been conducted with epirubicin. As agreed with the FDA, these studies were selected because they were conducted in patients with breast cancer, because they were completed, well controlled, randomized, Phase III studies, and because their symmetrical designs allowed for specific evaluation of epirubicin's effects at the proposed starting doses of greater than or equal to 100 milligrams per meter squared.

In addition, full study reports were available for these studies, and electronic data were available or the data could be made available on request from the study group.

Based on the results of these seven trials conducted in over 3,000 patients, Pharmacia and Upjohn proposes that epirubicin be indicated as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer at starting doses of 100 to 120 milligrams per meter squared.

The company also proposes that epirubicin be indicated for the therapy of patients with locally advanced or metastatic breast cancer at starting doses

of 100 to 135 milligrams per meter squared.

I would now like to describe to you the results of the adjuvant studies of epirubicin as therapy for early breast cancer. Data from three multi-center, randomized, controlled studies support the use of epirubicin based therapy for the adjuvant treatment of patients with axillary node positive breast cancer.

A total of 1,885 women participated in these studies. The pivotal study, designated here as EBC-1, evaluated the use of cyclophosphamide, epirubicin, and fluorouracil, in which epirubicin was administered at a starting dose of 120 milligrams per meter squared per cycle or ECF 120 as shown on this slide.

Comparison was made with patients receiving a standard regimen of cyclophosphamide, methotrexate, and fluorouracil, or CMF.

In support of study EBC-2, epirubicin dose response was prospectively evaluated. Patients in both arms were randomized to receive CEF. The only difference between arms was the epirubicin starting

dose, which was 100 milligrams per meter squared in the experimental arm, CEF 100, and 50 milligrams per meter squared in the control arm, CEF 50.

In support of study EBC-3, postmenopausal patients with early breast cancer were randomized to receive epirubicin and Tamoxifen, with epirubicin given at a starting dose of 100 milligrams per meter squared, E 100 plus T as designated on this slide.

Alternatively, patients were randomized to receive Tamoxifen alone.

Please note that for the ease of discussion, we have codified the early breast cancer trials a EBC-1, EBC-2, and EBC-3, as shown on the left of the slide. For clarity, the corresponding original protocol numbers are also included on each slide where applicable in parentheses.

The pivotal study, EBC-1, was a Phase III trial that evaluated the benefits of epirubicin based CEF regimen versus CMF. This study was conducted as adjuvant therapy, pre and perimenopausal women with axillary node positive breast cancer.

The trial was sponsored by the NCIC, or

National Cancer Institute of Canada, at 37 centers and enrolled patients between 1989 and 1993. Dr. Mark Levine of the Hamilton, Ontario Cancer Center was the principal investigator.

Dr. Levine, as well as Dr. Kathleen Pritchard and Dr. Dongsheng Tu, also of the NCIC, are here with us today to assist in answering any questions that you may have.

Following surgery, patients were stratified on the basis of the type of primary surgical procedure, receptor status, and number of positive axillary lymph nodes. Patients were assigned to treatment with CEF or CMF in a one to one randomization. Patients in the CEF 120 group were to receive prophylactic antibiotic therapy with cotrimoxisol or a fluoroquinolone for the duration of their chemotherapy.

Patients who had undergone a partial mastectomy were to receive radiotherapy at the completion of the six cycles of chemotherapy.

Now, please note by design the cyclophosphamide does and the fluorouracil dose in the

CEF regimen, both of these doses were lower than those of the corresponding agents in the CMF regimen. This design was based on extensive pilot work and insured that any incremental beneficial effects of the CEF regimen could be attributed definitively to epirubicin.

An additional comment upon the selection of the CMF control arm is also in order. The conduct of a CEF versus CMF comparison allowed isolation of beneficial epirubicin effects versus a standard regimen.

It is also important to note that CMF was the North American adjuvant standard when the EBC-1 trial began in 1989, and in fact, CMF remains a widespread standard adjuvant therapy today in 1999. Use estimates indicate that of the approximately 23,600 patients with Stage II breast cancer currently receiving adjuvant therapy in the United States, a full 39 percent are receiving CMF.

The primary endpoint of the EBC-1 trial was relapse free survival. Secondary endpoints included overall survival, safety as assessed by the

standard NCIC common toxicity criteria, and quality of life as measured by the breast cancer chemotherapy questionnaire.

The hypothesis of this study was that CEF would be associated with a ten percent absolute improvement in the five year relapse free survival. Consistent with NCIC practice and with the stratified design of the study, the primary analysis of differences in relapse free and overall survival employed the stratified two tailed log rank test.

To be included in the trial, patients were required to be pre or perimenopausal and to have histologically proven breast cancer amenable to primary surgical resection. Demonstration of axillary nodal involvement was requisite, but patients could have no evidence of distant metastases. Patients were not permitted to have received prior systemic therapy. Adequate baseline cardiac and other organ function was required.

This extensive list of patient evaluations is provided in order to indicate that patients were regularly and thoroughly assessed for adverse events,

quality of life, laboratory abnormalities, and cardiac function during and after chemotherapy.

Altogether 716 patients were randomized. Three hundred and fifty-six were assigned to treatment with CEF, and 360 patients were assigned to therapy with CMF. Of note, one patient in each group never received study drug, and one patient who was to have received CMF -- I'm sorry -- CEF was erroneously treated with CMF instead. However, these patients were included in all efficacy analyses as part of the intent to treat study population.

As shown here, patients characteristics of age, of performance status, of menopausal status, and of clinical stage were well balanced between the two treatment groups.

The type of primary surgery performed was similar in each of the treatment arms. Nodal sampling was extensive, with more than ten nodes examined in the majority of patients. Patients with one to three positive nodes predominated. Approximately 40 percent of patients had four or more positive nodes. Again, all of these treatment characteristics were well

balanced between the two groups.

Estrogen and progesterone receptor positivity were also similar between the two groups.

In assessing treatment administration, virtually all patients completed the full six cycles of chemotherapy. In practice, as in design, the cyclophosphamide and fluorouracil doses or dose intensities, as shown here, were lower in the CEF group than in the CMF group. Relative median dose intensities were approximately 80 percent of planned with CEF and 96 percent of planned with CMF.

Breast irradiation was to be administered after the completion of chemotherapy to patients who had undergone partial mastectomy. The proportion of patients who received radiation therapy was comparable in the two treatment groups.

Despite the lower cyclophosphamide and fluorouracil doses, relapse free survival was significantly longer with CEF, emphasizing the critical role of epirubicin in the combination. With a median follow-up of 54 months, the five-year relapse free survival is 62 percent in the CEF group and 53

percent in the CMF group.

When comparing the differences between the curves using the stratified log rank P value was 0.013. A similar P value, 0.011 was obtained with an unstratified test.

A multiple regression analysis was performed to evaluate the effect of treatment in the context of assessing the effects of other baseline variables on relapse free survival. As shown in this slide, when significant baseline patient characteristics, including tumor size and nodal status, were taken into account, CEF treatment was still significantly associated with improved relapse free survival.

The risk ratio indicates a 24 percent reduction in the risk of relapse with a P value of 0.021.

Most gratifying was the CEF treatment also benefitted patients in terms of survival. The five year survival was 77 percent in the CEF group and 70 percent in the CMF group. When comparing the differences between the curves using the stratified

log rank test, the comparison of overall survival was statistically significant with a P value of 0.043.

Of note, an unstratified analysis showed a P value of 0.13.

When accounting for the impact of significant prognostic factors of tumor size, receptor status, and nodal status on survival in a multiple regression analysis, CEF treatment was, again, significantly associated with improved survival. The risk ratio indicates a 29 percent reduction in the risk of death with a P value of 0.034.

This slide summarizes clinically relevant adverse events. As expected, Grade 3/4 neutropenia was common and was greater in the CEF arm. However, neutropenic fever was infrequent in both arms, perhaps in part due to the use of prophylactic antibiotics in the CEF arm.

Grade 3/4 anemia or thrombocytopenia also occurred more frequently in the CEF treated patients than in the CMF treated patients. However, these toxicities occurred in less than ten percent of the patients in either arm.

Grade 3/4 non-hematologic events of alopecia, stomatitis, and vomiting occurred more frequently in the CEF treated patients than in the CMF treated group, whereas Grade 3/4 diarrhea was more common with CMF.

Cutaneous toxicities were quite infrequent in either group. Although not shown on this slide, Hepatic toxicity was actually more common with CMF, although usually of Grade 1 or 2 in severity. Fewer than two percent of patients in either group discontinued therapy due to adverse events during treatment. There were no drug related deaths.

One patient in the CEF group died of an intracerebral hemorrhage that was not considered by the investigator to be drug related.

Now, as with any anthracycline or anthracenedione treatment, cardiac toxicity is a potential concern and did occur in 3.4 percent of the patients receiving CEF and 1.1 percent of the patients receive CMF.

In most instances, this manifested as an asymptomatic decline in left ventricular ejection

fraction. Symptomatic congestive heart failure was observed in five of the 354 patients in the CEF group, and this occurred after two to five years of follow-up. In one of the 360 patients on CMF, CHF was also noted at 15 months after follow-up. None of the episodes of CHF was fatal.

Secondary leukemias are also another low frequency event that can be observed following therapy with topoisomerase II inhibitors or alkylating agents. Leukemias were reported in five of the 354 patients in the CEF group and in one of the 360 patients in the CMF group.

The five cases of leukemia in the CEF group included four cases of acute myelogenous leukemia and one case of acute lymphocytic leukemia.

One patient in the CMF group developed AML.

As expected with topoisomerase II inhibiting agents, the leukemias occurred relatively early in the course of follow-up after a completion of chemotherapy, that is, from approximately 13 to 39 months after randomization.

This plot may help to put the AML risk into perspective. It depicts a life table analysis of both AML risk and overall survival. The life table analysis shows the same survival data that I previously showed you in the Kaplan Meier survival curves, but divided into one year intervals which results in a more stairstepped graphical appearance.

The curves at the top of the graph show the likelihood of remaining leukemia free over the seven years of follow-up. As you can see, the likelihood of remaining leukemia free is very high, and in fact, the occurrences of leukemia with CEF are confined to a period early in the course follow-up, as is typically the case with topoisomerase II inhibitors.

The curves in the middle of the graph show the likelihood of remaining alive over seven years of follow-up. These curves show that the risk of death from recurrent breast cancer is large and continuous.

Even taking the AML risk into account, as has already been done in calculating the overall survival curves, the likelihood that a woman will live

is enhanced with CEF as compared to CMF. The benefit clearly outweighs the risk.

Let us now turn to the quality of life assessment in the EBC-1 trial. The BCQ is an instrument specifically designed to measure quality of life in women receiving adjuvant therapy for early breast cancer. It consists of 30 questions which focus on emotional and physical symptoms. Each question has a seven point scale. A mean summary score is computed using information from all of the scales.

Of note, less than a 0.5 unit change in the summary score is not considered clinically important.

Quality of life was analyzed in a total of 715 patients. Now, this experience represents one of the most comprehensive quality of life analyses done in an adjuvant clinical trial.

This slide shows the mean summary quality of life scores in the two treatment groups. Despite an early statistically significant, but transient decrease in the mean summary score in the CEF treated

patients, the mean quality of life scores remained in the upper range of the scale throughout treatment and follow-up. No clinically relevant differences in the mean summary BCQ scores ere apparent between the two groups of patients.

In conclusion, the results of this well controlled trial demonstrate that superiority of epirubicin based CEF over CMF in approving both relapse free survival and overall survival in premenopausal patients with axillary node positive breast cancer. The critical role of epirubicin in obtaining these clinical benefits was emphasized by the greater efficacy of CEF despite the lower doses of cyclophosphamide and fluorouracil in the CEF treated patients.

Although the frequencies of acute adverse events were generally greater for the CEF regimen than the CMF regimen, 96 percent of CEF treatment patients completed therapy, and there were no drug related deaths during treatment. Late toxicities were infrequence, and on treatment decrements in quality of life were small and of short duration.

Let us turn now to study EBC-2, which was a Phase III trial that evaluated the benefit of giving an epirubicin based CEF 100 regimen versus a regimen of CEF 50 as adjuvant therapy of pre and postmenopausal women with axillary node positive breast cancer.

The trial was sponsored by the FESG, or French epirubicin study group, at 20 centers between 1990 and 1993. Professor Jacques Bonneterre of the Centre Ascer L'Ambrais at Lille was the principal investigator. Professor Bonneterre is also here with us today to assist in answering any questions.

Pre or postmenopausal women with axillary node positive breast cancer could be enrolled to this trial. After stratification, patients were assigned to treatment with CEF 50 or CEF 100. The only difference in the planned treatment administration between the two groups was the starting dose of epirubicin.

A total of 565 patients were enrolled. Patient characteristics were well balanced between the two arms. Overall treatment administration was,

again, excellent in this study as it had been in EBC-1. Virtually all patients completed the full six cycles of therapy.

As shown here, doubling of the epirubicin dose was actually achieved in this trial as had been planned. Relative median dose intensities were greater than 90 percent in both treatment groups.

Radiotherapy was administered to comparable proportions of patients in each treatment arm.

With a median follow-up of approximately five years, relapse free survival and overall survival data from the CEF 100 regimen in EBC-2 strongly corroborate the findings from the CEF 120 experience in the NCIC EBC-1 trial.

Five year relapse free survival was 65 percent with CEF 100 versus 52 percent with CEF 50. When comparing the differences between the curves, the log rank P value for the unstratified test was 0.007.

Five year survival was 76 percent with CEF 100 and 65 percent with CEF 50. The overall difference in the survival curves between groups was

statistically significant, again, with a P value of 0.007 for the unstratified test.

This slide summarizes the clinically relevant Grade 3/4 events in EBC-2. Grade 3/4 neutropenia was modest in both arms, and neutropenia plus fever or infection was infrequent at only four percent.

The lesser frequencies of hematologic toxicities in this trial as compared with EBC-1 may be related to differences in chemotherapy doses, schedules and routes of administration, as well as to differences in data collection methods.

Grade 3/4 nonhematologic events of alopecia, nausea and vomiting and stomatitis occurred more frequently in the CEF 100 treated patients than in the CEF 50 treated patients.

Serious diarrhea or cutaneous toxicities were not observed.

Discontinuation of therapy due to adverse events was acceptably low in both arms of the trial. As in EBC-1, there were no drug related deaths.

Based on our review of the data, three

percent of the patients in the CEF 100 group and 1.7 percent of the patients in the CEF 50 group had evidence of cardiac toxicity. This included patients with asymptomatic declines in left ventricular ejection fraction and a small number of patients who also had CHF.

One leukemia was reported in each of the study arms.

In conclusion, the results of this trial prospectively demonstrate a clear dose response effect for epirubicin. The data indicate the superiority of CEF 100 in improving both relapse free survival and overall survival in women with axillary node positive early breast cancer.

Toxicities were readily manageable, as evidenced by the high rates of completion of chemotherapy, the high relative dose intensities, and the lack of toxic deaths.

The results of this trial strongly corroborate those from EBC-1, again documenting the clinical benefits of epirubicin based adjuvant treatment.

Turning to study EBC-3, this was a Phase III study that evaluated the benefit of giving epirubicin at a starting dose of 100 milligrams per meter squared with Tamoxifen versus Tamoxifen alone as adjuvant therapy in postmenopausal women with axillary node positive breast cancer.

This trial was sponsored by the ICCG or International Collaborative Cancer Group at 13 centers between 1988 and 1995. Dr. Jacques Wils of the Sat. Laurentius Hospital in Roermond in the Netherlands was the principal investigator for this study.

Postmenopausal women with axillary node positive breast cancer could be enrolled to the study. Patients were stratified by study center and were assigned to treatment with epirubicin and Tamoxifen or Tamoxifen alone.

Epirubicin was to be given every four weeks for six cycles. Tamoxifen was to be given daily for four years.

A total of 604 patients were enrolled. Patient characteristics including estrogen receptor status were well balanced between the treatment arms,

although there was a trend toward larger clinical tumor size in the epirubicin containing arm. The median epirubicin dose intensity was 95 percent of that planned.

Patients who had undergone a partial mastectomy were to receive radiation therapy at the completion of six cycles of epirubicin. Radiation therapy was balanced in the two treatment groups.

With a median follow-up of 4.3 years, the relapse free survival in the epirubicin containing arm was 74 percent as compared with 62 percent with Tamoxifen alone.

The difference in the relapse free survival curves was statistically significant, with a P value of 0.023 for the unstratified log rank test. The difference in the survival curves is currently not statistically significant.

The toxicities of the epirubicin based therapy were modest. Grade 3/4 leukopenia was rare, and leukopenic fever was not observed. Grade 3/4 non-hematologic toxicities of alopecia, nausea and vomiting and stomatitis occurred more frequently in

the epirubicin treated patients than in the Tamoxifen treated group, as might be expected.

Discontinuation of therapy due to adverse events was acceptably low. One patient receiving epirubicin based therapy died following the fifth cycle of chemotherapy after a Grade 4 leukopenia. A potential relationship to epirubicin could not be excluded.

Four of the 303 patients in the epirubicin plus Tamoxifen group developed congestive heart failure. Two instances of AML were recorded in patients receiving epirubicin.

The results of this trial demonstrate that the addition of epirubicin to Tamoxifen resulted in significantly improved relapse free survival. The on treatment toxicities of epirubicin were modest. The results of this trial confirm the clinical benefit of epirubicin as a component of adjuvant therapy and add additional documentation of the benefits of epirubicin treatment for post menopausal patients with early breast cancer.

In summary, adjuvant use of epirubicin at

doses of greater than or equal to 100 milligrams per meter squared in CEF and when combined with Tamoxifen consistently improved relapse free survival in patients with early breast cancer.

More importantly, epirubicin based adjuvant therapy can significantly improve overall survival.

We would now like to describe to you the results of studies of epirubicin given at starting doses, again, of greater than 100 milligrams per meter squared in the therapy of advanced breast cancer, focusing first on the efficacy results from each trial and subsequently on an overview of safety from the two largest studies.

Data from four multi-center, Phase III, randomized controlled trials involving the therapy of 1,231 women support the use of epirubicin based therapy for the treatment of advanced or metastatic breast cancer.

The pivotal study, ABC-1, was a multi-national trial that evaluated the first line use of CEF 100. The comparison was made with a standard

regimen of CMF.

In supportive study ABC-2, epirubicin dose response was prospectively evaluated in the first line setting. Patients in this study were randomized to receive either CEF 100 or CEF 50.

Two additional supportive studies were also submitted to the FDA.

Study ABC-3 was similar in design to ABC-2, that is, comparing CEF 100 versus CEF 50.

In support of study ABC-4, patients who had experienced failure of first line CMF were randomized to receive single agent epirubicin, given either at a starting dose of 135 milligrams per meter squared or 75 milligrams per meter squared.

In study ABC-1, patients were stratified and then randomized to treatment with CEF or CMF. As in study EBC-1, the cyclophosphamide and fluorouracil doses in the CEF regimen were lower than those in the CMF regiment in order to accommodate the escalated epirubicin treatment and allow specific assessment of epirubicin effect.

A total of 460 patients were enrolled at

48 centers in multiple countries. Dr. Steve Ackland from Newcastle, Australia was the principal investigator. A majority of the patients had recurrent disease with visceral involvement of two or more organ sites. Approximately 30 percent had received prior adjuvant therapy.

Patient characteristics were well balanced between the two treatment arms. The median relative dose intensities for all agents were approximately 75 percent in both treatment groups, that is, both in CEF and in CMF.

Compared with CMF, CEF 100 therapy induced a significantly higher objective response rate, a trend toward an improved response duration, a significantly longer time to tumor progression, and a significant improvement in time to treatment failure.

While somewhat longer with CEF 100, survival was not significantly different between the two groups.

The lack of a survival advantage for CEF 100 may have been due to the fact that a substantial number of patients in the CMF group subsequently

received an anthracycline or anthracenedione based chemotherapy regimen after study treatment.

As shown here, 44 percent of the CMF treated patients subsequently received one of these therapies.

Study ABC 2 evaluated the impact of epirubicin dose response in the first line therapy of metastatic breast cancer. After stratification, patients were randomized to treatment with CEF 100 or CEF 50.

A total of 456 patients were enrolled at 38 centers in many countries. Dr. George Bruffman (phonetic) from Israel served as the principal investigator.

As in ABC-1, a majority of the patients had recurrent disease with visceral involvement of multiple sites. Approximately 30 percent had undergone prior adjuvant therapy. Patient characteristics were well balanced across the two treatment arms.

The median relative dose intensities were quite good for all agents, approximately 88 percent in

the CEF 100 group and 93 percent in the CEF 50 group.

An epirubicin dose response effect was documented in this trial. CEF 100 induced a significantly higher response rate than CEF 50, with a P value for the comparison of 0.009.

Other endpoints, while generally improved with higher dose epirubicin, were not statistically significantly different between the groups.

In study ABC-3, epirubicin dose response was again evaluated. In this trial both patients with locally advanced primary disease and metastatic breast cancer were enrolled. Patients were stratified by study center, menopausal status, and whether disease was locally advanced or metastatic.

Patients were then randomized to treatment with CEF 100 or CEF 50. A total of 164 patients were enrolled at nine centers in Belgium under the direction of Dr. Focan.

Approximately one-third of the patients in each group had locally advanced disease. Patient characteristics were well balanced in the two arms. Median relative dose intensities for all agents were,

again, good, 80 percent in the CEF 100 group and 90 percent in the CEF 50 group.

A dose response effect for epirubicin was again confirmed in this trial as it had been in ABC-2. CEF 100 induced a significantly higher response rate, a longer response duration, and a larger time to treatment failure than did CEF 50. Although not significant, a longer median survival was noted with the higher dose CEF regimen.

Study ABC-4 evaluated single agent epirubicin dose response in patients who had received prior CMF therapy. Patients were stratified by site of metastases and response to prior CMF.

Patients were then randomized to treatment with single agent epirubicin given either a starting dose of 135 milligrams per meter squared or 75 milligrams per meter squared.

A total of 151 patients were enrolled in 19 centers in Canada. Dr. Blackstein was the principal investigator.

Approximately 75 percent of patients in this trial had visceral metastases, and three-quarters

had relapsed within six months of prior CMF.

Patients characteristics were well balanced in the two arms.

The median relative dose intensities were excellent, again, 90 percent in the epi. 135 group and 97 percent in the epi. 75 group.

The trial again documented an epirubicin dose response effect. Epirubicin 135 therapy resulted in significantly higher response rates and a longer time to tumor progression in previously treated patients.

Also note that there was a trend favoring survival in the epirubicin 135 group.

This slide describes the clinically relevant adverse events noted in studies ABC-1 and ABC-2, the pivotal and main supporting studies for the advanced breast cancer indication. Data for patients who received CEF 100 are show in the first two columns on the left, followed by data for the patients who received CMF or those then on the right who received CEF 50.

Grade 3/4 neutropenia were observed in the

majority of patients who received either CEF 100 or CMF. The rates of neutropenic fever were modest, and other hematologic toxicities were of relatively low frequency with both regimens.

Grade 3/4 non-hematologic events of alopecia, nausea and vomiting occurred more frequently in the CEF treated patients than in those treated with CMF. The incidence of Grade 3/4 stomatitis. Severe diarrhea or cutaneous toxicities were quite uncommon with any of the regimens.

Congestive heart failure occurred, but was uncommon and never resulted in death. Rates of potentially drug related deaths were quite low in all of the treatment arms.

In summary, epirubicin can consistently provide highly significant improvements in tumor shrinkage as measured by objective response rates in all of these studies. Complete response rates were also consistently higher in the treatment arms than in the control arms on these trials.

And a theme of improvements in tumor control as assessed by time to tumor progression or

time to treatment failure is evident when comparing the arms of these studies.

In final summary, we propose that epirubicin be indicated as a component of adjuvant therapy in patients with evidence of axillary node tumor involvement following resection of primary breast cancer. The results of three large, randomized, well controlled studies demonstrate that epirubicin improves relapse free survival and overall survival.

We also propose that epirubicin be indicated for the therapy of patients with locally advanced or metastatic breast cancer. The results of four well controlled trials document that epirubicin improves time to tumor progression and increases overall and complete response rates.

Taken together with a clear clinical benefits seen in the adjuvant setting, these data in advanced disease support the inclusion of this indication in the labeling for epirubicin.

Thank you very much for you attention. My colleagues at Pharmacia and Upjohn, as well as Dr.

Levine, Dr. Pritchard, Dr. Tu, Professor Bonneterre, and I, would be pleased to answer any questions that you may have.

CHAIRPERSON DUTCHER: Thank you.

Questions from members of the committee for the sponsor?

MS. BEAMAN: I'd like to know do you have a sampling of the VCQ assessment that was used?

DR. MILLER: Do you mean a demonstration of the questions?

MS. BEAMAN: Yes.

DR. MILLER: Yes. It will take just a moment to pull it up here.

Here are some examples of questions. Can you hear me?

CHAIRPERSON DUTCHER: You need the microphone.

DR. MILLER: Okay. Here are examples of some of the types of questions. There were 30 questions altogether, and these focused on issues of hair loss, for example, more general questions about overall outlook. There were questions related to

neurotoxicity, while not commonly expected with the agents given in this trial. The instrument was designed at a time when vincristine, for instance, was included in chemotherapy regimens, and so this question was considered appropriate.

Issues related to inconvenience. There are issues related to then other symptoms of various types, and I can go on if you'd like.

MS. BEAMAN: Yes.

DR. MILLER: Okay. You want to see some others? Okay.

So here a question that probably focuses primarily on asthenia as a concern for patients. Have you felt low in terms of energy? And in general -- and issues related to depression. Have you felt down in the dumps or tearful?

PARTICIPANT: This is on MA-5, right?

DR. MILLER: This is on the MA-5 or EBC-1 trial.

Questions regarding nausea and vomiting, and also questions regarding appearance and feelings of loss of attractiveness.

Yes, Mark you may want to comment.

CHAIRPERSON DUTCHER: Please identify yourself for the recording.

DR. LEVINE: My name is Mark Levine. I'm the principal investigator of the study.

The breast cancer chemotherapy questionnaire was developed in the mid-'80s, published in the Journal of Clinical Oncology, validated on a cohort of women with node positive breast cancer receiving adjuvant therapy.

It has seven domains that focus on loss of attractiveness, fatigue, physical symptoms such as Langdon described, the inconvenience of waiting in clinic and so on, emotional distress, and feelings of hope and support.

DR. KROOK: What percent of people completed that, the majority of the questionnaire?

DR. MILLER: Do we have the slide with the actual numbers on it?

Altogether 715 patients were evaluated. As might be expected, not all patients completed the questionnaire at all occasions, but in general, the

compliance with this questionnaire was excellent and largely better than one might expect with many other experiences.

DR. KROOK: I think when you presented the slide you said there was an early difference in the quality of life issue with the CEF arm, and it appeared later to come together. Is there an explanation for that?

DR. MILLER: Yeah, I think that there is. Let me just comment briefly first on the issue of completely.

So as you can see here, the number of patients completing the questionnaire was universally over 70 percent at each prescribed visit and approached 90 percent on some occasions. Okay?

In terms of that initial early drop, I think it's likely related to the fact that CEF was acutely more toxic for patients; that the patients received the initial intensive chemotherapy, and then as doses were modulated to find a comfort dose of chemotherapy for each patient, that there was subsequent recovery of the toxicities or the

diminution in quality of life that came up then to parallel that of CMF.

DR. KROOK: Right. My one comment, having watched people who have taken anthracycline versus CMF, perhaps it was the hair loss issue, which is, again, predominantly in the CEF and females.

DR. MILLER: Right.

CHAIRPERSON DUTCHER: Dr. Honig had a comment.

DR. HONIG: I was just going to comment that in your study report it says that 19 percent of patients overall completed all of the questionnaires at each visit, and that only about, I think, 30 percent of patients filled out at least a portion of the questionnaire at subsequent visits, and there was a substantial amount of missing information.

DR. MILLER: Well, as with any instrument, there may be some missing information, but I think, again, we would maintain that these rates of completion, 70 percent or greater, visit by visit provide some considerable validity to the use of the instrument.

Mark, you may want to address this, as well.

DR. LEVINE: May I address the -- Mark Levine again.

When you analyze a quality of life questionnaire in a cancer trial, there is, firstly, was the questionnaire completely and then was every question of the questionnaire completed.

When we published our manuscript, we chose to in the quality of life comparison include all of the patients who completed the questionnaire, of which there were 270 of the patients, so where you had perfect compliance.

I think nonetheless, I think to ask, for example, at time zero when a patient has just been randomized and it's an emotional situation and you ask them in the questionnaire about hair loss, some people choose not to fill out the questionnaire, fill out that question, and that's perfectly reasonable.

But to get randomized to this trial, you had to have completed the questionnaire, although you may not have completed all 30 questions. That was an

eligibility criteria for randomization.

DR. MILLER: Sorry for the interruption.

The other thing that I should point out and, I believe, was in the FDA review of the trial was that we looked at all patients completing and then at the patients across all 715 patients who participated at all in the quality of life, and the curves were essentially the same in shape no matter how the analysis was done, I think, adding some validity to the results here.

DR. LEVINE: If I may add one final comment. Sorry. Mark Levine again.

As you all know, the standard approach in cancer trials is to complete toxicity scales, and this, as Langdon pointed out, was done.

Over and above this, we collected quality of life information, which is now being advocated quite a lot in cancer trials, but the point is this is almost over and above what is the usual pattern in the cancer clinical trial.

CHAIRPERSON DUTCHER: Dr. Krook.

DR. KROOK: A couple, going back to

perhaps the early discussions of MA-5. There obviously was a discussion of why the dose of the cytonan. I guess I would be interested in why that was somewhat different. In the other early breast cancers the doses were very similar. I realize one is a CMF arm, but that's going back historically.

It's of interest that the dose intensity of the cytonan in the 5 FU is greater in the CMF arm and despite that, the results are as you showed them.

DR. MILLER: Right.

DR. KROOK: I mean it's to your favor.

DR. MILLER: Right, exactly. Again, I think it really emphasizes the critical role of epirubicin.

DR. KROOK: Right.

DR. MILLER: This is truly epirubicin based therapy when given in this fashion.

The other thing that's important to mention is that the NCIC carried out an extensive pilot study, Phase I study, but in dozens of patients, not just the usual three to six per patient cohort, to determine the best dose of epirubicin to use in the

context of the cyclophosphamide and 5 FU that's applied here.

So this was something that was very well piloted before it was brought into the adjuvant setting.

DR. KROOK: Are there any adjuvant trials that you are aware of that use epi. as one arm and adriamycin as the other? I don't know of any. I'm asking do you know of any.

DR. MILLER: Yes, there have been studies of that type. Generally those studies have not been -- a number of them have not been completed, and in general, there are studies that have been done elsewhere that have looked at that type of comparison.

Oftentimes though the problem has been that the comparison was made at lower doses of epirubicin. The other thing that has occurred is that the designs were not symmetrical. That's one of the fundamental problems in so many trials. In terms of trying to isolate the effect of the drug under test, most of the other trials were not symmetrical in design.

But I think that's the beauty of these particular trials.

CHAIRPERSON DUTCHER: Any other questions? Dr. Santana.

DR. SANTANA: Yeah, Langdon. Obviously the occurrence of leukemia as a second event is a devastating occurrence even if the numbers are not very high in terms of incidence rates, but for the individual patients it is devastating.

Can you tell us in the trials that you presented how many of those patients developed second leukemia as an event were salvaged?

And the second question related to that is you presented data in the first set, but you didn't tell us whether there was any second leukemia in the advanced breast cancer trials. I know the median survival of those patients is much, much lower. So there may have been an overlap of competition between relapse and second leukemia, but I was just curious if you did see it also in the advantage breast cancer, in which the intensity of epirubicin was much higher.

DR. MILLER: Yes. Here are the data from

the patients who developed AML, and the FAB classification, as might be expected, was that consistent with the topoisomerase II inhibitor type of leukemia.

The time to onset, relatively early, and then unfortunately these patients did die.

Now, we do have data. I think the leukemia data for overall, our pharmacovigilance data.

We have examined this issue and probably the most concertedly of any group in the world, and have looked at thousands of patients in trying to determine what this risk entails, and as I think most people on the committee know, acute leukemia -- sorry. Let me just adjust this here -- is a well documented, rare toxicity of topoisomerase II inhibitors, etoposide, particularly in the pediatric setting, anthracyclines and anthracenediones. It classically manifests as a FAB M4/M5, myelomonocytic leukemia within three years of treatment, and potential risk factors include concurrent administration of an alkylating agent or a starting dose or dose intensity.

We've conducted a large surveillance

program at Pharmacia and Upjohn, and in the course of the last nine years, between 1990 and 1999, have documented 43 total cases of leukemia. This is in spontaneous reports, clinical trials, literature reviews, and so on.

We also have established a clinical trials database looking at 27 large, randomized trials that were selected because we had adequate follow-up and we could really look at survival.

And so over 11,000 patients were looked at in these trials. Twenty-two total cases of leukemia were documented, 19 AML, three ALL, but most of these cases were in early breast cancer. Very low actual incidence as you can see, and only two cases of AML in advanced breast cancer.

DR. SANTANA: Have there been any cases reported of AML in patients receiving Tamoxifen and epirubicin or another anthracycline?

DR. MILLER: Yes, in the EBC-3 trial there was one patient, yes.

So we feel that we have very extensive documentation of this issue and have gone to great

lengths to try to collate those data, and of course, those data would be reflected in our package insert.

CHAIRPERSON DUTCHER: Do you have cytogenetic data?

DR. MILLER: There are some cytogenetic data available from some of the patients. It hasn't been as uniformly done as one might hope. In a number of patients, as might be expected, chromosome 11 abnormalities have occurred, yeah.

CHAIRPERSON DUTCHER: But also (inaudible).

DR. MILLER: That's been relatively infrequent. In some of the cases you occasionally see an M-1 or M-2 histology. There have been such abnormalities. There has been a 15-17 promyelocytic leukemia. Whether that was related or not I don't know.

Yeah?

DR. MARGOLIN: It seems as though if you get this drug approved and people start using it in the adjuvant setting, you have patients that are getting something like two-thirds to three-quarters of

what would be considered the cumulative dose associated with a steep rise in the cardiotoxicity incidence, and if this drug in combinations works well in the adjuvant setting, you may see a fair number of patients getting it first line and then doing well for a while and then being considered for something like the second line at first relapse.

And so the question is how much research efforts are being addressed at use of dextrosoxane, use of alternative schedules perhaps for lowering the risk of cardiotoxicity without compromising the anti-tumor effect.

DR. MILLER: Well, what we know about the late cardiotoxicity associated with epirubicin is that it is a low frequency event, as with doxorubicin or with mitoxantrone; manifests primarily as congestive heart failure, and the biggest risk factor, of course, as with doxorubicin, is cumulative anthracycline dose.

CHAIRPERSON DUTCHER: Excuse me. Can you push yours up just a little bit higher for the back of the room?

DR. MILLER: Too low? Is that okay?

CHAIRPERSON DUTCHER: Better. Thanks.

DR. MILLER: Okay. There's something here. Let me just adjust this.

(Laughter.)

DR. MILLER: Tastefully presented.

And cumulative anthracycline doses, of course, the greatest risk factor, prior irradiation is well established as a risk factor, and age is a known risk factor. Particularly pediatric patients are very susceptible to doxorubicin induced cardiotoxicity, and so it's a particular concern there.

We have evaluated the risk of CHF. This is symptomatic CHF, in over 9,000 patients on clinical trials, and this graph, the numbers are a little small here, but basically a four percent incidence, which is often that quoted, occurs at about 900 milligrams per meter squared cumulative dose.

Now, it's not the optimal way to do. This is a different way of plotting those same data from the same patients. It's not optimal. It's a life table sort of analysis, but compares the results in a way historically with the old data from Dr. Von Hoff,

and you can see or get a sense of the relatively likelihood of cardiotoxicity at a given dose of either epirubicin in blue or doxorubicin in yellow.

I think that the important message here is that it's unlikely that clinicians are going to give excessive epirubicin. If this relationship were the other way around, one might be concerned, but this actually adds a safety factory for the use of epirubicin in breast cancer.

DR. KROOK: But that's a little bit misleading because the starting dose that you're recommending for epirubicin is 100, and we may be between 60 or 70 from either squared --

DR. MILLER: Right.

DR. KROOK: -- for the adriamycin. So --

DR. MILLER: No, I want to be clear. I'm not indicating to compare cardiac risk per se. All I'm saying is that to get to the same level of cardiotoxicity, you have to give more drug. We're giving more drug, so we may get there sooner.

The thing is that if you look at the MA-5 study, for example, 720 milligrams per meter squared

would be the planned cumulative dose, and about 85 percent of patients got six -- the median dose was 600 milligrams per meter squared, and about 85 percent of the patients got over 500.

So a fair amount was given. The one percent incidence of cardiac toxicity of CHF fits exactly on this curve and so is quite consistent with what we would expect from the drug. In other words, you know, we're at roughly 600 milligrams per meter squared, about a one, one and a half percent likelihood of cardiotoxicity.

So I think that the trial is quite reflective of our experience in large numbers of patients with the drug.

DR. TEMPLE: That didn't answer the question. You didn't answer the question.

DR. MILLER: Okay.

DR. TEMPLE: You've now used up some of your anthracycline capacity. What are you doing to find out how someone who does get a tumor can be treated?

Isn't that was your question was, not that

you can't defend yourself?

(Laughter.)

DR. MARGOLIN: I was going to just let it go.

DR. MILLER: Well, as you well know, Pharmacia and Upjohn also has dexrazoxane as one of its drugs, and we have conducted studies with dexrazoxane in conjunction with epirubicin, and it is very clear that dexrazoxane can protect patients from cardiotoxicity from either doxorubicin or epirubicin. So the drug is effective in that regard.

And further studies are clearly warranted. It may be very interesting to consider the combination of both of these drugs in some sequence or combination ultimately with herceptin, for instance, particularly if an animal model could be examined that would show protection from cardiotoxicity from the three drugs together or the two drugs together, the anthracycline and herceptin.

DR. KROOK: The question may come up with the FDA reviews though, and I bring it up now, the radiotherapy issue. If I look at in the MA-5, again,

the partial mastectomy, 49 percent, 45 percent, and 46 percent received radiotherapy, and the sequencing of that particularly in the pivotal trial, pertinent to questions that are now before the whole community.

DR. MILLER: Mark, did you want to address that?

DR. LEVINE: The 49 percent is a little misleading. Remember in this trial half the patients had lumpectomy and half of the patients had mastectomy. So of the 50 percent of women who had lumpectomy, virtually all of them, virtually all of them, 99 percent, underwent breast irradiation post completion of chemotherapy, which is the standard approach amongst all of the cooperative groups.

So it's not 49 percent. It's 49 percent of all 720, but not of the patients who had lumpectomy.

DR. MILLER: Dr. Krook, I have the data here actually.

DR. KROOK: Okay.

DR. MILLER: As you can see, those with partial mastectomy, 75 patients here, 76 patients

here, essentially all of them or near all of them got the irradiation. Those with total mastectomy, it was quite infrequent that they would get irradiation as per protocol.

DR. KROOK: Okay.

CHAIRPERSON DUTCHER: Dr. Simon.

DR. SIMON: Could you clarify the selection of the studies? It's always a little troubling to me when studies are selected after they're completed from a larger database and when the results are essentially available.

Were there other studies that isolated epirubicin, the contribution of epirubicin, or other studies at around that dose that isolated epirubicin? I wonder if you could clarify those issues.

DR. MILLER: Yes. This --

DR. SIMON: Particularly for the adjuvant situation.

DR. MILLER: Yeah. This represents the basis for selection of the studies, and obviously the trials had to be conducted in breast cancer. They had to be completed, well controlled, and randomized in

Phase III, and a critically important issue was the symmetrical design.

And as I mentioned before, too many of these trials that have been done have used three drugs versus two or four drugs versus two and that sort of thing or changed the doses and schedules of the drugs in ways that made it difficult to assess the specific effect of each drug. So we focused on studies that had symmetrical designs.

The other thing was that for --

DR. SIMON: Were these the only studies that had symmetrical designs?

DR. MILLER: In essence, yes, and then the other issue was the epirubicin starting dose, 100 milligrams per meter squared. We were focusing on studies that had used this as the starting dose for the agent, and the initial issue was that the studies had to be available so that the FDA could review them, and so that was also --

DR. SIMON: Were there other studies with symmetrical designs that had starting doses of, say, 75 or higher for adjuvant studies?

DR. MILLER: Yeah, the highest dose was 60. Here's the data. In one study, with 50 milligrams per meter squared, CEF 50 versus IV CMF, a totally symmetrical design, increased relapse free survival and overall survival; when the CEF 50 IV was compared with the MCF oral -- so here again changes in schedule, and these is some sense that oral CMF may deliver more dose intensity -- you don't see the same result.

On the other hand, here, again, a symmetrical design reported at ASCO this year, CEF 60 versus CMF in premenopausal patients particularly, there was an improvement, significant improvement, both relapse free and overall survival, and in all patients when the data were looked at as well.

There are two additional trials ongoing, one looking at CF 50 versus CMF and one looking at a CEF dose response, but these trials, of course, the results aren't available yet.

DR. SIMON: Now, what does this slide represent? All of the studies with symmetrical designs?

DR. MILLER: Yes, exactly.

So I think that the results, in general, corroborate those, but we felt that we have the best data with the CEF 100 versus a community standard CMF. That's why the importance of MA-5, and then corroborating evidence from the EBC-2 trial looking at those same doses of epirubicin.

DR. WILLIAMS: Dr. Simon, I should also mention that at a pre-NDA meeting we were involved in, it had a table of all the different studies and helped with the criteria for selection. So we felt that no important studies were overlooked.

DR. SIMON: Okay, because that's important. You know, it's potentially impossible to pick a dose threshold, you know, after the fact.

CHAIRPERSON DUTCHER: Could you just comment? It looked like the ongoing studies were actually at a somewhat lower dose, 75, right?

DR. MILLER: Yeah, that's correct.

CHAIRPERSON DUTCHER: So, I mean, are you not certain about your dose range yet?

DR. MILLER: No, I think we're quite

confident about our dose range. It's greater than 100 milligrams per meter squared in the adjuvant setting in the --

CHAIRPERSON DUTCHER: But you had comparative studies at 50 that were better. At least one, I think.

DR. MILLER: Yeah.

CHAIRPERSON DUTCHER: And the others are at 75.

DR. MILLER: Yeah, but I think for simplicity of labeling, we're willing to propose one set of doses.

DR. KROOK: When you first started, you said that epirubicin is approved elsewhere as a single agent between 60 and 90, in combination 50 to 75. If I'm reading right, you're now coming in at 100.

DR. MILLER: Right.

DR. KROOK: In this country. It's --

DR. MILLER: Yeah. I think that it's important to understand that initial doses were defined. Part of this was related to the fact that the glucuronidation patterns and murine models of the

drug were very similar to those of doxorubicin.

DR. KROOK: Okay.

DR. MILLER: Once the drug was actually tested in human beings, we found out that the glucuronidation was enhanced, and this allowed then expiration of dose more than had initially been anticipated, and as I showed you, doses of 180 milligrams per meter squared of epirubicin can be given, in part related to the fact that it has, on an equimolar level, has less neutropenia and less hand-foot syndrome as a problem as compared with doxorubicin.

Yeah, Kathleen.

DR. PRITCHARD: -- 100 milligrams in the dose we chose in our study.

CHAIRPERSON DUTCHER: Give your name.

DR. PRITCHARD: It's Kathy Pritchard from the NCIC.

I'd just like to make a comment about the dose and the comparison. I think the other studies you're looking at do show it at a lower dose compared to some other comparator, or not standard comparator,

that 50 or lower doses may be better. The question is better than what.

For example, in Morrison's study, it's better than IV CMF, which we know from randomized studies at least in advanced disease is not as good as classic Bonadonna CMF, and I think the NCIC study compares to a standard adjuvant regimen, which is classic PO-cyclo-Bonadonna CMF. I think that's the issue.

CHAIRPERSON DUTCHER: Dr. Margolin?

DR. MARGOLIN: I think this is more rhetorical than anything because I don't think there's an answer, but I'd just like to hear your comments.

I don't think CMF is standard adjuvant therapy anymore for most patients with breast cancer, and you know, the question is: what do we say about this drug that isn't already being said about doxorubicin?

You know, we're moving towards more complicated, more dose intensive therapy in the adjuvant treatment of breast cancer. We're also using more conservation surgery with, therefore, more

radiation, as well as more radiation even in those patients who had a mastectomy who have positive lymph nodes that wasn't the case a few years ago.

I think that opens up a lot of questions about what will be unique about this drug that we don't already have.

DR. MILLER: Well, I think if we go back to 1989 when the study was designed, CMF was the North American standard at that time. You have to remember that the study, the NSAPB 15 study was not published until 1990 that established that AC was equivalent, and in 1,400 patients, was equivalent to CMF, and the reason that AC was chosen, as they say in the paper, was because it was more convenient for patients, in essence, to get four cycles rather than six.

We're coming here. I know that one can't compare across studies, but we're coming here with data that say that CEF, when given in this fashion, is better than CMF, and I think that that is the message that needs to be conveyed to American women.

I think this gives us an opportunity, too, to start to do some new things in terms of moving from

what Mark and Kathy and others at the NCIC have done, the new trials that look at dose intensive or dose escalated EC, for example, followed tax taxitere and start to build on this result in the future.

CHAIRPERSON DUTCHER: Other questions, comments?

(No response.)

CHAIRPERSON DUTCHER: No? Okay. Thank you very much.

DR. MILLER: Okay.

CHAIRPERSON DUTCHER: Great. A quick break, 15 minutes, while the FDA gets ready to present.

(Whereupon, the foregoing matter went off the record at 3:34 p.m. and went back on the record at 3:54 p.m.)

CHAIRPERSON DUTCHER: Okay. We're going to go ahead with the FDA presentation. Dr. Honig.

DR. HONIG: Thank you.

I'm going to present the FDA analysis of epirubicin, and as you've heard, there are two separate indications under consideration, one for

early stage breast cancer and one for the first line treatment of metastatic breast cancer.

I'd first like to acknowledge all of the members of the epirubicin review team. As you've already heard, epirubicin has been extensively marketed worldwide. There's a tremendous amount of data both published and unpublished, and it took a lot of effort from a lot of people to be able to look at all of this in detail.

Again, I don't want to repeat things that have already been said previously. The point that I would make from this slide is one that you have heard before: that epirubicin is widely marketed; that an NDA was first submitted in July of '84 for treatment of advanced breast cancer. That was not first line treatment, as you're heard, the application was essentially incomplete, resulting in a not approvable letter.

So it was not that there was some major lack of efficacy that was found in the FDA review. I think it's fairer instead to characterize it as incomplete data, not permitting any kind of conclusion

to be drawn at that time.

The current NDA, however, includes new data, studies that were not previously submitted, as well as two different indications from those in the original NDA submission.

Again, Dr. Miller has already discussed these points, but again, I think it's worth reiterating the fact that the original recommended dose for epirubicin came from some early Phase I trials in the late '70s which said that a dose of 50 to 75 milligrams per meter squared in combination was the recommended dose.

A new set of Phase I trials that were performed for a variety of reasons redefined the optimal dose as somewhere between 100 to 150 milligrams per meter squared as a single agent, and that doses of 100 or even higher in some cases have been used in combination therapy, and that these are the doses, around 100 or so, that we are discussing today.

I'm going to discuss the trials MA-5 and GFEA-05 submitted in support of the adjuvant breast

cancer recommendation. You've already heard about a third adjuvant trial. We received a study report, but did not receive primary data from this trial, and so I'm not going to discuss that particular study. That was one of epirubicin plus Tamoxifen versus Tamoxifen.

These trial had a number of features in common. Both enrolled women that had node positive breast cancer. Women with T-4 tumors were excluded. Both trials used six cycles of chemotherapy. As was mentioned in the discussion, for women who had a lumpectomy the radiation therapy was delayed until the completion of chemotherapy, and in both trials there was stratification by nodal groups.

The primary endpoints were disease free survival and overall survival with a follow-up in both trials of approximately five years or so.

Quality of life was a stated endpoint in MA-5, and honestly, I had not planned to spend any time on that because in our estimation there was a significant amount of missing data. It was very difficult to analyze it well or in a meaningful fashion, and I think that the best statement that Ruth

Anna Davey, our statistician, and I could come up with was that the curves for CEF looked somewhat lower than CMF throughout therapy, and that at the conclusion of treatment, the quality of life on both arms improved substantially, probably beyond the level seen at baseline by about month 12 to 15 or so.

What were the differences between these two adjuvant studies? First of all, the patient population. MA-5 enrolled only premenopausal women. GFEA-04 also included postmenopausal women as well.

Also in the selection of the nodal groups, to get onto MA-5, patients were required only to have one or more involved lymph node. GFEA-05 was designed to theoretically have a higher risk group, and so these criteria were designed along those lines. You could either have four or more positive nodes. Women with one to three positive nodes were eligible, provided that their tumors were estrogen and progesterone receptor negative and had a histologic tumor grade of two to three.

What were some of the other differences? These involved permissible concomitant therapy. On

MA-5 you've already head that antibiotic prophylaxis was used on the CEF 120 arm. In GFEA-05, post mastectomy chest wall irradiation was permitted. I mention this predominantly because of recent literature suggesting that post mastectomy chest wall irradiation could influence survival.

In fact though the use of this modality was balanced between treatment arms. In addition, on this study post menopausal women were to receive Tamoxifen 30 milligrams daily for three years. Again, it's unlikely that this substantially influenced the outcome. The distribution of postmenopausal women was similar between the two treatment arms, and not only was receptor status balanced between the arms. It was also balanced within the subset of postmenopausal women, so that that should have been approximately equal on both arms of the study.

In addition to stratifying by the number of modes, on MA-5 patients were stratified by the type of surgery in their receptor results, and on GFEA-05, randomization was balanced by center.

I don't want to go through these in

detail. You've already seen the trial regimens that were used on these two studies. If one looks at the differences in does and schedule, one can look at the different arms within each study and can then compare arms in a general sense between studies.

On the MA-5 study, as you're already hear, the doses of cytonan and 5 FU were higher on the CMF arm than on the CEF 120 arm, presumably then allowing one to attribute any effects of therapy to the epirubicin itself on this arm.

In FEC 50 versus FEC 100 on the GFEA-05 study, the only difference was in the dose of epirubicin since this was designed to be a dose response study. The cytonan and 5 FU doses were constant.

If one looks across the studies, the dose of epirubicin was higher on MA-5. It was 125 milligrams per meter squared per cycle and 100 milligrams per meter squared per cycle on the 05 study.

The schedules were also slightly different. MA-5 used a day one, day eight, every 28

day schedule. GFEA-05 gave all drugs intravenously on day one and repeated them every 21 days, and again, the doses of CMF were slightly higher on MA-5 than on GFEA-05.

These are the efficacy results for the study MA-5. This looks at disease free survival and overall survival, and the green are the CEF 120 arms; the red are the CMF.

And I will come back to this P value in just a couple of slides, but you can see on both sides here, the CEF 120 arm curves are on top, statistically significant here, and as I said, we'll come back to this P value in just a minute.

In GFEA-05, the red line is the FEC 100 arm and the green is the FEC 50, and you can see again that in both cases the FEC 100 treatment was associated with statistically significant improvements in both disease free and overall survival.

This slide summarizes it in terms of the Kaplan Meier estimates of relapse free survival and overall survival at five years. These numbers you've seen before and are those that were reported by the

applicant.

What are the differences between what you're heard from the applicant and what I've presented here?

The original protocol for MA-5 was unclear on the exact nature of the statistical comparison. It did say the disease free survival and overall survival would be compared using a life table and Mantel Haentzel test.

It was not specific at all about whether the stratification factors used to balance randomization would be used in the analysis or not. In general, it has been our default position to look at a nonstratified intent to treat analysis overall, and that's what we had performed.

The applicant had presented analyses that were stratified by the randomization factors, which I understand has been the common practice in the NCIC.

There really is no difference in the results that we got. We actually got curves that were very similar. The CEF 120 arm was consistently on top no matter how you did it with the same five-year

Kaplan Meier estimates. The only difference is that the P value for overall survival is either significant or non-significant depending on how you look at that.

We discussed this issue in detail with our statistician who felt that in this particular case, the use of the stratified log rank test was acceptable because when you look at the overall population and then you look at the individual randomization strata, you see the same results consistently. The strata were not powered to show a statistically significant effect within the randomization strata, but it does not appear that one particular subset accounted for the entire effect seen consistently.

I'm sure Dr. Simon will have more to say about that or questions about that, but I think that the bottom line, the take home message for us is that we see a positive effect associated with FEC 120 that we can reproduce and we can believe, that appears to be clinically meaningful regardless of the P value that you would assign to that.

One other thing that we were concerned about between MA-5 and GFEA-05 was whether all of the

benefit was accounted for by premenopausal women. Remember that in MA-5 there were only premenopausal women. We saw benefits. Could we see it also in the postmenopausal women?

And, yes, in fact, when you analyze by menopausal status, again, they were not powered to look at a statistically significant difference there, but you do see the same effect and generally the same magnitude of effect, which suggests that both groups are benefitting.

Toxicity, again this slide is intended not to be a comprehensive listing of all of the toxicities observed in this trial. Clearly there are more toxicities that are associated with chemotherapy, but to highlight just a few points, febrile neutropenia, as you've already heard, was greater on CEF 120 than CMF, and again, appeared to be higher on the FEC 100 versus the FEC 50 arm.

Nausea and vomiting was fairly significant. I would point out that serotonin specific antiemetic therapies, such as endansetron and granesitron, were not available when these studies

were done or were not used.

Diarrhea on MA-5 was somewhat higher on CMF compared to the CEF 120, and was relatively low incidence on the GFEA-05 study.

Finally, stomatitis was greater with CEF 120 than CMF and also was more predominant on the FEC 100 than the FEC 50 arm, although this incidence was less here than on MA-5.

What about long term toxicities of therapy? Again, this shows all deaths that occurred on study during the course of treatment, and we agree with the applicant's assessment that none of these were related to specific drug toxicity.

Leukemia though and cardiac toxicity are problems that we worry about whenever we look at adjuvant therapy. Again, I don't want to spend a lot of time on this because I think Dr. Miller addressed some of these points during the committee's questions.

In these two trials, the leukemias were associated with cumulative doses of 495 milligrams per meter squared or higher. It has occurred at lower doses in the database that Dr. Miller also referred

to.

These have the typical characteristics of treatment related leukemias with a short latency, M4/M5 subtypes. Many of these patients did not have chromosomal analysis done, but in the few cases where it was performed, it was consistent with the treatment related change, and again, I think that the applicant in their reporting really did a very nice job of estimating the entire group of women that were treated in trying to present some meaningful percentages.

It's always very difficult to look at even a 716 patient adjuvant trial and get a true sense of what the incidence is going to be if it's used more widely. These were their best estimates from their database of .24 percent risk at three years and .77 percent at give years.

In terms of cardiac toxicity, on study MA-5, LVEF, left ventricular ejection fraction, measurements were mandated at regular intervals throughout the study. Five patients on CEF 120 and one on CMF developed congestive heart failure, and as you might expect, a higher number experienced drops in

LVEF that were asymptomatic.

On GFEA-05, it's very difficult probably to get a true sense of cardiac toxicity because the cardiac evaluations were optional at the completion of chemotherapy, which is really when you would expect to see most of the events, sometime afterwards in follow-up.

Nonetheless there were four patients on FEC 100 versus one on FEC 50 that were reported to have congestive heart failure.

The applicant performed a similar analysis of their database as they did for leukemia and estimated, again with the curves that you saw during the discussion period that there was about a four percent incidence of CHF at a cumulative dose of 900 milligrams per meter squared.

And just to put this in perspective, I listed what the maximum epirubicin doses were anticipated to be from the protocol specified treatment: 720 on MA-5, 600 on GFEA-05.

So if we look at adjuvant breast cancer and the trials that were submitted overall, we can

talk about the strengths, the weaknesses, and perhaps some neutral findings that we see in these trials.

For MA-5, CEF 120 was compared to CMF, and again as has been mentioned during the discussion, the most dose intense CMF comparator was chosen, the classic Bonadonna regimen. In GFEA-05, which was designed as a dose intensity study, that was able to be accomplished with maintenance of a two to one ratio of epi. dose between the two arms, and there was a significant difference in overall survival for the high dose arm compared to the lower dose arm.

Both studies showed significant differences in disease free survival in favor of the higher dose epirubicin arm.

The weaknesses, again, you may want to move this around on the slide depending on your interpretation of the statistical analysis. There was a survival trend that was seen for CEF 120 compared to CMF. It was not statistically significant if you performed an unstratified P value overall intent to treat. If you stratified it by the randomization factors, it moves over to the significant level.

Again, these higher doses of epirubicin were associated with a significant incidence of acute toxicity, and the benefits of this treatment need to be weighed in comparison to the cardiac toxicity that was observed, as well as the leukemia risk.

In the neutral category, I simply put this point, which was that at least from the reported rates of in breast recurrence, there did not appear to any difference between the two treatment arms in that the reported rates were comparable to those that have been reported for delaying radiation therapy after chemotherapy in some of the other publications, such as the Joint Center randomized trial.

So in summary, there was an improvement seen in both disease free survival and overall survival with epirubicin given at the planned doses of 100 and 120 milligrams per meter squared, and that the delivered dose intensity for cytonan and 5 FU was higher on the CMF arm than the CEF 120 arm in the MA-5 study, again suggesting that we could attribute this effect directly to the effect of epirubicin rather than an additional effect of cytonan/5 FU interaction

in the regimen.

Now, if we look at the advanced breast cancer trials, I will talk about HEPI-013, HEPI-010, which were the applicant's advanced breast cancer trials one and two. Again, I will not discuss trials three and four. We had study reports for those, but no primary data.

These also shared a number of common design features. Both of them enrolled metastatic breast cancer patients with no prior chemotherapy for metastatic disease. Patients with measurable or evaluable disease were eligible and were required to have had a disease free interval of greater than 12 months.

Patients were stratified by the number of organ sites of disease and by the presence or absence of visceral disease, and both of these studies incorporated a design where six cycles of treatment were given followed by observation. There were some provisions to give additional cycles to responding patients, either two or three.

What were the differences? You could have

had prior adjuvant anthracycline therapy on the 010 study, but a relatively small amount, less than 60 milligrams per meter squared.

The other difference was the way that the endpoints in these trials were prospectively defined. For study HEPI-013, the first study, the primary planned endpoint was time to progression followed by response rate, followed by quality of life, followed by survival.

In the 010 study, which was the dose response study, overall survival was the protocol specified primary endpoint. Response rate was second, then time to progression, and then quality of life.

Unfortunately, the quality of the quality of life data in both of these studies was poor. There was incomplete data collection, and it precluded any analysis at all. So we will not be discussing quality of life for these studies either.

Again, you've seen the trial regimens for these studies. What were the differences? In the first trial which compared CMF to FEC 100, again, the cytonan and 5 FU doses were higher on CMF than on the

FEC arm, and again, for the 010 study, which was the dose response study, only the epirubicin dose differed.

There was some difference between these two studies. The high dose epirubicin arms in both the 013 study and the 010 study gave the identical dose of epirubicin, 100 milligrams per meter squared per cycle, but delivered it with a differing schedule: day one, day eight, every 21 days compared to all IV day one every 21 days, and again, some differences in the cytoxan and 5 FU doses between studies.

This shows the results of these studies. The first one is HEPI-013, where again the green curve on top is the FEC arm. The red is CMF.

There was a statistically significant improvement in time to progression. There was no difference at all in the overall survival, although, again, you can see the green curve is here.

The median time to progression on this trial was 8.8 months for the FEC 100 arm compared to 6.3 months for the CMF arm with a significant P value.

Median overall survivals showed a somewhat

longer survival for FEC 100 compared to CMF, but these were not statistically significantly different.

As you have already heard, as well, 44 percent of patients on the CMF arm went on to receive anthracycline based therapy, raising a question echoed from this morning's discussion as to whether second line therapy can obscure a potential survival benefit from first line therapy. This speaks, I think, to Dr. Temple's example this morning.

And, again, no matter how we analyze this, there were some issues here again about whether the analyses should be stratified, nonstratified, et cetera. We really come up with the same findings.

In the 010 study, there was no difference in overall survival or time to progression. The only observed difference was in response rates. Forty-nine percent on FEC 100, 36 percent on FEC 50, with a significant P value, and we were able to go back to the primary tumor data and verify these response rates.

What about the toxicities that were observed? First are deaths on study, five percent on

the FEC 100 compared to three percent on CMF, three percent versus one percent.

I will show you the details of these deaths on study because I think this is a little misleading. I mean we tend to think about deaths on study as the ones that are directly related to toxic effects of the drug. So I will detail those in just a minute.

Cardiac toxicity we'll also talk more about. Febrile neutropenia here, ten percent on FEC 100 versus eight percent on CMF; eight percent versus .4 percent on the dose response study. Again, significant incidence of Grade 3 to 4 nausea and vomiting. Again, serotonin specific antiemetic therapy was either not available or used in a minority of the patients on these trials.

Anemia was also observed in this study, 12 percent on FEC 100 compared to nine percent on CMF, seven percent versus one percent for the dose response study.

If one looked at the incidence of blood transfusions, they were fairly constant across all

trials. So that patients certainly had this observed and reported. It's not entirely clear what the clinical consequences of this were. It may have contributed to lethargy, et cetera, but certainly not to an increased need in blood transfusions.

Mucositis, 12 percent on FEC 100 and in contrast to the adjuvant studied was actually higher slightly at 15 percent on the CMF arm in the metastatic studies, but again, a difference here with FEC 50 compared to FEC 100, .4 percent compared to ten percent, suggesting that there is an increase.

The deaths on study I said I would show you overall. Some of these were potentially related to complications of therapy. A number of them were due to progressive disease.

Two deaths on each arm in 013 were due to febrile neutropenia compared to two on FEC 100 versus none on FEC 50. Pulmonary emboli were seen presumably related more to malignancy and to the general administration of chemotherapy rather than an epirubicin specific effect.

And a number of other problems that,

1 although they look ominous, were not always clearly
2 related to drug administration, such as respiratory
3 failure or cerebral infarction.
4 In terms of the cardiac toxicity, on HEPI-
5 013, there were serial mandated evaluations, as you
6 can see, and 71 percent of patients randomized to the
7 CEF arm were compliant with those. Remember that on
8 this study responders could receive up to 900
9 milligrams per meter squared of epirubicin, and that
10 in this trial, by my analysis, ten patients or 4.5
11 percent on the FEC arm had congestive failure. None
12 were observed on the CMF.
13 This is a little bit different from what
14 was reported by the applicant where the numbers are
15 four and zero, and we will discuss this further as to
16 how we view these cases.
17 For HEPI-010, evaluations were also
18 mandated, but overall there was relatively poor
19 compliance with the schedule. Patients on this trial
20 who were in complete remission could have received up
21 to 800 milligrams per meter square of epirubicin, and
22 here the incidence of congestive heart failure was

quite low, one patient on FEC 100, two patients on the FEC 50 arm.

So how can we look overall at the advanced breast cancer studies? Again, the 013 trial was designed to look at a dose intense CMF regimen. This was an IV one. This was not classic oral Bonadonna, but this particular IV schedule was chosen because it was the IV schedule that came as close as possible to the Bonadonna delivered dose intensity.

There was a statistically significant difference in time to progression for FEC compared to CMF. I'm going to leave that in the strength column for now, and the committee will be discussing that shortly.

In 010, this study was able to maintain a two to one ratio of the epirubicin dose in this planned study, but again, there was no difference in time to progression at all in this study, and in neither study was there any difference in overall survival.

There was increased incidence of acute toxicity with epirubicin. There is the incidence of

cardiac toxicity to consider in the risk-benefit ratio as well, and what I left in the neutral ground here is the better response rate for FEC 100 compared to FEC 50 on 101.

Also as we've alluded to in the discussions this morning, we usually consider response rate in the context of accelerated approval, and this is not an accelerated approval application.

One other thing that we've talked about through the morning's discussion of time to progression is this. What do we think first line treatment conveys in terms of the survival benefit for metastatic breast cancer? And in general, doxorubicin has been considered to be the standard. We have often said it conveys a six month survival benefit. We've heard this morning it could really be anywhere from two to six, depending on the literature.

And it has been generally FDA's position that new drugs for first line treatment of metastatic breast cancer should demonstrate that this benefit is preserved, that you're not losing a survival benefit by using a new therapy.

So at our request, the applicant performed a mini meta analysis looking at doxorubicin in first line treatment of breast cancer and comparing their drug. Again, I don't want to spend a lot of time going through the statistical analysis for this. They did provide a prospective statistical plan for us, look at the literature and do it.

The overall odds ratio of doxorubicin to epirubicin for survival was 0.98 with 95 percent confidence intervals of .8 and 1.20. Because the lower bound of the confidence interval here is .8, this has been our general standard for comparability and would suggest that the two treatments are comparable in this situation.

This clearly is not a perfect comparison. There's always a problem with publication bias. Positive studies are published more often than negative.

Also the difficult of what's actually included in a publication. This was looked at by our statisticians. They noted the same drawbacks and potential problems that the applicant noticed in their

review of this issue, but also stated that this was about the best analysis that one could expect given the limitations of this kind of analysis.

So what are the regulatory issues for metastatic breast cancer with epirubicin? In 013, benefit was measured by time to progression, but not by survival. There is the argument that was discussed this morning that survival could be potentially confounded by the 44 percent crossover rate or I should say subsequent use of anthracycline rate on the CMF arm.

In the 010 study, response rate was the only endpoint that was significantly different between the two arms. Why is this the case? Is it that the outcome is somehow sensitive to the schedule? Is it that there needs to be a threshold dose rather than a dose response relationship for epirubicin? And would this be different in the metastatic setting rather than the adjuvant setting where we did see a dose response benefit?

So this slide summarizes a few of the questions that you'll be discussing specifically with

regard to the metastatic indication. I don't want to spend time reading them, but I think that they pick up on the discussion this morning and look at the endpoints that were measured in these trials and hopefully we look forward to some interesting discussion by the committee and some input.

Be happy to answer any questions if there are ny.

CHAIRPERSON DUTCHER: Thank you.

Are there questions from the committee for Dr. Honig?

Ms. Zook-Fischler.

MS. ZOOK FISCHLER: Yeah, I have a very general question. It's not specific, and I guess I could have asked it of the drug company as well.

I see some benefits, but I don't see significant ones, and I hear you saying no survival benefit, and I just wonder why the time, money, and energy is being invested in drugs that don't provide the patient with any really significant long term benefits of survival. I mean I see it's comparable to doxorubicin, and I see in some instances they do show

some benefit, but when we talk about a two month survival rate, it goes back to what we were discussing this morning. It doesn't answer the needs of the patients.

So it's just a very general question as to why.

CHAIRPERSON DUTCHER: Anybody have a comment for her? What is the niche for this drug? Dr. Miller, do you have any comment?

(Laughter.)

DR. MILLER: Yeah. Well, I just want to make sure to emphasize again there is a survival benefit with this drug, and the survival benefit is clearly documented in the adjuvant setting in two studies, major studies.

And I think what we're saying here in essence is the drug provides tumor control and tumor shrinkage that in the early setting can result -- in the adjuvant setting can result in survival advantage and disease control and in the advanced setting can result in disease control, and that the two, in essence, go together, very symmetrical designs of

studies which document, I think, the same basic principles for this drug in both early and advanced breast cancer.

MS. ZOOK-FISCHLER: I guess my concern has to do with the cardiac toxicity, which for me, you know, it's a risk that I'm not sure for me offsets the benefits. I guess I'm just posing -- I'm just expounding some of my concerns. I'm not sure there are concrete answers, but as a patient and as an advocate, I would love to see those drugs that offer substantial survival benefit, and if they can't offer substantial survival benefit, then significantly less toxic effects, one or the other.

But in this case I see it has some survival benefit, but with significant toxic effects. So when you propose it to the average patient, I'm not quite sure how excited about it she can be, and statistically it may be very exciting.

CHAIRPERSON DUTCHER: Well, I think one of the comments made by one of the speakers at the open public hearing was that it might provide some economic competition.

Dr. Levine, did you want to make a comment?

DR. LEVINE: If I may.

I'm very sympathetic to the comments that were just made, but nonetheless if you look at the survival benefits demonstrated in adjuvant chemotherapy, if we look at the PETO overview, the meta analyses, which is what's quoted to most patients by physicians, the magnitude of the survival benefit from chemotherapy in general in the adjuvant setting is small or modest, at best, and many of those trials that went into that overview were with CMF.

The benefit that you're seeing with this epirubicin containing regimen or regimens is almost of the same magnitude improvement over and above that with CMF. So that when Kathy and I use this in Canada and we explain it very carefully to patients, the risks and the benefits, some people do choose to take the medication or the regimen because the magnitude of the benefit is over and above that which is commonly accepted. So it is an improvement.

CHAIRPERSON DUTCHER: Dr. Margolin.

DR. MARGOLIN: Dr. Levine, don't sit down yet.

(Laughter.)

DR. MARGOLIN: I think that brings up an interesting questions for those of us who are still concerned about what this drug will do that doxorubicin doesn't or not do that dox. does. In Canada you have both drugs available?

DR. LEVINE: Yes.

DR. MARGOLIN: So when do you decide which drug to use and what do you tell the patient?

DR. LEVINE: Madame Chair, can I answer the question?

CHAIRPERSON DUTCHER: Please.

DR. LEVINE: Well, the first issue is I think I'm addressing the issue first from the early stage breast cancer adjuvant therapy, and the literature as it is does not demonstrate an advantage for CAF or CAF or FAC containing regimens compared to CMF. Not too many trials, mind you, but the SEG study which was only published in abstract form was a negative trial. That's the first point.

So the SEF trials are the only ones that are positive in terms of benefit over SMF.

The second point is dox. and epi. are not the same in the early setting, in the early disease setting, because the typical Bull and Tormey CAF regimen, which is a day one/day eight schedule exactly like we used, the total milligram -- it's 30 milligrams per meter squared day one and day eight. So it's 60 milligrams compared to 100 of epi.

If I would try to double the dose of adria. in CAF to make it comparable to the doses of epirubicin in CEF, I could not give it even with growth factor because of the toxicity to the patient. One hundred and twenty milligrams per meter squared per month of adria. or doxorubicin in a day one/day eight regimen, the toxicity because of mucositis and myelosuppression, you couldn't do it. It would be too toxic.

So we take the premise that, you know, CAF cannot be substituted for CEF in the adjuvant setting, and when we explain this to patients, we explain that a common standard in Canada had been CMF. We did this

national trial in which CEF was superior, and we presented the data like was so eloquently presented by all speaker this afternoon.

We do present the toxicity and the problems with heart failure and leukemia, and we, you know, try to help the patient make the right choice for them, a fully informed patient.

If they choose to take CMF, not to take CEF, that's okay, and we would offer them CMF or AC or something like that, but that's the way we go about it, and some women who are fully informed choose to take -- actually many choose to take CEF, but some decline.

DR. KROOK: Can you put a number on that, three to one, four to one, in your own experience?

DR. LEVINE: Am I allowed to do that, Madame Chair?

CHAIRPERSON DUTCHER: Sure.

DR. LEVINE: In our center, in our center, and in Kathy's center, two large cancer centers that see about 7,000 new cancer patients a year, not all breast, but so they're tertiary, large cancer centers,

in our new node positive premenopausal women, I would estimate that between 60 and 70 percent of Canadian women are opting to receive CEF.

DR. KROOK: Of those who choose chemotherapy?

DR. LEVINE: Correct. Most premenopausal women, as you know, node positive, would opt for chemotherapy. So it's --

CHAIRPERSON DUTCHER: Dr. Temple.

DR. TEMPLE: Do I understand that even though everyone would like to see studies against adriamycin, there are no data showing that an adriamycin regimen is better than CMF, and there are data showing that this epirubicin regimen is better than CMF? So that there's a survival advantage over an active survival increasing regimen. That's what you're contending is the benefit here.

DR. LEVINE: Yes, sir. There --

DR. TEMPLE: That's why someone might choose this you're saying?

DR. LEVINE: Yes, that CAF has not been compared to CEF, and the trials of CMF versus CAF have

been negative.

CHAIRPERSON DUTCHER: Any other comments? Thank you. Dr. Simon.

DR. SIMON: I just wanted a clarification in one of the metastatic trials. What's the distinction between time to progression and time to treatment failure? And if it's in time to treatment failure you're counting other events as events, like withdrawal from study for toxicity, how were they handled in time to progression analysis?

DR. HONIG: I'll have to refer that over. Time to treatment failure was not a prospectively defined endpoint. So we at the FDA limited ourselves to time to progression. Time to treatment failure I'll let Dr. Miller discuss. That came up afterwards.

DR. MILLER: Well, we used what we consider a fairly standard approach in that for patients to general progression, at times general progression was censored if they went off study or there wasn't an ability to assess progression. In patients in the case of time to treatment failure, patients who discontinued due to death, to toxicity,

loss to follow-up -- I'm sorry. Just death and toxicity, those sorts of things would constitute failure, as well as progression would be considered failed. So it's a matter of censoring.

DR. SIMON: I would just like to say I think censoring patients who die or go off study because of toxicity is a very questionable thing to do. I would actually favor the time to treatment failure endpoint because censoring the others, that their subsequent prognosis would be no different than had they not -- that they would be sort of representative patients, I think, is very questionable.

DR. MILLER: But I would want to emphasize that we did analyze TTF for that very reason in these studies and did show significant benefits in that endpoint.

DR. SIMON: Well, with time to treatment failure, the difference was between -- the median was five months to 6.2 months.

DR. MILLER: Yeah.

DR. KROOK: Turn this on.

Following this morning's discussion, I take for granted that those people who were on the metastatic studies were basically asymptomatic. As I look at it, they were all performance status of zero to one.

DR. HONIG: That's correct, and I did mean to mention that. There was a nice submission in the NDA, too, that had collected a number of symptoms at baseline, and nearly everybody was scored as grade zero on those selected symptoms.

DR. KROOK: As you read the case reports, and I realize the limitations, judgments, you're reading somebody else's, did you get the feeling that the quality -- and we're coming back to this --

DR. HONIG: Yes.

DR. KROOK: -- the quality changed as the perception, and I realize that when I as a physician in the presence of somebody who is receiving these drugs, it's what I put in the notes. Did you have a perception of improvement of whatever that global assessment is?

I realize there's not scales.

DR. HONIG: Right. I mean, it's a good question, and it's a multi-focal issue. I mean, first of all, as you said, most of the patients were asymptomatic at baseline so that a lot of the case report forms simply reflect the fact that they had a fair amount of nausea, vomiting, some mucositis, and ultimately would develop progressive disease and go off.

But the case report forms, you know, sometimes you get room for an investigator to write in a lot of additional information, but these case report forms were not designed that way. So they're really check boxes.

I mean I think the best you can do overall is to say that most people were asymptomatic in terms of their tumor as best you could sort out, had treatment related effects, and that there did not seem to be excessive dropout by the patients by patient choice.

DR. KROOK: And one short question only because it comes up, toxicity. Did those people who had decreased left ventricular ejection fraction, were

these the same people that got heart failure or were they two separate -- in other words, they did correlate?

DR. HONIG: Yes, there was overlap.

DR. KROOK: Okay.

CHAIRPERSON DUTCHER: Thank you.

We're going to have one more comment for open public hearing, very briefly. Ms. Fonfa.

MS. FONFA: Thank you very much for allowing me to speak.

This is not at all to be taken as specifically against this drug. I want to say a sort of global thing.

CHAIRPERSON DUTCHER: Name and --

MS. FONFA: I'm Ann Fonfa, representing the Annie Appleseed Project, New York City.

My perspective is, and I think it was brought out by the word "significant," I don't see significant change in survival, and I don't see significant change in time to disease progression or any other thing, and as a cancer patient, I want to reiterate long term survival is what we care about.

Advances in quality of life, and if it has to be time to disease progression, we want a lot of time, and I don't see that here, and I don't see it on anything that we have.

And I want to say that if we don't hold drug companies to very high standards, we get drugs that are only an eentsy-teensy (phonetic) bit, and this is the measurement I use, better than what we have.

It's no good. We have to get you folks to look a little higher. You're spending millions of dollars, and you're not getting anything that matters to cancer patients, and now it's 30 years later. For me it's personally six and a half years later. I'm very unhappy, and I represent thousands, hundreds of thousands of people who feel the same way.

Please, please, aim higher. I beg you.

CHAIRPERSON DUTCHER: Thank you. Thank you very much.

So we have some issues. We'll go on to the questions at hand. Okay. The first question, talking about the two randomized controlled trials,

for adjuvant therapy in the evidence of axillary node involvement following resection of primary breast cancer, Stage II and III. Study MA-5, randomized, pre and perimenopausal women with lymph node positive breast cancer to receive FEC 120 versus CMF. GFEA-05 in women with high risk, node positive, greater than four positive nodes or one to three with ER negative, and Grade 2/3 tumors, and randomize them to receive FEC 100 or FEC 50.

The table presents the results of these trials. The actual delivered dose intensity in both trials was about 100 milligrams per meter squared per cycle.

Question to the committee: do these randomized trial demonstrate that epirubicin at the planned doses of 100 and 120 milligrams per meter squared in combination with 5 FU and cyclophosphamide is effective for the proposed indication?

And that's looking at both relapse free survival and overall survival. Dr. Nerenstone.

DR. NERENSTONE: I'm just confused as to which recipe they want us to consider for up front