briefing document, you talk about the patients who were over 65 years old. 94 percent of your patients were less than 65

years of age. Dr. Henderson went through a nice step-wise progression of how he counsels a patient regarding the benefits of chemotherapy. For those breast cancer women who are estrogen receptor negative who are over 65 or for those breast cancer women who might be candidates for chemotherapy who are over 65, do you feel comfortable in proceeding to the last step of your progression, which includes AC followed by Taxol, based on this data?

DR. CANETTA: Before we discuss the efficacy subset, let me make a statement that I think is pertinent to this. As part of our study report, we did analyze toxicity in this subset of patients, and I can tell you that when you look only at the AC plus Taxol arm and you compare younger patients or 65 and older patients, the incidence of grades 3 and 4 granulocytopenia in the entire population is 50 percent for the younger patients, 55 percent for the older patients. The incidence of infection is 6 percent, 6 percent. So, it doesn't appear at this level of safety consideration that this population suffers significantly more.

I should add an important thing, though. In August, we submitted to the FDA a complete reanalysis of all our NDA pivotal trials done with Taxol in breast cancer, in all the other tumor types, where we reanalyzed the safety according to the age of the patient. These

encompassed actually a review of a fairly large database, more than 3,000 patients. It has been submitted to the agency as part of the modification of the package insert so as to provide this type of information to the care provider. And there doesn't seem to be an increased risk of toxicity in the older population. That is consistent not only with the finding of the study but with the overall experience with this compound.

DR. BLAYNEY: So, the febrile neutropenia is an acute toxicity. I think part of the issue I face in dealing with over 65 women is sort of the more the chronic or longer-term toxicity.

DR. CANETTA: We can show the data, but again in terms of mere incidence, there is no difference between the younger patients and the older patients in this study, nor in the overall database for Taxol for other stages of this disease and for other tumor types.

Can we show the data?

DR. NERENSTONE: We're running short on time. Did that answer your question, Dr. Blayney?

DR. BLAYNEY: There's a small number of patients, 6 percent of your 3,000. That's 180 patients were over 65. Is that significant? How comfortable can we be in advising the FDA that this is relevant to 65-year-old and older women?

DR. CANETTA: Again, when you put things in perspective, the reason of our comfort is that this is almost 200 patients in this study, but we have the entire experience with Taxol in the treatment of cancer that supports that. That's what makes us more comfortable with the fact that elderly patients will not be at an undue risk of toxicity receiving Taxol at these dosages and at this schedule.

DR. BERRY: I just want to make one comment about that. It is, of course, a very small subset. I just looked at the disease-free survival effect of Taxol in the greater than 65. It's exactly the same as in the younger patients.

DR. BLAYNEY: Thank you.

DR. NERENSTONE: And, Dr. Pelusi, did you have one more question?

DR. PELUSI: I just want to make a comment in terms of quality of life and I think that that is some of the things that have come out either in the long term, cardiac toxicities, as well as our older patients. I think it becomes very valuable to all of us as we're trying to decide which patients should go or be encouraged, if you will, or given options in different treatment, what really is the effect of quality of life because as we start to see different approaches to the same thing, the question is

what is the quality of life. Nowhere did I see any quality of life studies at this particular time, and I think it might be interesting long term to see if that can be added, not just necessarily toxicities, but what do those toxicities translate into for quality of life for the patients.

DR. CANETTA: Unfortunately, for this particular trial, instruments of quality of life were not used. I have to say that the surrogate marker for quality of life would be the interpretation of toxicity, acute and chronic toxicity. As you have seen, we've been monitoring in the longer follow-up for cardiac events, for secondary malignancies.

I can tell you that the toxicities that were induced by Taxol during the Taxol phase consisted chiefly of neurosensory toxicity. The vast majority of the patients who dropped out of Taxol did so because of neurotoxicity, and that was reversible, and 14 patients altogether dropped out for hypersensitivity reaction out of the 1,400 patients. Obviously this stopped as Taxol was stopped. The other toxicities. Alopecia, unfortunately, is a side effect of Taxol. It's fully reversible. And there is no sign that Taxol added toxicity.

On the other hand, again we're talking about a survival advance here. Therefore, I think you need to put

that in perspective with the efficacy.

DR. PELUSI: And I do appreciate that, but again when we look at overall quality of life, there are additional things other than those specific things. I do agree with you on that, but again there are family issues as well.

DR. NERENSTONE: I'd like to thank everyone and the sponsor.

We'll take a break now and I'd like everyone back at 10:20. We are running behind. Thank you.

(Recess.)

DR. O'LEARY: Good morning, members of the committee, ladies and gentlemen. My name is James O'Leary and I will be presenting the FDA review of the supplement for Taxol for adjuvant treatment of breast cancer.

Before I begin, I would like to recognize the members of the review team who were instrumental in helping the FDA perform this review.

As I said, I'll skip this first slide since the sponsor already went over the proposed indication.

We're all familiar with the title of the study, and the sponsor also addressed this.

So, I will go on to the third slide. I would just like to bring at this point that the applicant has performed the first interim analysis as prespecified in the

protocol to take place at 450 events. The data presented in this analysis represents an update to that first interim analysis. Two more interim analyses are scheduled to take place at 900 events and 1,350 events, and the final analysis will take place when 1,800 events have occurred.

Accrual by arm, the sponsor already addressed this. There was equal distribution of patients to each arm.

And I'll get right into the FDA analysis. The FDA agrees with the applicant's analysis of the overall disease-free survival in the population studied. However, the core of my discussion will focus on results of this study in subgroups defined by hormone receptor status, particularly those patients with estrogen receptor and progesterone receptor negative tumors, those patient with estrogen receptor positive and/or progesterone receptor positive tumors, and finally those patients with ER and/or PR positive tumors who received tamoxifen. Although these analyses represent subgroup analyses, I think that the large number of patients in each group and the notable number of events occurring in each group lends credibility to these analyses.

First of all, in the group of patients with receptor negative tumors composed of over 1,000 patients, the apparent beneficial effect of Taxol is dramatic, with

the hazard ratio of 0.66 suggesting almost a 34 percent reduction in risk of recurrence.

When the results of the disease-free survival analysis for the receptor negative patients are plotted, this graph, which was submitted by the sponsor, shows a substantial difference in disease-free survival in favor of the Taxol treated patients. The agency estimated disease-free survival estimates at 3 years using unadjusted Kaplan-Meier curves. The results of this analysis showed that the Taxol treated patients had an estimated 3-year disease-free survival rate of 67.3 percent compared to 56.8 percent for the control group. This difference represented by the two survival curves at 3 years is quite noteworthy at 10.5 percent.

The next subgroup that we analyzed in terms of disease-free survival consisted of over 2,000 patients who had ER positive and/or PR positive tumors. The agency derived a hazard ratio of 0.93 with a p value of 0.56, which is similar to the sponsor's value for this analysis.

These statistical calculations at this interim analysis provide little justification for believing that Taxol, sequential to AC, confers added benefit to patients with ER positive and/or PR positive tumors. The following graph, which was also included in the sponsor's submission, shows that there's no appreciable difference between the