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ONCOLOGIC DRUGS ADVISORY COMMITTEE

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P R O C E E D I N G S (8:00 a.m.)

Agenda Item: Call to Order and Opening Remarks

DR. DUTCHER: Good morning. This is the second day of the 56th Oncologic Drug Advisory Committee Meeting and we're here today to discuss two supplementation indications for paclitaxel (Taxol). We're going to be having some changes in the people at the table, so we're going to go around the table and introduce ourselves and then Dr. Somers is going to read a conflict of interest statement.

I'm Jan Dutcher from Albert Einstein Medical Oncology in New York.

[Introductions were made.]

Agenda Item: Conflict of Interest Statement

DR. TEMPLETON-SOMERS: Okay. I now need to read the conflict of interest statement for Taxol for the ovarian cancer indication. The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests and firms regulated by the Center for Drug Evaluation and Research

present no potential for conflict of interest at this meeting with the following exceptions.

In accordance with 18USC Section 208 and 505 of the FD&C Act, a full waiver has been granted to Dr. Kim Margolin. A copy of this waiver statement may be obtained by submitting a written request to FDA's Freedom of Information Officer located in Room 12A-30 of the Parklawn Building.

Further, we would like to disclose for the record that Dr. Schilsky and Dr. Swain have interests that do not constitute a financial interest in the particular matter within the meaning of 18USC 208, but which could create the appearance of a conflict. The agency has determined, notwithstanding these involvements, that the interests in the government in their participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Dr. Schilsky and Swain may participate fully in today's discussions concerning Taxol for ovarian cancer.

Finally, we would like to disclose that Dr. Robert Ozols will be excluded from participating in all matters concerning Taxol.

In the event that the discussions involve any

other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

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

Agenda Item: Open Public Hearing II

DR. DUTCHER: Thank you. We're now going to proceed with the open public hearing, which will be for both the morning and the afternoon session. Our first speaker is Mr. A George Forbeck.

DR. TEMPLETON-SOMERS: Please give your name and any affiliation and any support from the pharmaceutical sponsor.

MR. FORBECK: George Forbeck and I have no sponsorship other than cancer.

Good morning. I gave Karen a fact sheet of a little bit about myself. It's short. I want to thank the committee for the opportunity to present my thoughts on Taxol. My protocol, when I was undergoing treatment for

cancer, H. Lee Moffitt and the consideration, the knowledge and the ability of H. Lee Moffitt itself. My treatment was aggressive. My statement today will be short.

I have been most fortunate that I am a survivor of cancer and also have the privilege of serving on the Patients Rep Committee for the Eastern Cooperative Oncology Center. Also, all the committee members on the PCOG(?) Group are survivors and of more than one cancer in some cases.

In the late fifties, my father passed away of cancer in a veteran's hospital in Chicago. I had just come out of the Korean War and had never heard of cancer. I saw the pain and anguish that we went through because there was nothing at that time.

In 1983, my son Bill Guy, five of six children, was diagnosed with neuroblastoma, a childhood cancer. Despite the best efforts of the Mayo Clinic in Rochester, and the Rosewell(?) Park Pediatric Oncology Center, Billy passed away at the age of 11 in 1984. He had a quality of life at that time that wasn't bad, due to the expert help of the people at Rosewell and a protocol that was aggressive.

After Billy's death, my wife and I started a foundation that holds a scientific forum each year. A small

group of leading cancer and research scientists are invited to participate in a roundtable discussion in the hope of building each other's ideas, knowledge and experience. The objective is to provide a forum for cross fertilization of ideas, concepts, observations in the hope of shortening the cancer research timetable.

My background is not one of scientific knowledge or medicine. My experience is living with the disease of cancer. In 1994, at the age of 67, I was diagnosed with Stage IIIB adenocarcinoma lung cancer at the Mayo Clinic in Jacksonville. I was told I would probably die within a year to two years. I was treated at the H. Lee Moffitt Center over a three month period. My protocol involved chemotherapy with a combination of Taxol and Cisplatin and my menu had other things on it, with radiation each day for approximately 36 days. Aggressive treatment, that's what I needed and that's why I'm here today, Taxol.

Within five months, I was pronounced in remission and I continue to be in remission today. The outstanding clinical help made Taxol work. I have to say this for the H. Lee Moffitt. I've sent approximately 50 to 100 people there over the past six years and our average is outstanding. The encouragement that you receive from

Moffitt helps fight the disease.

Although three months of aggressive treatment was not pleasant, I was able to live somewhat normally. Most days I could walk at least a mile. I did have problems eating and lost about 30 or 40 pounds during the treatment. However, I weigh exactly today 181 pounds, the same as when I went in the Marine Corps in 1945.

I got to know some of the other patients who were following the same protocol as I was. In fact, I was delighted today because the nice lady right behind me is going to speak to you. We have had the same treatment and again Taxol has won.

I am convinced that the protocol using Taxol and Cisplatin was significant to my survival. Since my experience, I have recommended H. Lee Moffitt and their protocol to a number of others with similar diseases. I personally observed results far better than those of other protocols.

Since having my work on lung cancer at Moffitt, I also have had prostate cancer, which I'm a survivor of, with the new procedure at Moffitt. Just three weeks ago, I had four or five basal cells removed from my cheeks. So I am still a patient and still working at curing cancer.

The finale of this is a story about a friend of mine, Bernie from Wisconsin. It illustrates the success of Taxol and Cisplatin. Through friends of friends, I was put in touch with Bernie about four months ago. He had been diagnosed with the same type of cancer that I had in Chicago. His chances of survival were less than mine. I told him to point his car south and don't stop until you get to Tampa. He took my suggestion and two weeks he left in remission. I was at Moffitt two weeks ago. We were doing some work on the National Coalition for Prostate Cancer, and I watched Bernie get his last two hour treatment of Taxol. My treatments, I think they made a mistake, were somewhere between Monday until Wednesday night. But things have improved.

So anyway, that's my experiences. My work with cancer is ongoing. I spend probably somewhere between six and 10 days a month working with various parts of the disease. Our foundation is quite active and I'm delighted now to be associated with the Coalition of Prostate Cancer. Thank you so much. Any questions, I will be delighted to answer. Any thoughts about my treatment, byproducts, anything.

DR. DUTCHER: Thank you very much. We appreciate

it.

The next speaker is Phyllis DeAngelis.

MS. DEANGELIS: Good morning. I want to thank you all for giving me this opportunity to speak to you. As I said, my name is Phyllis DeAngelis and the purpose of my coming here is to tell you that there is life after lung cancer and there's life with quality. Excuse me, that's not from my cancer.

Also, people who smoked shouldn't really be looked down on. We didn't know any better when we started smoking. The only thing we were told was don't smoke out on the street because you look cheap. Other than that, it was okay.

I was pretty well hooked and I was a smoker until the day I was diagnosed, which was in November of 1993. I was fortunate enough to end up at Foxchase Cancer Center in Philadelphia. I happened to be in the right place at the right time. I was diagnosed with Stage IIIB non-small cell lung cancer. I had an eight centimeter tumor and the outlook was very bleak.

I went for seven weeks of radiation and went home and thought that I would try and enjoy the rest of my life. I had five children and six grandchildren, so I had a lot to

be thankful for, but I was only 56 and I really didn't want to die yet and I just didn't believe I was going to.

So, I found a little lymph node over here on the other side in my neck and I called the cancer center, went back up, was biopsied, and yes indeed, I had it in my lymph nodes. So we went for the clinical trial at that point. It was Taxol. I was put into the computer and randomly was chosen for the highest degree of Taxol and Cisplatin, supported by Nupogen(?) which was given to bring my blood back up where it needed to be. I also had that superior vena cava. There was no chance for surgery. I never say this right, the mediastinoscopy was done -- did I get through that? They said definitely, it was the original cancer that was in my lymph nodes.

So we started it and it wasn't fun. It was hard to find anything that was really appealing to eat and I did lose quite a bit of weight. I was down below 100 pounds. And here I am all these years later. I've had no recurrence of any kind. Today, I chose to come here rather than to go to my sister-in-law's funeral in New York State. She is being buried this morning. She died of lung cancer. She did not go to a cancer institute. She was not offered a protocol. I know she would be happy that I am here instead

of up there today.

It's just so important that lung cancer be brought out, you know it's kind of put in the closet. All we ever hear about is breast cancer, we hear about AIDS, we hear about prostate cancer. I never knew until I came down here that somewhere there is a little group, a support group for people that have had lung cancer. I've been to a lot of cancer facilities. But you're kind of pushed aside, well, you smoked, you know, but there are lot of people that were in that program that didn't smoke and had lung cancer.

It's something I just have to really sincerely hope that the message will get out that there is life after lung cancer. Cisplatin is the thing, Cisplatin with Taxol was my answer. I know that the Cisplatin got to be a little bit toxic for me. After all my required treatments for that, the Cisplatin was dropped and I stayed on Taxol for several more months. In January of 1995, there was no more tumor. Today, there is no more tumor. All they see is just a little scarring.

So, I don't know what else I can say, I'm not much of a speaker, and I don't know what else I can say except that I think maybe this is what I was spared for. The good Lord had to have a reason to leave me here. I buried my

husband last summer, so I guess now my job is to see to it that other people that are faced with these same problems can get the same kind of help that I got. Thank you very much. Does anybody have any questions?

DR. DUTCHER: Can you just tell us whether you have any sponsorship from the sponsor?

MS. DEANGELIS: I was asked by my doctor in Foxchase if I would be interested in doing this and I said yes. A few days later, I received a phone call and was told that Dr. Cory Langer(?) from, he was the head of the ECOG(?), that he would be happy to pay my expenses to come down. But regardless, I would have come down anyway. Thank you.

DR. DUTCHER: Thank you very much for sharing.

Is there anyone else in the audience that wishes to speak before we go on with the presentations?

Once again, thank you to the individuals who took the time to come and talk to us, we appreciate it.

Okay. With that, I think we will go ahead with the sponsor's presentation. We are going to be talking this morning about Taxol indicated as first-line therapy for the treatment of advanced carcinoma of the ovary.

Agenda Item: Sponsor Presentation

DR. CANETTA: Good morning. My name is Dr. Renzo Canetta. I'm with Bristol-Myers Squibb Pharmaceutical Research Institute. We are very pleased today to present to you the data on the use of Taxol in the first-line treatment of ovarian cancer.

Following my introduction, Dr. Steve Williams from Indiana University will review the status of the primary chemotherapy of ovarian cancer before Taxol became available. Dr. David Tuck from the Pharmaceutical Research Institute of Bristol-Myers Squibb will present the data of the pivotal trial conducted by the Gynecological Oncology Group. Dr. Benjamin Winograd, also from Bristol-Myers Squibb Pharmaceutical Research Institute, will provide the summary and conclusions for this presentation.

We are very pleased to have with us today the principal investigators of the other two recently completed phase III trials of Taxol, Dr. Piccart, principal investigator of the EORTC/Intergroup study and Dr. Franco Muggia, principal investigator of the GOG 132 Study.

Taxol was first approved as a single agent in the secondary treatment of ovarian cancer in December of 1992. Since that time, as you might remember, several presentations were made to this committee and several

approvals have ensued. Today we are presenting for the first time mature results of Taxol used in combination and in the therapy of previously untreated patients.

The role of Taxol in ovarian cancer has been clearly demonstrated in the second-line setting. Single agent efficacy and safety have been established after failure of first-line or subsequent chemotherapy. Lack of cross-resistance with platinum drugs has been clinically proven. Combinations with platinum compounds in the primary treatment of the disease represent a logical and an attractive choice.

We're going to present today mature data on the first completed phase III study. These results demonstrate a statistically significant and clinically relevant efficacy advantages for Taxol and cisplatin over the control of cyclophosphamide and cisplatin. The combination of Taxol/Cisplatin produces an acceptable safety profile without unexpected side effects.

The GOG-111 was the first phase III trial to be completed in this setting. Recently, two additional phase III trials have been completed and reported publicly at the ASCO meeting last year. The EORTC/Intergroup, conducted by Dr. Piccart and collaborators, administered Taxol over a 3-

hour infusion and the results of this trial fully support the therapeutic advantage for Taxol/cisplatin over standard therapy. The GOG-132, conducted by Dr. Muggia and collaborators, shows a better therapeutic index for Taxol and cisplatin as compared to high-dose cisplatin.

Today, there are several ongoing randomized phase III trials that are exploring the role of Taxol and carboplatin often in comparison to Taxol and cisplatin. These trials include those of Dr. Neijt and collaborators in the Netherlands and in Scandinavia, and of Dr. duBois and collaborators for the German cooperative group. Their preliminary results have also been reported. In fact, Taxol in combination with a platinum compound provides a new standard of care in the treatment of the disease.

We believe that based on the results that we represent in our submission, the proposed indication is warranted. Taxol in combination with a platinum compound is recommended for the primary treatment of patients with advanced carcinoma of the ovary.

Dr. Steve Williams will review the status of the primary chemotherapy of ovarian cancer before the introduction of Taxol. Steve.

DR. WILLIAMS: Good morning. I'm deeply honored

to have the opportunity to speak with you today.

Next slide please. As all of you are well aware, ovarian cancer represents a very significant health problem for women in the United States. It is estimated that there are about 25,000 cases diagnosed every year, and it is responsible for about 14,500 deaths in the United States annually. This represents four percent of all cancer diagnoses in women and five percent of all cancer deaths in women. It is the fifth most common cause of cancer death in women.

Next please. Ovarian cancer is staged according to a system proposed by the International Federation of Gynecology and Obstetrics. In this system, localized ovarian cancer, stage I or stage II disease, is disease that's localized to one or both ovaries with or without extension to other pelvic organs. Stage III and stage IV disease are more advanced stages of the disease. Unfortunately, it is somewhat unusual for ovarian cancer patients to be diagnosed when the disease is early, and thus most patients with ovarian cancer at the time of diagnosis have advanced disease. These women are treated with surgery and chemotherapy and are the ones that are relevant to our discussion today of chemotherapy for ovarian cancer.

Next please. Women with early ovarian cancer have a relatively good prognosis with substantial numbers surviving for long periods of time. Unfortunately, as I mentioned earlier, these are the minority of patients with ovarian cancer.

The prognosis for women with advanced disease is substantially less favorable. Stage III disease, or involvement of the peritoneal cavity is defined as being optimally resected after the initial surgery if there is less than one to two centimeter as the largest residual tumor remaining after surgery. Suboptimal stage III ovarian cancer is the situation when there is bulky residual disease after the initial surgery. As you can see, that is an important prognostic factor, the amount of residual disease after the initial surgery. Women with stage IV disease fair very poorly.

Next please. Important prognostic factors in ovarian cancer are, as we have seen, stage which is very important. Age at diagnosis is an important consideration. For reasons that are not totally clear, younger women with ovarian cancer fare better than older women with ovarian cancer. Histologic type is important. Patients with mucinous and clear cell tumors fare substantially less well

than their more common serous histology. Finally, as we've seen, volume of residual disease for stage III patients is an important consideration and an important prognostic factor.

Next please. Well, in the 1970s, it was recognized that platinum compounds were very important drugs in ovarian cancer. At that time, cisplatin was noted to be an active drug and actually have substantial clinical activity after failure of alkylating agents. Alkylating agents at that time were considered the standard of therapy for ovarian cancer. This led, as we will discuss more in a little bit, the use of cisplatin in first-line therapy.

Somewhat later than this, similar activity, coupled with improved tolerance over cisplatin, led to the widespread use of carboplatin in first-line therapy. A number of clinical trials were conducted with this agent.

Either cisplatin or carboplatin combined with an alkylating agent was shown to have superior therapeutic results, and at this time, and certainly by the eighties, became the standard of care for women with advanced ovarian cancer.

Next please. Of historical interest are a couple of the initial randomized trials done in the United States,

one by the Northern California Oncology Group and one at the Mayo Clinic. These are, of course, very old, and included only a small number of patients, but there was a suggestion in both of these trials that platinum added to the combination of cyclophosphamide, with or without an anthrocycline(?), had the potential of improving the results of chemotherapy for advanced ovarian cancer.

Next slide. A subsequent very important study was done by the Gynecologic Oncology Group and reported by Dr. Omura in 1986. In this study, the then standard combination of the GOG, cyclophosphamide and doxorubicin, was compared to the new combination which was the addition of cisplatin to this regimen. So it was two drugs versus three drugs.

In patients with measurable disease, the platinum containing combination produced a higher complete remission rate, longer remission duration, and improved survival when compared to the non-platinum containing combination. A follow-up publication from the GOG in 1991 showed similar results for progression-free interval in survival in the population of patients with non-measurable disease also, clearly a positive study supporting the role of cisplatin as a component of first-line therapy for ovarian cancer.

Next please. Another study done by the GOG, and

it should be emphasized that this was a somewhat different patient population. This was GOG protocol 52 and this study was conducted in women with small volume residual stage III disease, or what we refer to as optimal stage III ovarian cancer. This looked at the three-drug regimen, including doxorubicin, versus the two-drug regimen. It was determined that these two arms were comparable in pathologic response rate, time to progression and survival. The deletion of the doxorubicin, of course, improved the therapeutic index.

A number of other studies also led to the conclusion that the standard of care for women with ovarian cancer was the two-drug regimen of cisplatin and cyclophosphamide. This was adopted by virtually all institutions and cooperative groups in the United States at this point in time. Admittedly there is some controversy, but I think the vast majority of investigators felt that the two-drug regimen at that time was the standard of care.

Next please. Well, this was looked at in more detail, or these issues were looked at in more detail in an overview that was published in the British Medical Journal in 1991 by a group of individuals, an advanced ovarian cancer trialist(?) group. This represented an overview of a total of 45 randomized trials involving more than 8,100

patients. The conclusions from this group, and this was as you might imagine a very complicated study, but the conclusions from this group were that platinum treatment was superior to chemotherapy regimens that did not contain platinum, that platinum combinations were better than platinum as a single agent, and finally that cisplatin and carboplatin were equally effective. So these were the conclusions that were suggested from this very large overview trial.

Next please. Well, in the late eighties, things started to change rather dramatically. What really led to that was the first recognition of the activity of Taxol in ovarian cancer. This was first noted in a study by Dr. William McGuire, then at Johns Hopkins. In this initial trial, there was a substantial single agent activity in patients that had previously been treated with platinum. In reality, these patients on the whole were very heavily pretreated patients. Taxol induced a substantial objective response rate in this patient population.

Another single institution study from Albert Einstein confirmed these results. Since then, of course, there have been many other trials of Taxol as a single agent.

Next please. The GOG version of the trial was an arm of GOG protocol 26, with the study chairman of Dr. Kate Thigpen. This study, that was published in 1993, showed that Taxol was the most active single agent that the GOG had tested in a large number of phase II trials over several years, producing an overall 37 percent objective response rate. In the GOG experience, it was the first drug that was shown to have significant activity in patients that were refractory to cisplatin with a 24 percent response rate in this patient population.

Next please. This led to what we thought at the time was the rational further development of Taxol, namely the investigation of Taxol and platinum in combination chemotherapy. This, of course, seemed rational because by this time the preclinical activity of Taxol was well demonstrated in platinum resistant models. As we've seen, there were substantial clinical activity in women with ovarian cancer using Taxol as second-line therapy. So this seemed to be a logical choice for investigation as a combination regimen.

Next please. A phase I trial of the combination was done by Dr. Eric Rowinsky and colleagues, then also at Johns Hopkins. Their observations from this clinical trial

were that the dose limiting toxicity of the combination was neutropenia. Alternating a sequence of administration of Taxol and cisplatin led to the observation that cisplatin given before Taxol led to increased toxicity and thus their recommendation of this regimen for subsequent study was that Taxol be given at a dose of 135 milligrams per meter squared over 24 hours followed immediately by cisplatin at a dose of 75 milligrams per meter squared.

They also observed in this phase I study that of five patients previously untreated with ovarian cancer, four of them had a complete or partial response, certainly an early suggestion that the regimen, as one would expect, had substantial activity in ovarian cancer.

Next please. So in summary, regarding the development of Taxol, at least in the Gynecologic Oncology Group, the sequence is that preclinical activity of the drug was noted. Subsequent studies by the GOG and a number of others documented significant clinical activity in women with refractory disease. The combination regimen of Taxol and cisplatin was piloted and this yielded acceptable toxicity and early evidence of activity. This led, I think in a very logical and organized fashion, into the design of the initial phase III trial of Taxol and combination

chemotherapy for women with ovarian cancer. That, of course, was GOG protocol 111. The results of that study will be described to you by Dr. David Tuck.

DR. TUCK: GOG-111 was a multi-center randomized phase III trial in patients with suboptimal FIGO Stage III or stage IV ovarian cancer. Stratification was for clinical measurability and the participating institution. The patients were to receive a maximum of six cycles unless there was progressive disease or toxicity. Second look laparotomy was required for all patients who were clinically free of disease after cycle six.

The study was intended to evaluate the relative activity of this new combination, Taxol plus cisplatin, as compared to the standard combination cyclophosphamide/cisplatin. The major endpoints were time to progression, overall survival, frequency of complete response in patients who had measurable disease and toxicities.

The primary endpoint for the calculation of the sample size was time to progression. An accrual of 360 patients was calculated to provide nearly 85 percent power to detect a 40 percent increase in time to progression.

Patients were randomized to receive the regimen

that Dr. Williams just noted, Taxol 135 milligrams per meter squared over 24 hours, followed by cisplatin 75 milligrams per meter squared or cyclophosphamide 750 milligrams per meter squared with cisplatin 75 milligrams per meter squared. The doses of cyclophosphamide and Taxol were to be dose reduced based on grade IV hematologic toxicity. There was no dose reduction plan for cisplatin.

Eligibility criteria included histologically confirmed epithelial ovarian cancer with the central pathologic review by the GOG, FIGO suboptimal stage III disease which is defined as one centimeter residual mass or FIGO stage IV disease. Patients were to have no previous chemotherapy or radiotherapy, a GOG performance status two or better and entry into the study within six weeks of staging surgery.

The study was conducted under NCI IND as part of the CRADA between NCI and BMS for the development of Taxol. The study was performed according to GOG procedures. Clinical evaluation was prior to each course and radiological evaluation every two courses. Cardiac monitoring was required during drug administration for every course for patients on the Taxol/cisplatin arm. A second look laparotomy was to be performed within six weeks from

completion of chemotherapy. Follow-up after completing study therapy was to be every three months for the first two years, every six months for the next three years and annually thereafter.

Between April 1990 and March 1992, a total of 410 patients were randomized to 86 GOG sites, 196 to the Taxol arm and 214 to the cyclophosphamide arm. Somewhat more than half the patients had measurable disease in each arm. A total of 386 patients were identified by GOG as eligible and were considered in all of their analyses.

The study accrued more rapidly that expected and preliminary results were presented by Dr. William McGuire, the principal investigator at the May 1993 ASCO meeting. At that time, the available results, based on an adequate number of events for the primary endpoint showed a significantly favorable response rate and time to regression for the Taxol/cisplatin arm.

At the ASCO meeting in May 1995, final data were presented, including survival, which all confirmed the preliminary findings. The final results were published in 1996 in the New England Journal of Medicine.

In the Bristol-Myers Squibb submission for this application, all 410 randomized patients are considered in

the analysis of pathological response, time to progression and survival. All 240 patients who had measurable disease at baseline are considered in the analysis of clinical response. All 409 patients who received protocol therapy were analyzed for safety.

Overall, pretreatment characteristics were well balanced between the two arms. The median age was 59 in both arms. Approximately 90 percent of patients in each arm were caucasian. Approximately two-thirds of patients had FIGO stage III disease and the majority of patients had some impairment in performance status.

The one pretreatment factor in which an imbalance between the two arms was noted was in the proportion of patients with the histological cell type of serous adenocarcinoma. All other cell types were equally divided between the two arms. This imbalance was addressed in the regression analysis for the primary endpoints.

The size of the largest tumor diameter was well balanced between the two arms. Patients with stage IV disease could be admitted with less than one centimeter disease. The majority of patients had more than two centimeter residual mass. The great majority of patients had ascites at the time of initial surgery.

Clinical response could be assessed in 240 patients with clinically measurable disease at baseline. Eighteen patients who did not meet the GOG central pathology review criteria for documentation of ovarian cancer were considered as treatment failures in this analysis. The overall response rate for patients on the Taxol/cisplatin arm was 60 percent, and for the cyclophosphamide/cisplatin arm 50 percent in this analysis. The complete response rate was 35 percent in the Taxol arm versus 25 percent in the cyclophosphamide arm. Neither of these differences reached statistical significance.

The pathological response rate is presented for all patients. The complete response rate for patients on the Taxol/cisplatin arm was 21 percent and for the cyclophosphamide arm 16 percent. In addition, since all patients had at least a one centimeter residual mass, the presence of microscopic disease only at the time of second look surgery could be considered an objective response, and therefore those patients were combined leading to an overall response rate of 34 percent for the Taxol/cisplatin arm, compared to 20 percent for the cyclophosphamide/cisplatin arm and the difference between these two was a statistically P value of 0.001.

The primary endpoint of the study was time to progression, which was assessed from the date of randomization until clinical evidence of disease progression or recurrence. At the time of this analysis, the great majority of patients had progressed. The median time to progression is longer for patients who received the combination of Taxol/cisplatin, 16.6 months, compared to 13.0 months for patients on the cyclophosphamide/cisplatin arm. This difference was highly statistically significant with a P value of 0.0008. This represented a reduction of more than 30 percent in the risk of disease progression for patients receiving Taxol/cisplatin.

When adjusted for factors identified as significant prognostic factors in advanced ovarian cancer, the improvement in time to progression for patients receiving Taxol/cisplatin remained highly statistically significant. No other factor, including the histological cell type except for the stratum of clinical measurability were identified as significant prognostic factors in that analysis.

As expected, many patients received several subsequent therapies. Approximately three-quarters of the patients on each arm did receive at least one subsequent

chemotherapy regimen. The most common regimen for patients who had received Taxol/cisplatin was carboplatin and the most common regimen for patients on the cyclophosphamide/cisplatin arm was Taxol.

Here is the analysis of survival, which includes all 410 randomized patients. At the time of this analysis, 266 patients had died. The median survival for patients receiving Taxol/cisplatin was 35.5 months and for patients receiving cyclophosphamide/cisplatin was 24.2 months. This difference was highly statistically significant with a logrank P value of p=0.0002. This represents a reduction of more than 35 percent in the risk of mortality for patients receiving Taxol/cisplatin.

It should also be noted that the results for the control arm are entirely consistent with the results in the previous GOG and other studies in this population of patients.

A Cox(?) regression analysis was also performed to adjust the survival data for the same set of prognostic factors used in the analysis of time to progression. After adjustment, the improvement in overall survival for patients receiving Taxol/cisplatin remained highly statistically significant. The only other factor identified in that

analysis has a significant factor associated with improved outcome was residual diameter less than or equal to five centimeters at the time of initial surgery.

The median number of courses for the patients on each arm was six. Dose reductions tended to be more common for patients on the Taxol/cisplatin arm. However, the percent of courses delayed was higher for patients on the cyclophosphamide/cisplatin arm.

Overall, taking these modifications, reductions or delays into account, there was a significantly higher dose intensity of cisplatin for patients on the Taxol/cisplatin arm compared to the patients on the cyclophosphamide/cisplatin arm, compared to the planned dose intensity of 25 milligrams per meter squared per week. Patients on the Taxol/cisplatin arm received 24 milligrams per meter squared weekly compared to 21 milligrams per meter squared on the control arm.

Now looking at the adverse events on this study, severe neutropenia was more common for patients receiving Taxol/cisplatin. The number of patients who had fever and grade IV neutropenia was also significantly higher in the Taxol arm. However, this occurred in only three percent of all courses and did not lead to in general a high incidence

of serious sequelae. There was no difference in either serious infections or overall infections. In fact, the three subject deaths which were reported in this study within 30 days of therapy all occurred in patients on the cyclophosphamide arm.

Looking at severe grade III/IV non-hematologic toxicity, for most adverse events there was no difference in the incidence of severe events between the two arms. Severe hypersensitivity reactions, not surprisingly, were more frequent on the Taxol/cisplatin arm. Five patients were removed from the study due to hypersensitivity reactions to Taxol.

Overall, the incidence of peripheral neuropathy was not different between the two arms, but the incidence of severe hypersensitivity(?) was higher for patients receiving Taxol/cisplatin, three percent of patients.

Eleven patients were removed from the Taxol arm for treatment related to toxicity, most commonly hypersensitivity reactions. Fifteen patients were removed from the cyclophosphamide/cisplatin arm for treatment related toxicity, with the most common reasons being renal toxicity, ototoxicity and mild depression.

Six patients died with 30 days after the last

treatment with Taxol/cisplatin. Only one patient with a myocardial infarction was considered to be possibly related to study therapy. Four patients died on the cyclophosphamide/cisplatin arm within 30 days of therapy, two who had active sepsis were considered by the investigators to be therapy related, and another patient had sepsis as well as widespread disease progression.

So in summary, Taxol/cisplatin as compared to cyclophosphamide/cisplatin produces a significantly better pathological response rate, time to progression and overall survival.

Taxol/cisplatin is well tolerated, with no differences in treatment related discontinuations or deaths, as compared to cyclophosphamide/cisplatin. The adverse events observed with Taxol in combination with cisplatin are consistent with the established safety profile of single agent Taxol.

In conclusion, for GOG-111, Taxol in combination with cisplatin provides a statistically significant and clinically relevant advantage in the first-line treatment of ovarian cancer.

Now, Dr. Benjamin Winograd will have some concluding remarks.

DR. WINOGRAD: We have just presented data from the first completed phase III study that demonstrated clinically relevant efficacy advantages for Taxol/cisplatin over standard therapy. The combination of Taxol/cisplatin produces an acceptable and predictable safety profile.

Results from two subsequent trials with Taxol/cisplatin in the first-line treatment of advanced ovarian cancer have been presented at ASCO 1997. All data and material available to BMS on these studies have been part of our present submission to the agency. Both studies support the conclusion that Taxol/cisplatin should be considered the treatment of choice for women with ovarian cancer.

Study GOG-132 followed chronically the completion of GOG-111 and was aimed at a similar patient population with suboptimal stage III or stage IV disease. Between March 1992 and May 1994, 648 patients were randomized to receive either high dose cisplatin at 100 milligrams per square meter every three weeks, Taxol at 200 milligrams per square meter over 24 hours or the regimen that was used in the GOG-111 study. Stratification factors were clinical measurability and GOG-111 institution. A maximum of six cycles were to be followed by second look.

In summary for this study, as stated by GOG at ASCO 1997, Taxol/cisplatin and high-dose cisplatin are significantly more active than Taxol alone with respect to clinical response, pathological response rate and to tumor progression. Taxol/cisplatin required fewer dose modifications and fewer treatment discontinuations for toxicity than high dose cisplatin. Taxol/cisplatin has a better therapeutic index and therefore remains the regimen of choice.

After the first results on GOG-111 became available in May 1993, this study was mounted by the EORTC, the Canadian NCI, the Scandinavian group and the Scottish Gynecology Oncology Group in order to confirm the GOG results. There were several differences in the design and patient selection for the study as compared to GOG-111. Unlike study GOG-111, this study also accrued patients with stage IIB-C and stage III optimally developed(?) disease.

Six hundred and eighty patients were randomized between April 1994 and August 1995 to receive Taxol at 175 milligrams per square meters at that point, as three hours infusion in combination with cisplatin 75 milligrams per square meter or to receive the standard cyclophosphamide/cisplatin regimen. Stratification factors

in this multinational study were the participating institution, FIGO stage, residual disease, performance status as well as tumor grade. Up to nine courses were given and second look surgery was optional. Secondary therapy was considered progression in the protocol design.

In summary, as stated by the investigators at ASCO 1997, Taxol/cisplatin is significantly more active than cyclophosphamide/cisplatin with respect to time to progression, clinical response rate, as well as for survival. The survival update was submitted to us for 1998, and to the Food and Drug Administration at the point it became available to us.

Taxol/cisplatin is associated with a higher incidence of neurotoxicity and a lower incidence of severe emesis. This trial fully supports the conclusions of GOG-111.

Taxol/cisplatin prolongs time to progression and survival as compared to cyclophosphamide/cisplatin. This combination has an acceptable safety profile with no unexpected toxicities as compared to single agent Taxol. Taxol/cisplatin can be considered as the new standard of care for women with advanced ovarian cancer.

Therefore, our proposed indication is that Taxol

in combination with a platinum compound is recommended for the primary treatment of patients with advanced ovarian carcinoma. Thank you. I am happy to take questions.

Agenda Item: Questions from the Committee

DR. DUTCHER: Thank you. Are there questions from the committee for the sponsor? Dr. Temple. Oh, you're pointing to me, Dr. Krook.

DR. KROOK: Just a couple of small things. As I looked at this and listened to the review, a little bit of my interest was the second look. There were some people at least on GOG-111 which had microscopic disease. Were these people continued on with treatment? I suspect they were. Were they crossed over, was it the same treatment? These were people who obviously responded with debulking with chemotherapy. My question I guess is were they continued on with the platinum Taxol arm?

DR. WINOGRAD: Those patients who had remaining disease at second look I think GOG policy is to -- medical logic demands that you continue treatment. Do you want to give any other comment as to whether that's a GOG a policy, Dr. Williams?

DR. WILLIAMS: I don't think there's any formal GOG policy. I don't specifically know the answer to your

question, but my guess is that they were treated with a host of different regimens at the choice of the individual responsible physician. There is no official GOG policy.

DR. KROOK: Some of us at that point, at least having been here, will continue the same program that we've debulked. I was just wondering whether these continued on with Taxol. Some may, some may not have.

DR. CANETTA: Basically we have shown in the presentation the type of secondary therapy that was given and the fact that patients randomized to Taxol, ended up receiving Taxol again attests to the fact that they were continuing therapy. However, it was not stated in the protocol. It was left to investigator choice.

DR. HONIG: If I could add something, in review of the case report forms, patients did not appear to continue on the same regimen. I believe that there was another GOG protocol that was open for patients with microscopic residual disease. Some patients went on IP therapy, for example, but they didn't necessarily continue on the study regimen.

DR. WINOGRAD: I think what should be added that they couldn't really continue on Taxol at that time because it might not have been available. The protocol ended after

the six courses. For the major part of that study, Taxol was not available.

DR. SCHILSKY: I have a question about the proposed indication, which states that Taxol would be indicated in combination with a platinum compound. All of the data that's been presented deals with Taxol in combination with cisplatin. So could you review with us whatever data you have with respect to the use of Taxol in combination with any other platinum compound in ovarian cancer?

DR. WINOGRAD: As you know, there have been many publications in the literature of non-randomized studies using Taxol in combination with, for instance, carboplatin or other agents. The two randomized studies that are using carboplatin in combination with Taxol have not completed and they were just alluded very briefly to by Dr. Canetta in the introduction. Whatever is available was presented at ASCO so there are no definite, there are no final randomized studies using Taxol and carboplatin. On the other hand, carboplatin is registered for the use in ovarian cancer on its own.

DR. CANETTA: If I might add, the reason why the wording is that way is because of the results of GOG-132.

We thought that it would be inappropriate to recommend Taxol as a single agent for primary treatment of the disease, and therefore that's why we recommend a combination. In our recommended dosage, we refer specifically to the GOG regimen with Taxol given at 135 milligrams per square meter over 24 hours followed by cisplatin at 75 milligrams per meter. These are the data that were available to us, that we made available to the agency. Obviously in the future, we can think about providing the agency with additional data, but that's what we have available today.

DR. SCHILSKY: So the more precise wording of the indication would be Taxol in combination with cisplatin.

DR. CANETTA: That's what we recommend.

MS. SOLANCHE: Could you tell me what you mean by acceptable safety profile?

DR. WINOGRAD: Dr. Tuck has reviewed and he was focusing on the incidence of severe events, either laboratory measurements or clinical events. So he was focusing on the incidence of severe events. If you looked at that, there was, if you looked at the numbers and we could go back to those slides -- if you give me the slides of David and start at slide 22 please.

What was reviewed is the incidence of grade III/IV

neutropenia, the incidence looking at per patient or per the number of courses that grade IV neutropenia would occur at the same course as the patient without fever. What you see is that the incidence, that happens in three percent of the courses with Taxol/cisplatin therapy, in one percent of the courses with cyclophosphamide/cisplatin.

What is more important is what is the clinical consequence from that. If you look at the incidence of infections either by patient or by course, there's no relevant difference between the two treatment arms, and with regard to patients that die related to their toxicity, he alluded to that there were three patients who died on the control arm in relation to a sepsis and no patient on the Taxol arm.

If we go to the next, to the incidence of severe grade III/IV non-hematologic toxicity, this lists the incidence per patient.

DR. DUTCHER: Could you comment just a little bit more on the more recent GOG study with the platinum alone versus the Taxol/platinum, some of the differences in toxicity and differences in efficacy or lack thereof?

DR. WINOGRAD: Where do you want to start? You said --

DR. DUTCHER: With toxicity and dose reduction.

DR. WINOGRAD: Toxicity, again, we have the data as it was presented at ASCO. Could you put up slide A18 and we have Dr. Muggia here who is the principal investigator of the study and presented the study. Maybe that's the most appropriate person to comment on it.

MR. MUGGIA: Yes, as you can see here, this was a three-arm study in the same population as GOG-111. It was initiated before the results of GOG-111 were known. We're set to compare the single agents cisplatin versus Taxol versus a combination. The high dose cisplatin was chosen really to make it a valid comparison. As you heard, the results of the meta-analysis suggested that single agent was not as good as combination, but that encompassed all doses. So the idea was to get a dose that was to be comparable, or at least had a chance of having efficacy versus -- to compare it with single agent Taxol where there was no data at the time in the front-line versus the combination.

So, when one looks at the toxicity profile that we obtained in this study, you can see in terms of neutropenia and leukopenia, the Taxol containing arms are the ones that have most of the grade IV and they're equivalent in other ways. On the other hand, the cisplatin containing arms have

more anemia.

On the next slide, you can see that in terms of GI toxicity, however, the cisplatin was significantly more toxic in terms of grade III and IV than the Taxol containing arms, including the combination that contains Taxol and cisplatin at 75 milligrams per meter squared. When it comes to neurotoxicity, you just have to focus on grade III and IV neurotoxicity. Again, the cisplatin, the 100 milligrams per meter square of cisplatin was considerably more toxic than what one had with the combination.

DR. WINOGRAD: Can you go to slide 11 please.

DR. MUGGIA: There was a question about the relative efficacy and I think we can go actually to slide 10 to show some aspects about the study therapies. You see in the number of patients that were randomized to the median number of courses received, but when you look at the patients completing treatment, and that's really very telling, the 83 percent of the combination completed treatment, which is about the same as in GOG-111. I think GOG-111 had 86 percent.

But when you look at cisplatin, at the single agent completion, only 69 percent of the cisplatin and 71 percent of the Taxol completed the course of treatment, with

a large percent of patients stopping treatment.

In the next slide, one can see the reasons for off study and they actually differ -- well in combination, only six percent went off study because of progression and four percent because of toxicity and one because of refusal. The same number of deaths in all three arms, early deaths mostly related to progression. But when you look at the single agents, you have, with cisplatin you have 12 percent going off study because of toxicity, six percent refusing further treatment. This is considerably higher than in the combination. With Taxol on the other hand, 19 percent went off study because of progression.

That reflects some of the study characteristics. This is shown in the next slide what the results are. When you look at the actual results in terms of response, you see that the single agent cisplatin did fare as well as the combination in this particular study. So this was somewhat unexpected but it reflects perhaps the fact that single agent cisplatin at high doses may at times approach the response rate of the combination. Taxol was significantly inferior. These results are consistent with GOG-111.

The next slide shows the second look laparotomy and this is quite interesting. Actually, of the patients

who were on the single dose cisplatin, there was a large refusal rate, mainly because these patients had neurotoxicity I suspect and a number of other reasons. But they refused second look laparotomy and they had more clinically persistent disease. The Taxol patients on the other hand, a large number of patients, had clinically persistent disease and they did not go into second look laparotomy. But the patients that underwent second look laparotomy, it is a selected population because of the large refusal rate here in the cisplatin arm. One can see there is a trend favoring the combination in terms of negative, pathologic CRs and microscopic disease with 33 percent in the combination and 25 percent in the cisplatin arm.

So this supports the statements that were made that the combination had a more, had a better toxicity profile and at least equivalent efficacy.

DR. DUTCHER: Dr. Johnson.

DR. JOHNSON: I have several questions pertaining to this trial then because it seems like there's a bit of a conundrum that's developing. I would like to walk through a scenario here. It's not specifically addressed to Dr. Muggia, this is just addressed to the group.

This trial is actually very interesting to me,

because not being an ovarian specialist by any means, I saw what the more important data to me would be, as a patient, is that survival looked to be better with the single agent high dose cisplatin. I recognize the lack of statistical difference there, but nevertheless, the trend is there. Trends sometimes are very important I think.

It goes back to the question that was asked by Dr. Schilsky vis a vis platinum. I think he very specifically asked what platinum compound one is talking about. My presumption is, although Dr. Canetta said that the group mean to say cisplatin, that's not what the application in fact says. It says a platinum compound. Am I to understand that you are now requesting approval for cisplatin and Taxol, not carboplatin and Taxol or oxiloplatin and Taxol or GM216, is that correct?

Okay. Then cisplatin, you're arguing in this study that cisplatin is inferior because of a therapeutic index benefit that one sees with the combination over the single agent, which is actually sort of an interesting phenomenon, but nevertheless, that's the argument that's being made with GOG-132. Is that correct?

DR. CANETTA: I think again, we can discuss a lot about this prior -- one has to keep on mind one thing that

because of the early dropout from the high dose cisplatin arm, which again was 100 milligrams per square meter given every three weeks, a fairly aggressive type of approach, many, many patients ended up receiving Taxol afterwards because this trial was when Taxol had become available to the public. Therefore I think that you end up comparing a situation where you have combination therapy versus sequential therapy. That's my first comment. Obviously, this is opening a Pandora's box and probably this type of discussion is more interesting and challenging than the discussion about the other two studies that are much more clear-cut.

The other consideration has to do with toxicity. As you know, the way toxicity is collected by cooperative groups pertains to toxicity that occurs on the protocol. Obviously, if you go off protocol on high dose of cisplatin, after a relatively smaller number of courses, whatever happens afterwards is not really accounted for, or if you go off study because of a certain type of toxicity, you wouldn't have any time to develop cumulative toxicities. I think that's another challenge that I'm afraid Dr. Muggia had to reckon with in analyzing the results of GOG-132. It's not a simple study.

DR. DUTCHER: Excuse me one moment. We have to make a quick announcement and then you can finish.

DR. TEMPLETON-SOMERS: Is there a Richard Kim in the audience from Room 506? It's a parking problem, go right ahead.

MR. JOHNSON: I'm just trying to get at understanding this trial because certainly one could improve the therapeutic index of high dose cisplatin in a variety of ways, or one could use a less toxic platinum compound and achieve the same potential result, for example using single agent carboplatin. I was just wondering if we have any data, maybe Dr. Williams could address from either GOG experience or other experience that addressed that particular issue?

DR. CANETTA: I can only say one thing that we made a special effort to make available to the agency what type of data was available from completed and also from ongoing randomized trials. There is an ongoing randomized trial that I cited in my presentation in Europe which is called the ICON-3(?). That trial compares a single agent carboplatin at full dosages versus carboplatin and Taxol versus CAP(?). I don't know whether God(?) knows, but the FDA knows that we went through tremendous effort to obtain

the data of this study and the DMC(?) of the ICON study basically told us we would not have access to this data until it would be mature enough. But that trial is ongoing and we hope to have the results as soon as the accrual is closed.

DR. WILLIAMS: I just want to make a comment. I think these are important discussions to have and to continue, but you have to keep in mind that we have the data from only one trial, the real data. We have graphs and descriptions, but most of our decisions wouldn't be based on the data from the GOG trials.

DR. TEMPLE: I guess I want to follow up on something that was discussed yesterday a little bit. We're told repeatedly that survival advantages cannot be expected in trials any more because people will cross over and that we therefore have to look at time to progression or even response rate. The GOG-111 trial showed a modest advantage in terms of response rate that was not significant by most measures, showed a very small improvement in time to progression and what has to be described as a gratifying difference in survival time.

I just wonder if the company has a view as to why that might have happened, whether it's changed their

attitude toward looking at survival more in other trials? What should we make of this? There seem to be a lot of discontinuities between response rate and survival time.

DR. WINOGRAD: I think you have to take into account what disease you're dealing with and at what stage of the disease you're discussing the results. What you know also from the past is that there were major advances made in ovarian cancer and they were and they are bigger than in other diseases. So I think you cannot talk in a generality.

DR. TEMPLE: Do you have any theory as to why survival looks so much better than the other measures that increasingly people are choosing to rely on?

DR. CANETTA: Yes, but before we get into that, let me make a point. As you have seen, we have shown in our analysis that there is no statistically significant difference in response. We reported a 60 percent versus 50 percent for Taxol/cisplatin versus the control arm. I would like to point your attention to two facts, that both the GOG publication and the FDA review claims a statistically significant advantage for response rate. The reason why our analysis doesn't is because you can call it paranoia, but we always have used in all our submissions a very rigorous review of responders, a WHO criteria that calls for

confirmation four weeks apart of an objective shrinkage of the tumor of more than 50 percent. The reality remains that whatever the P value, there was evidence of increased response rate in the Taxol arm. So that's just to put the thing in perspective.

The other question is actually much more challenging because I think it impinges upon the mechanism of action of these compounds. It's evident that something is happening at the cellular level that somehow slows down the growth of the tumor. That's probably why you gain time to basically keep the treatment going and keep the tumor at bay. One would say perhaps the advent of new drug, but yet when we looked at the secondary treatment, you have seen what type of drugs have been used, not much was done with novel agents. So I don't think that that impinged upon the overall survival figure in this particular case.

What is actually remarkable is that when you put the GOG-111 results in perspective with the European study, the type of effect that you see is actually extremely similar, including survival, even in presence of the fact that you are dealing with different study design, different study population, and the study done in an era when Taxol was available as a rescue type of treatment, and you still

see the type of difference. To me that indicates that probably the optimal therapeutic approach is to keep the two agents as part of the primary approach to the disease.

DR. MUGGIA: Can I add something on the perspective with ovarian cancer? Response rates refer only to the subset of measurable disease. I think that's the key in the differences between some of these studies. In fact, in the GOG-132, we have a greater amount of measurable disease which would blunt some differences between the various regimens. In the European study, I think there are more non-measurable, and also in the GOG-111. So the survival reflects both measurable and non-measurable. There are differences between those populations in the GOG trials done by the Ovarian Committee.

DR. DELAP: I think I would just like to follow up on that a little bit, because this is a very interesting subject, the notion of what the endpoints should be. Again, as has been commented, not only in the GOG-111 study, but also in the EORTC/Intergroup Study, there's what looks at least like a fairly modest difference in median progression-free survival and a more striking difference in overall survival. Again, as Dr. Temple said, we've been told that progression-free survival is a better endpoint than survival

because of crossover and you just can't get survival data any more and the data seem to suggest otherwise, at least for these two studies.

I wonder if part of it might be that it's simply harder to measure the progression-free survival precisely so there's more fuzziness about that endpoint and you simply don't see as big a difference because you can't measure it as precisely as you can measure survival. Noise obscures a positive finding.

So I come back to what I think Dr. Canetta was just saying, what you do first, my point at least is what you do first is really important. You can't say that salvage(?) therapy later is going to be as good as doing the best treatment first. Again, my take on all this still is that survival seems to be the standard here still for me at least, and progression-free survival is of interest as an intermediate endpoint, but it doesn't at least from studies we've seen so far, doesn't seem to have been as useful. That includes a study that was done in the era when Taxol was available as a salvage therapy.

DR. WINOGRAD: But again, I think this is very particular for ovarian cancer and specifically so at the point that you do second look laparotomy and you decide

right there whether there is still tumor that you can A, not measure, B, not see other than by surgery. At that point, when you have minimal residual disease, you continue therapy with something else. In another disease you just don't know.

DR. TEMPLE: Well, it looks particular for ovarian cancer because you have therapies that make a substantial difference in ovarian cancer. With a lot of other solid tumors, you're talking about a month and six weeks. So it just may be that this is a more general truth, but you just can't recognize it usually because everything you're looking at is so tiny.

DR. MARGOLIN: I have a couple of questions that are somewhat related to these discussions but sort of more of a design nature. Given the quite favorable toxicity profile from phase I and the smaller phase II studies of the combination regimen, in the design of 111 and 132, I'm just curious why only suboptimally debulked disease was included and whether that was more of a practical question to allow for a sufficient number of events over a finite period of time. The point being that I think we all agree that the impact of small differences in therapy may be much greater on more favorable disease in this small fraction of patients

we may be able to cure are going to be the ones where you can't see anything and who have been optimally debulked.

DR. WINOGRAD: I think that's a question for Dr. Williams because it pertains to how GOG planned their studies.

DR. WILLIAMS: There were mainly practical considerations. At the time 111 was open, we had an interperitoneal study and so obviously women with bulky disease should not be treated with interperitoneal chemotherapy or it would not be a logical choice. So that's why that was.

There was another study that we had in optimal disease that was asking a similar question to 111, but when the results of 111 became available we closed the non-Taxol containing arm of that study. It started out as a three arm trial. a

DR. MARGOLIN: So then it's safe to assume that the recommendation here will be for all patients with stage III and IV, perhaps even stage II disease, and not just suboptimal patients?

DR. WILLIAMS: I can't say from Bristol-Myers point of view, but from the GOG point of view, we no longer use chemotherapy that does not contain Taxol.

DR. CANETTA: I'm sorry, just to conclude the discussion, there is data in our submission that has not been presented. There's raw data that is part of the ROTC study. The ROTC study did include the patients with optimal debulked disease, and also a few patients with stage IIB and with stage IIC. In their presentation at ASCO, that only pertained to response and time to progression which was the primary endpoint of the trial. They did present a graph with a subset analysis split by amount of residual disease.

I think we can show this. Basically that curve shows that the amount of advantage that is brought about by the Taxol containing combination is very similar in the two subsets. Here is the graph. The graph is not clear, but basically this is the optimal disease treated with Taxol, this is the optimal disease receiving the standard treatment, and these other two curves are the suboptimal disease. This is the same number of patients as the GOG-111. These have not been formalized with statistical analysis. This is a subset.

DR. SIMON: Are we being asked is the indication for suboptimal disease?

DR. DUTCHER: The indication is for first-line therapy in ovarian cancer, advanced ovarian cancer.

DR. SIMON: Okay, well, the only data we've been shown in terms of optimal disease is that slide. Is there, do you have a similar slide for survival for the international study?

DR. WINOGRAD: I think Dr. Piccart can answer that because the data has been submitted to ASCO 1998. Maybe you can go to B28, that's the overall curve.

DR. PICCART: I don't think we have the curves broken down. These are the survival curves that we hope to be able to present at the next ASCO meeting. We are currently doing exactly the same analysis, breaking down by residual disease, but we don't have this available right now.

DR. DUTCHER: Okay. If there are no urgent questions, we have one more announcement.

DR. TEMPLETON-SOMERS: There are two more cars that are double parked and in danger of being towed.

[Announcement was made.]

DR. DUTCHER: All right. We're going to push ahead, so we're going to take a break right now and will be back in 15 minutes.

[Brief recess.]

Agenda Item: FDA Presentation

DR. DUTCHER: We are going to get started and Dr. Honig is going to present the FDA review.

DR. HONIG: Thank you. I'm going to present the FDA review and evaluation of the supplemental NDA. Much of what you see may be familiar to you after the sponsor's presentation.

First, I would like to thank all of my colleagues in the different disciplines who helped to review this application. As you've heard, the sponsor submitted one trial, GOG-111 as the pivotal trial for consideration which was a randomized study of cisplatin and paclitaxel or PT versus the standard regimen of cisplatin/cyclophosphamide or PC.

This was a study that was conducted by the GOG and one aspect that has not been touched on is the actual database that was submitted for review. When the GOG conducts a trial, they have investigators fill out case report forms. They're also asked to submit a lot of supporting documentation including slides for central review, operative reports, et cetera. These documents are then abstracted to create the GOG database, which is used for reporting.

The sponsor went back and used the GOG database as

well as all of the available primary source documentation to create their own database and all of these things were submitted to us for review. It was a very complete submission. The differences between the databases can be summarized here. Bristol essentially used more extensive and detailed AE reporting. The GOG tends to collapse their adverse events into certain well defined categories, and in some cases many ask investigators to only report adverse events that they feel are attributed to the drug therapy. The sponsor instead included a complete listing of all adverse events and also used all available tumor measurements to follow these patients.

Bristol also took the extra step of going back and auditing approximately 97 of the patient records at the primary site and then comparing those records to the GOG database, to their own database, making sure that these were all concordant, and in fact they were, with really minimal differences between these that did not affect any of the analyses.

The supportive evidence that was submitted for this trial came in the form really of a literature review. I will talk a little bit about the European Intergroup study and GOG-132 when we put the results of this study in

context. The sponsor has also mentioned ICON3. I would just like to mention this trial briefly.

This is a study that is being performed in Europe based in Britain, and randomizes patients to receive either paclitaxel in combination with carboplatin or carboplatin or CAP at the discretion of the investigator. This study has a target accrual of approximately 2,000 patients. They have 1,300 on study already. It's just worth pointing out that when that study is ultimately completed, it will contain the largest database of paclitaxel's first-line therapy in ovarian cancer.

The other cited studies, again as you've heard, are looking at the various contributions of other platinum compounds and have used paclitaxel in both arms. There are no results available on these studies to date.

The objectives of GOG-111 as originally written were first to determine response rate, response duration and survival in this patient group. The protocol was subsequently amended and changed progression-free survival to the primary endpoint, looked at survival as a secondary endpoint and then response as a third endpoint, and then to look at relative activity and toxicity.

As you've heard, patients that were entered on

this study were untreated, suboptimally debulked stage III and stage IV ovarian cancer patients. As I mentioned, it was conducted by the GOG at their centers. These centers had a number of subcenters affiliated with the major center so that overall approximately 86 hospitals or medical centers participated in the study.

Patients were stratified by whether or not they had measurable disease and were balanced by center, and were then randomized to receive six cycles of either cisplatin 75 milligrams per meter squared IV day one, in combination with cyclophosphamide 750 milligrams per meter squared day one, the standard regimen, or paclitaxel given at 135 milligrams per meter squared over 24 hours in combination with the same dose of cisplatin. Cycles were repeated every 21 days.

In terms of the assessments, all patients were required to have had a staging laparotomy to get on study. A baseline post-operative CT scan was required in order to increase the number of patients that had measurable disease and could be stratified that way. A second look laparotomy was required for patients that had had a clinical complete response after therapy, unless they had a persistently elevated CA-125 level.

There was a substudy that was conducted at nine

sites for neurologic assessment. I will say more about that in a moment. There was a requirement for cardiac monitoring.

The important protocol amendments are listed on this slide. It's important to note in this study that CA-125 was not used as a criteria for response, nor for progressive disease, but it seemed reasonable to spare patients with a significantly elevated CA-125 level the morbidity of a second look surgery.

The study endpoints, as I mentioned, were changed shortly after study entry and really did not affect the analysis or conduct of the trial. It occurred approximately a month after the study opened. There were only nine patients on study, not all of whom had even finished their first course of therapy.

For neurologic assessment, seven sites were entered for this. The idea was to get more detailed information about neurotoxicity and try to correlate that with the adverse events and the outcome. Several study sites were entered throughout the course of the study, some of the assessment time points changed, all of which affected the quality of the data. There were obviously a number of missing pieces of information meaning that this information

could be analyzed only qualitatively and not quantitatively.

This last point is important when we talk about the differences in observed adverse events. Cardiac monitoring was initially required for only the first two cycles of the Taxol arm, but because of literature reports about the cardiac effects of Taxol in general, the protocol was amended to require monitoring on all cycles of Taxol.

The eligibility criteria you've already heard about in detail. I don't want to dwell on that except to point out that the measurable lesions needed to be at least three centimeters in size.

In terms of enrollment, 410 patients were entered on study, 196 on the PT arm and 214 on the PC arm. There is an inherent difference between these numbers, but again, remember that patients were stratified for measurability and were also stratified by center. That accounts for these small differences in the patient numbers.

Two hundred and forty, over half the patients had measurable disease. One patient who was randomized to PC did not receive drug therapy. She died of a post-operative pulmonary embolus before she could be treated.

I wanted to spend just a minute on the demographics. We've already talked in the discussion before

about how really small differences in response rate or time to progression led to such a big difference in survival. So one thing that we wanted to look at was whether there was any apparent imbalance in the treatment groups that could account for some of these changes. In fact, there were not. Most of the patients had very good performance status, equally distributed. Although optimally debulked patients were not permitted on study, there were some protocol violations that were equally distributed. I think this is less important since all of these patients actually had stage IV disease regardless of what their staging lapse showed.

The only imbalance which the sponsor has mentioned was the incidence of the serous adenocarcinoma cell type, which was greater on the PT arm than the PC arm. Both the sponsor and the FDA performed a series of adjusted analyses of both time to progression and survival and this did not come out as a significant prognostic or predictive factor in any of those analyses. So overall these patient groups appeared comparable.

Eighty-six percent of the patients on the PT arm were able to complete all of their therapy compared to 78 percent of the patients on the PC arm. There was an

approximately equal percent of patients that were removed for drug related toxicity and the real difference, I think, in the reason for completion was disease progression which was higher on the PC arm.

Protocol violations could be classified as major or minor and again I want to spend a minute on this because it will have a bearing when I present some of the response data and the differences between our analysis and the sponsor's analysis. Most of the violations were for the wrong primary. On review of the case report forms, there were some patients that had endometrial cancer, some that had GI primaries, but overall, these were mostly patients who had ovarian cancer who did not fit the strict eligibility criteria for this study.

I will give you two brief examples that may make that clearer. There were some patients who had primary peritoneal cancer without an obvious ovarian focus but who clearly looked like an ovarian cancer patient. Another example was a patient who at the time of staging laparotomy had an enormous intra-abdominal, intra-pelvic mass. The operative report noted that no individual organs could be distinguished. Representative biopsies were taken, were consistent with ovarian cancer, but the patient was

considered to have the wrong primary because there was not actually a piece of tissue from the ovary itself.

I think it's important to consider these patients in an attempt to treat analysis. I think they're all patients that we would consider clinically to have ovarian cancer and are the type of patients that would be treated with this regimen.

In terms of on study therapy, no dose reductions, only treatment delays were allowed for cisplatin. Violations were approximately equal on both arms. There was a 27 percent incidence of dose reduction for paclitaxel compared to 21 percent for cytoxan, but of note, again as you've already heard, there was a significant difference in the percent of patients who required a treatment delay, 21 percent of courses delayed on the PT arm, compared to 55 percent on PC.

This translated to a difference in the dose intensity that was delivered on these arms. Both arms were planned to receive the same cumulative dose of platinum, the same dose intensity of platinum. If you look at the median delivered dose intensities, there is some difference in favor of the PT arm.

I think that this calculation, which the sponsor

submitted, perhaps illustrates this even more graphically. If you look at all of the patients and look at the delivered dose intensity over the planned dose intensity expressed as a percent, and then group these patients into whether they were able to receive greater than or equal to 90 percent of their planned dose, 80 to 90 percent or less than 80 percent, the differences I think are really striking. Seventy-two percent of patients on PT were able to get greater than 90 percent of their planned or relative dose intensity for platinum, compared to 41 percent of the patients on PC.

In terms of subsequent therapy, again there was a significant amount of crossover therapy on this study. As you can see, most patients got something. For the PC arm, 38 percent ultimately received Taxol, although only nine percent of them got it as second line therapy. On the paclitaxel containing arm, 47 percent ultimately received carboplatin. They also received similar sorts of drugs, including cyclophosphamide.

I want to spend a minute also talking about the definitions of the endpoints used in this study, because this would account for some of the differences between the sponsor's reports and our analyses. Time to progression was

measured by the sponsor in two ways. The first way was looking at the date of entry onto protocol to the date of reappearance of increase in parameters of disease or date of last contact, the conventional way really of doing this. The sponsor did method two, which I believe is probably a check on the fact that patients did not always have objective evidence of progressive disease at the time that they received a subsequent therapy. Patients with microscopic residual, for example, could receive IP therapy, et cetera. This seemed to me to be a way to make sure that any time to progression advantage that you had didn't disappear if you corrected or adjusted for subsequent therapy.

One difference in the way that the sponsor and the FDA censored these patients was that the sponsor classified patients who died without progression as progressing on the date of death. When I started to review the case report forms, it became clear that there were some patients who had a long lag time between the last time that they were actually seen and examined by a physician or a reputable individual and the time that they died or that a date of death was given. For this reason, I defined this a little bit differently to be sure again that the time to

progression difference wouldn't vanish. I said that these patients progressed on the date of the last visit.

Again, a couple of examples may make this clearer. One patient was censored at a date that a nurse submitted a form stating that the patient had been lost to follow-up for three years and seven months. Another patient was censored on the date that the family called to say that the patient had died when in fact she had not been seen or examined by anyone for 19 months. As I said, there were approximately 14 percent of patients that fell into this category. It was a check to look at the robustness of the time to progression analyses.

For response, the protocol used the classic definitions of response. Confirmation was required at three weeks, again based on the chemotherapy intervals. Progressive disease was defined as a greater than 50 percent increase rather than the more traditional 25 percent increase. When we looked through this, both the sponsor and FDA counted a second look laparotomy procedure as confirmation of response, not just a radiographic response. Again, pathologic response was defined as having pathologic confirmation of a CR at a second look. Then you've also heard about the category of microscopic residual disease.

Overall, 240 patients on this study had measurable disease, 113 on PT, 127 on PC. All patients were analyzed in an intent to treat analysis by both the sponsor and the FDA. As you can see, the response rates reported by the sponsor were 60 percent for PT, 50 percent for PC with a nonsignificant P value. This may be a first in FDA history, but ours were 62 percent and 48 percent with a P value of .04.

The differences really on summarized on this slide. I think the primary difference in the response rates has to do with adding patients that had the wrong primary. The sponsor included all of these patients in the denominator, but did not allow them to count for response. I permitted them to count for response when they were these cases where it seemed to me that they were clearly ovarian cancer patients who did not fit the criteria because of the kinds of deviations that I've already discussed in those examples.

For the PT arm, we excluded one patient that we felt had inadequate documentation of response. The sponsor and FDA have agreed to disagree on this patient. We excluded four patients on the PC arm for this. The sponsor agreed with us that three of the four did not respond and

then there was inadequate documentation for the fourth.

I think the real point here is that with a net difference of about five patients, the result goes from non-significant to significant. I think what that tells you is that it's probably difficult to measure these patients' response just because of the nature of this disease.

Pathologic response was reported, and you've already heard that. The pathologic CR rate was not different between the arms. If you added in the category of microscopic residual disease in the face of a clinical CR, that result became significant. We validated these numbers through both database and case report form reviews.

In terms of time to progression, the Bristol analysis showed an absolute difference of 3.6 months, which is a highly significant P value. Even with our more conservative, if that's the correct term, censoring for the progression dates, you can see that the actual numbers are slightly different, the absolute difference here is 3.1 months and remains highly significantly different.

This is our curve for this difference in time to progression. You can see again that clearly these curves are separated.

In terms of survival, I would like to point out

that our analysis yielded the identical result to that of the sponsor. We were able to confirm dates of death by looking at the Bristol database, the GOG database, the case report forms and finally by the audit by FDA of primary centers. Again, you've seen this, this is our analysis of survival.

In terms of toxicity, myelosuppression was really the predominant toxicity that was seen on either arm. There was a high incidence of any type of neutropenia on both arms. Grade IV neutropenia was significantly greater on the PT arm. Infection rate was not significantly different, but if you looked at febrile neutropenia, there was a significant difference in the percent of courses, more on the PT arm than the PC arm. The sponsor also showed you what percent of patients that represented as well.

I would point out that although febrile neutropenia was significantly greater on the PT arm, I would just like to remind everybody that more of these cycles were actually delivered on time than the PC arm.

This slide summarizes the non-hematologic toxicities that were significantly different. I don't want to spend a lot of time on these, I would rather phrase it that most of the toxicities that are reported here are

really consistent with the labeled adverse events of Taxol and with clinical practice. Peripheral neuropathy, I mentioned that there was a neurologic assessment substudy that can only be analyzed qualitatively, and not surprisingly, it supported this result that patients on PT were more likely to have clinically evident neuropathy than patients on PC.

Many of these side effects were really significantly different in the grade I to II range, suggesting that they cause patients tolerable side effects.

Cardiovascular events I think is the other one that bears mentioning. Remember that there was a difference in the monitoring requirement. Patients on PT had cardiac monitoring throughout all of their therapy. Patients on PC did not. I think that that led to a reporting bias clearly that there were more of these events recorded on PT.

I think we're all familiar with the cardiovascular problems associated with Taxol, but again, the significant difference was in the overall number of events. Grade III to grade IV events were not significantly different between the two arms.

Mortality, 10 patients died within 30 days of study therapy, six on PT and four on PC. The reasons are

listed here.

In terms of what has already been published about GOG-111, and what was submitted in the study report, the predominant difference between the published report and the study report is the difference in the response rate. Again, as we talked about in the discussion, the published report showed a statistically significant response rate in favor of the PT arm, compared with PC. There was a greater absolute difference in the median progression-free survival and survival than in the study report. However, overall they were comparable, all in the same direction.

I think that some of the difference here is that when this paper was published, the GOG report excluded 24 patients from analysis who were not considered to be evaluable or eligible for the protocol and did not always require confirmation of response. We've already seen how just even a few small differences in the absolute number of responders can change the statistical significance of that parameter anyway.

Now, whenever we want to approve a drug for a new indication, it's important to consider it in the context of what is in the literature. I also wanted to refer to the European Canadian Intergroup trial and to GOG-132. Again, I

would like to preface those remarks by noting that we do not have primary data for review for either of these studies. We were given abstracts, copies of the ASCO presentations and slides. Dr. Piccart and her colleagues were kind enough to give us also this 1998 abstract, which was mentioned before.

In this study, there were 679 evaluable patients that were randomized to either the same standard PC regimen or the paclitaxel and cisplatin. There were some differences between these two studies. First of all, GOG-111 only allowed the suboptimally debulked stage III and stage IV, whereas the EORTC Intergroup Study allowed patients with state IIB through disease on the study. The dose and schedule of paclitaxel were different also. This study used 175 milligrams per meter squared over three hours. Escalation was permitted to 200 milligrams per meter squared. In the GOG study, the dose was 135 over 24 hours without escalation.

Again, up to nine cycles of chemotherapy could be given at the discretion of the investigator compared to six in GOG-111. Paclitaxel was permitted as salvage therapy, but in the Intergroup Study patients were not permitted to receive crossover therapy until they had objective evidence

of progression. In the GOG-111, that was not always the case. Some investigators treated these patients before that point occurred. Second look laparotomy was not required for the Intergroup Study and interval debulking was permitted.

Nonetheless, you can see on this slide that if you used the GOG-111 results as reported by the sponsor and compared them to the Intergroup Study, they're strikingly similar. The Intergroup Study has a significantly different response rate, although again, the numbers here in percent of response are not that different. The median progression-free survival times are almost identical, as are the survival times. Again, the survival data is from the abstract submitted to ASCO 1998.

In GOG-132, as you've heard, in this study patients were randomized to either high dose platinum, single agent paclitaxel or a combination of the two. Again, a higher percent of patients were able to complete the PT regimen compared to either single agent platinum or single agent Taxol.

In the discussion period, you saw the reasons for discontinuation. Patients did not continue predominantly because of toxicity or refusal to continue. Also, 19 percent of patients on the Taxol alone arm had early

progression disease, i.e. on therapy, compared to smaller percentages in the other arms.

These efficacy results again from submitted publications, but not from primarily reviewed data, show a significant response rate that the combination or single agent platinum was better than the Taxol arm. In terms of median progression-free survival, the paclitaxel arm was inferior to the other two arms, but overall there was no significant difference in survival.

Dr. Johnson asked me earlier in some of the discussion about crossover rates on this study. On the paclitaxel alone arm, 71 percent of patients then received platinum. Remember that there was a high rate of early discontinuation because of progressive disease. On the platinum alone arm, 54 percent subsequently received paclitaxel.

So overall, these unreviewed data would suggest that single agent paclitaxel may be inferior to using a single agent high dose platinum or the combination in terms of clinical response, pathologic CR and time to progression. There was no survival difference between the three arms. This is different from what's been reported for GOG-111 and the European Intergroup Study. And overall, PT appeared

comparable to single agent high dose platinum for efficacy, but more patients were able to complete the planned number of cycles and appeared to have an overall better patient acceptance rate.

So in summary, I would like to again show you the GOG efficacy results as reported by the sponsor and the FDA. Again, very similar median progression-free survival times, identical survival times in both analyses and both statistically significant and clinically significant. That's, once again, outlined on this slide that these differences are both statistically and clinically significant. They are supported by the published literature. The toxicity profile is consistent with prior experience with this drug and the toxicity profile seemed acceptable by patients as measured by their ability to complete therapy and by the grading of the adverse events. Thank you. I would be happy to answer any questions.

DR. DUTCHER: Dr. Williams.

DR. WILLIAMS: Susan, I just wanted to clarify on your endpoint slide says FDA classified patients as progressing on the date of last visit. I think that was meant to be censored on the date of last visit.

DR. HONIG: I'm sorry, yes, censored.

DR. SIMON: Just a clarification. On GOG-111, did you say there were more treatment course delays on the cyclophosphamide/platinum arm than on --

DR. HONIG: Yes.

DR. MARGOLIN: Does that explain why there seems to be a discrepancy between the incidence of febrile neutropenia in the platinum and Taxol arm versus the much lower planned dose versus dose administered in the platinum and cytoxan arm?

DR. HONIG: You mean were patients treated while they still had low counts?

DR. MARGOLIN: No, did the recovery occur so much faster with Taxol and it was actually the delays that accounted for -- rather than the incidence of febrile neutropenia that accounted for the lower percentage of planned dose in the cytoxan arm.

DR. HONIG: We actually wondered that question too, but we did not have enough granulocyte data presented to us. We could track it all the way through a cycle. The sponsor may have some information.

DR. MARGOLIN: It would just be a matter of finding out how long it took to give cycles to patients in the two arms.

DR. SCHILSKY: Just a couple of comments I guess. There are a couple of interesting points in the analysis that I guess at least makes you think about a few things. I found the dose intensity analysis to be very revealing, because it makes you wonder if one of the advantages of platinum/Taxol is simply that you're able to give more platinum. That's not an inconsiderable advantage because platinum is clearly a very active drug. But particularly taken in the context of the GOG-132 study, it does make you wonder whether an advantage in GOG-111 for the Taxol combination arm derives at least as much from the greater dose intensity of the platinum. Do you agree, disagree?

DR. HONIG: Yes, we were thinking quite a bit about that as well. I don't think that we have any data to say that's true, but we would draw that conclusion looking at all of these studies.

DR. SCHILSKY: It's interesting to speculate about that.

DR. HONIG: I believe also in the Intergroup Study that the PT arm was associated with fewer treatment delays also wasn't it, if I remember correctly?

DR. PICCART: It reproduced these findings.

DR. SCHILSKY: The other question actually, maybe

while Dr. Piccart is there, relates to the Intergroup Study, because there were I guess some number of patients in that study with earlier stage disease than in the GOG-111 study. Yet, the results are pretty much spot(?) on with GOG-111. You might have expected that because of some earlier stage patients that the results might be even better in the EORTC Study.

Of course, one of the differences has to do with the dose schedule of the Taxol. I'm wondering if anyone would care to speculate about what is the optimal way of giving Taxol in combination with platinum in ovarian cancer.

DR. PICCART: This is a difficult question you are raising. My guess is that there must be differences in patient selection between these two studies. For example, we do not have in the Intergroup Trial a clear description of patients in relation with the tumor bulk after the primary surgery. You heard that patients in GOG-111 who had less than five centimeter tumor mass remaining did better. We do not have this category, we just have less or more than one centimeter. So I'm hoping that the fact that all results look slightly worse given the fact that we have one sort of patient with optimally debulked disease could be related to this difference.

Regarding the optimal combination regimen, as you know, we encountered far more neurotoxicity. Now, of course, we kept treating patients for longer, up to nine cycles, but if you only analyze the first six cycles of treatment, we had three times more grade III/IV neurotoxicity with the original. So based on that, I think we can say they are equally effective, but the GOG regimen is probably better tolerated for this aspect. On the other hand, we had less febrile neutropenia, only two percent versus 15 percent of patients.

DR. KROOK: I was just going to ask Dr. Piccart while she was up there, I think I heard what you said that one-third of the patients on that Intergroup trial were optimally debulked. So two-thirds would fit the GOG study basically greater than one. Okay.

DR. DELAP: I just wanted a point of clarification on the dose intensity issue. I think, as I understand the data, that what we're talking about is the time it took to deliver the courses of therapy, but that the total amount of cisplatin delivered in the two groups was the same. It took longer to deliver it in the control arm.

DR. JOHNSON: Is that in fact correct because that's not exactly what the slide says? I was just asking

is that in fact correct, but I'm not sure that's exactly what the slide says.

DR. HONIG: Dose reductions were not permitted for cisplatin, so that while there were a few people who had their dose of cisplatin reduced, there were very few. Everything was handled predominantly by a dose delay, so the cisplatin arms are looking at giving it on time essentially.

DR. JOHNSON: So this less than 80 percent of scheduled dose is really relative dose intensity.

DR. HONIG: Correct.

DR. DELAP: If you look at the first line there, I think it says the cumulative dose.

DR. JOHNSON: But I would like just to make one point while Dr. Temple is in the room. That is I think that, because it's very germane to the earlier comment that was made vis a vis survival as the sole endpoint for determining efficacy. Had these two studies been reversed, GOG-132, we would have determined that, I think many would have said there's no difference in outcome period. You have exactly the same survival.

Here's a situation where a sequential therapy did make a difference and impacted on survival, this is my interpretation of these data. As opposed to the first

study, GOG-111, where there was a marked survival difference, I think had we had the sequence of these studies been done differently, one would have been, I hate to use the word again, conflicted when you were trying to determine the outcome or the relative value of Taxol.

I think my interpretation of GOG-132 is that there is something to sequential therapy and it does impact on survival as an endpoint. Therefore in that situation, I think we would have had a difficult time making a decision. So I think it does depend a little on disease, it depends on study design and it obviously depends on the effectiveness of that drug in that disease. My interpretation would be that this drug is quite active in ovarian cancer, which is why it has this impact.

DR. KROOK: One more question. I have I guess an interest in the fact that those patients who had a pathological complete remission, did most of those continue in complete remission? What was the relapse in those people who had a pathological complete remission? Was it substantial?

DR. HONIG: I don't know the answer to that offhand. I'm sure you have it.

DR. KROOK: I guess my question is once you are it

said clear, are you cured? I think the answer is no, but I'm interested in the percentage since we have substantial people.

DR. TEMPLE: From the time to progression curve, it does not look like there's a very large tail at the end of it. It's well under 10 percent.

DR. CANETTA: I'm sorry, I apologize, there's a slide that was included as a figure in our report. The duration of pathological completed response and microscopic lumped together as a group at a median of 33 months in the Taxol/cisplatin group and a median of 18.5 months in the cyclophosphamide/cisplatin group. The stratified logrank for this comparison was 0.1672, not statistically significant. We are dealing with a group of 67 patients in the Taxol arm and 43 in the control arm.

DR. SCHILSKY: I guess just one other comment, Susan, I think is worth drawing out, David and I were whispering about this, but your analysis of the response data I think is also somewhat informative because basically I believe there was a change made in the classification of response in a grand total of five patients out of the 240 with measurable disease. By changing the response

classification in those five, the P value for significance went from .153 to .04. I think that it just illustrates the care with which we have to consider response data, because by disagreement or just thinking about things differently, it's all in the eye of the beholder, we go from what everybody would be satisfied is a non-significant difference to something that most people would accept as a significant difference. There probably really aren't differences there.

DR. HONIG: Right, I agree.

DR. MARGOLIN: I think you could use those numbers just as much to apply to any number that affects a P value, not just response. The same thing could have happened to survival, but that's easier to measure.

DR. SCHILSKY: But survival is a much more precise endpoint. Here we have a very soft endpoint, small swings can make a big difference.

Agenda Item: Committee Discussion and Vote

DR. DUTCHER: Thank you. If there are no more questions or comments, I want to thank both the FDA and the sponsor for excellent presentations. On behalf of the committee, we're very grateful for the quality of the data that was submitted because it makes our job a lot clearer.

Should we go on to the questions for the

committee? I will give you a moment to read the preface and the table. I will read part of the preface. GOG-111 was a prospective randomized comparison of cyclophosphamide and cisplatin versus paclitaxel and cisplatin as first-line therapy of patients with suboptimal stage III and state IV ovarian cancer. The primary endpoint was progression-free survival. Survival was the secondary endpoint. Response was the tertiary endpoint.

The efficacy findings from the study report and from the FDA analysis are presented in the table, briefly review.

So, question number one, is trial GOG-111 an adequate and well controlled trial demonstrating the efficacy and safety of paclitaxel in combination with cisplatin in patients with advanced stage ovarian cancer?

DR. KROOK: I would answer this question yes, based on the fact that I have seen this data looked at by really three groups, the GOG, Bristol-Myers and also the excellent FDA presentation. So I would feel that this is an adequate and well controlled trial.

DR. DUTCHER: All those who agree, please raise your hand.

[Show of hands.]

One, two, three, four, five six, seven, eight, nine yes. No no's.

Number two, should paclitaxel in combination with cisplatin be approved for the first-line treatment of patients with advanced ovarian cancer?

MS. SOLANCHE: Question. Does his preclude the approval of cisplatin and -- I mean carboplatin and Taxol or is it two separate issues?

DR. DUTCHER: It's two separate issues. Dr. Krook.

DR. KROOK: I would make the motion that this question be answered yes. I think with the data that's available and particularly the survival data, that the answer be yes.

DR. DUTCHER: Any other discussion? All those who agree?

[Show of hands.]

One, two, three, four, five, six, seven, eight, nine yes. No no's. Any further discussion, comments?

Okay, thank you.

Now, since we are very much ahead of schedule, a five minute break.

We are going to proceed with the sponsor's

presentation for Taxol and lung cancer at 10:45 approximately. Then we're going to go through that before we have lunch.

[Brief recess.]

DR. DUTCHER: Okay. We are going to move ahead since our schedule is working very well. We're going to discuss a new drug application, supplement Taxol for indication in the treatment of non-small cell lung cancer in patients who are not candidates for potentially curative and/or radiation therapy.

Before we start with the sponsor's presentation, we have to read a conflict of interest statement.

DR. TEMPLETON-SOMERS: I promise this will be the last conflict of interest statement I read at this meeting. You can probably all quote along with me here.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with

the following exceptions.

In accordance with 18USC Section 208 and 505 of the FD&C Act, full waivers have been granted to Dr. Kim Margolin, Dr. James Krook, Dr. Janice Dutcher and Dr. Kathy Albain. In addition, full waivers under 18USC Section 208 have been granted to Dr. Richard Schilsky and Dr. Sandra Swain and a limited waiver has been granted to Dr. David Johnson.

Under the terms of this limited waiver, Dr. Johnson will be permitted to participate in the committee's discussions concerning Taxol for non-small cell lung cancer. He will, however, be excluded from any vote related to this product.

A full copy of these waiver statements may be obtained by submitting a written request to FDA's Freedom of Information Officer located in Room 12A30 of the Parklawn Building.

Further, we would like to disclose that for the record, Dr. Schilsky and Dr. Swain have interests that do not constitute a financial interest in the particular matter within the meaning of 18USC 208 but which could create the appearance of a conflict. The agency has determined, notwithstanding these involvements, that the interests of

the government in their participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Drs. Schilsky and Swain may participate fully in today's discussions concerning Taxol for NSCLC.

Lastly, Dr. Robert Ozols will be excluded from participating in all matters concerning Taxol.

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

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

DR. DUTCHER: Just as a comment, we're joined at the table by Dr. Kathy Albain as an ODAC consultant and Dr. Chico as the FDA reviewer. Our patient representative, Selma Rosen will be here at noon, but we're going to go ahead and proceed since otherwise we're going to lose half of the committee if we don't keep moving.

We're going to go ahead with the sponsor.

Agenda Item: Sponsor Presentation

DR. CANETTA: I guess I should say good morning again. We will present to you now our submission for Taxol in the treatment of non-small cell lung cancer. I will introduce the proceedings and Dr. Ruckdeschel from the Moffitt Cancer Center will review the current status in the treatment of the disease. Individual presentations for each one of the three pivotal studies submitted will be given by Dr. Phil Bonomi for the ECOG study, by Dr. Giuseppe Giaccone from the EORTC Study and by Dr. Karen Ferrante from the Bristol-Myers Squibb Pharmaceutical Research Institute for the multicenter international study. Dr. Winograd again for the BMS group will provide the concluding remarks.

We welcome today our external consultants, all of whom have been involved in the conduct of the pivotal trials.

Our NDA contains individual patient data from four phase II trials and from three larger phase III trials. Altogether, this includes data from more than 1,500 patients. These seven trials are the first clinical trials that have been completed with Taxol in the disease first as a single agent and then in combination with cisplatin in a

randomized setting. In addition, we did provide within the NDA a detailed review of all the published clinical trials performed with Taxol in non-small cell lung cancer. Forty-seven different studies that involved an additional more than 1,500 patients and represent an extensive worldwide experience with the compound.

The first trial of Taxol in lung cancer was completed by ECOG in 1991. Actually, this was a randomized phase II trial, but you won't see P values concerning this trial today. In this trial, Taxol achieved a response rate of 17 percent after auditing and that was the first time ECOG achieved such results with a new drug out of 10 consecutive phase II trials with new agents in the treatment of the disease. Not one of these other 10 agents exceeded the five percent objective response mark.

Of note, there was an unprecedented figure of 40 percent survival at one year. All the other experimental agents that have been attempted in this setting by ECOG did not exceed 20 percent one year survival.

Now, both response rates and one year survival results have been confirmed by three other studies performed in the U.S. or in Europe. It's very interesting that these results were confirmed and very consistent irrespective of

the dosage or the schedule of Taxol utilized.

The safety profile in these phase II trials in previously untreated patients was consistent with the prior experience with the compound. In fact, also in reviewing the literature data that I alluded to before, there was a large number of studies, 11 studies, that consistently reported the response rate of single agent Taxol of about 30 percent. Again, these are unaudited responses. Again, this was obtained irrespective of the schedule utilized.

Taxol and platinum combination, and there were 26 different trials with this combination, consistently appear to produce increased response rates of about 40 percent. In these trials, the safety profile of Taxol alone or in combination with platinum drugs is well established and acceptable.

Now, these are the three phase III trials of the combination of Taxol and cisplatin that have been completed in non-small cell lung cancer. The first one was performed by ECOG and compared a Etoposide and cisplatin to two different regimens of Taxol and cisplatin, and the high dose Taxol regimen contained a support of GCSF.

The EORTC Study performed in Europe also adopted [word lost] and cisplatin as the control arm and compared it

with a regimen of Taxol and cisplatin where Taxol was given at 175 milligrams per meter over three hours.

Finally, a multicenter group of international investigators adopted a high dose cisplatin regimen with 100 milligram per square meter given every three weeks to the same type of regimen that had been utilized by the EORTC study with Taxol given over three hours.

We will present to you today the results of these phase III trials which demonstrate that Taxol and cisplatin consistently provided a greater clinical benefit when compared to standard therapy. In these trials, Taxol and cisplatin produced increased response rates, prolonged time to progression, as well as advantages in quality of life.

In fact, in each of these trials, a statistically significant superiority in response rate was observed consistently for the Taxol-containing arm. In two of these trials, and in fact in both of the Taxol-containing arms of the EGOC trial time to progression was significantly longer for the Taxol containing regimen as compared to control.

We are aware of the complexity of evaluation of quality of life in this type of pathology. Using the different instruments and the fact [word lost] for the ECOG study, and the EORTC Q30(?) in the other two studies, each

one of these trials showed clear advantages either in lung cancer symptoms or in quality of life domains that all favored the Taxol-containing treatment. In all of these trials, survival was at least as good, if not better, as compared to standard therapy.

Taxol and cisplatin in these trials has an acceptable safety profile as compared to each of the respective cisplatin-containing controls. Today, the combination of Taxol and a platinum has become the reference regimen in all of the currently ongoing cooperative group trials.

We propose that Taxol is indicated for the treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or potentially curative radiation therapy. Dr. Ruckdeschel will now review for you the current status of the treatment for the disease.

DR. RUCKDESCHEL: Thank you, Renzo. There is in this disease, very different from ovarian cancer, a pervasive belief in the clinical community that except for surgery of early disease that non-small cell lung cancer is a completely incurable disease. Both of the patients you heard this morning were eloquent testimony to the fact that

this is not always so. We feel that this attitude is wrong, its application in the provision of care for non-small cell lung cancer patients denies thousands of patients a year a chance for cure.

Next slide. It is the commonest cause of death for both men and women. In fact, lung cancer kills more patients every year than breast, colon and prostate put together. A hundred and seventy thousand cases a year in the United States, 460 new cases every day, one every three minutes. Progress has been slow and incremental.

The overall current five year survival is about 13 percent. That's up from perhaps eight or nine percent 20, 25 years ago. But each one percent change in survival results in 1,700 lives saved. That's more than curing all the cases of Hodgkin's disease in the United States.

Chemotherapy for non-small cell lung cancer is not just for stage IV disease any more. It's had a clearly demonstrated benefit in sequential chemotherapy regimens, chemotherapy radiation regimens and stage IIIB non-small cell lung cancer, both in the CLGB and the Intergroup. There's increasing evidence that concurrent radiation and chemotherapy, whether at sensitizing dosages or in full dosage, improves survival in stage IIIB as well. There are

impressive early results from Texas and from Spain for pre-operative usage of chemotherapy in stage IIIA non-small cell lung cancer.

Well, what are the issues that we faced in the late eighties, early nineties as these trials that you're to hear about were coming forward? Unfortunately, these are the same issues that are still raised in some areas in this country and abroad. Is it better than supportive care? Do symptoms ever get palliated? Is it cost effective? Who benefits most? How do you compare the various regimens?

Next slide. Well, is it better than the best supportive care? Yes, we now have a large meta-analysis, 11 trials on almost 1,200 patients. There's an overall improvement in survival for the use of cisplatin-containing regimens, median survival and more importantly one year survival were improved, one year survival to 20 percent.

Therefore, I feel very strongly, and those of you who have known me over the years have felt this for many years, that best supportive care as a control arm or even as adequate therapy for good performance status patients with non-small cell is inappropriate and this is a dead issue as we move forward. Perhaps a bad pun.

Does chemotherapy for non-small cell palliate

symptoms? Yes, there are two good trials, one from New York, one from Great Britain, showing that cough, dyspnea, pain, hemoptysis, significant symptoms in patients with metastatic disease are improved. A very similar 84 percent improvement or stabilization of performance status in the New York Study and a 75 percent symptom improvement in the British study, both published. You will see in the report from Dr. Bonomi on the ECOG study a significant improvement in patient symptoms across the board.

Next slide. Well, in this era, we have to deal with cost effectiveness as well. Many people have questioned giving chemotherapy at whatever cost for short gains in survival. However, Evans and his colleagues in Canada have demonstrated that metastatic disease and locally advanced disease, and even in the adjuvant setting, that clearly when we use the cost per year of life gained or any of the other economic measures, that chemotherapy for non-small cell lung cancer is consistent and equivalent to most other useful health care interventions, and significantly better than things such as dialysis. In fact, in one of the trials for metastatic disease, the cost of not treating patients is greater than the cost of treating patients.

Well, who benefits from the chemotherapy? There

are enumerable trials and enumerable summaries now from the various cooperative groups and they agree on these three issues. Patients in good performance status do better. Patients who present in performance status two or less do poorly with chemotherapy. Minimal weight loss and a limited number of metastatic sites are the other major positive prognostic factors. In any study being analyzed or compared, these need to be taken into account.

Well, how do we measure treatment effect? As someone who has been active in non-small cell for almost 25 years, I wish we had the response rates that we see in lymphoma and ovarian and several other areas in oncology today. We don't, so most studies you will see are going to discuss median survival. As most of you know, I have been a strong proponent of using one year survival as a more relevant measure for metastatic non-small cell lung cancer. At a minimum, we need to consider both. In point of fact, we're interested in the entire curve, not just individual points.

Response rates have had a bad name and they get a bad rap in the setting of clinical trial analysis. We looked at this in ECOG and several of the large trials during the eighties when we went back and went down our list

of prognostic factors and treatment factors to try to isolate who were the patients who were doing better. One of the striking things we found is that it's this definition of response that causes us some trouble. The patients who have what we call no change do just about as well in survival as the patients who have what we call a partial response.

Now, a no change patient is someone who has less than a 50 percent response and that's anything from one percent to 49 percent, or zero to 49 percent. That's a very different patient than one who progresses rapidly on the disease. So in non-small cell, and I've published several of the trials or contributed to them, showing that there's this discontinuity or this lack of linkage between response and survival. The issue is if we lump the no change with the progressive disease, we come up with a wash in this relationship between response and survival. I'm not proposing we lump these patients with the responders, but I think that's where some of the disconnect is.

If I put on my hat, however, as a clinician, as someone who has treated literally thousands of patients with non-small cell lung cancer over the years, this is the measure that we use in the clinic. We tell our patients that if they respond to the therapy, they are the ones who

will benefit, they are the ones who will live longer. That is absolutely the clearest and most positive tool we have to tell a patient whether we should continue with therapy or not. There is not a clinician alive who will contradict that approach to managing these patients.

Time to progression, you've heard for all sorts of reasons, is not a bad measure when we have secondary therapy. More difficult to study are symptom control and quality of life for several reasons. Number one, these are complex issues, difficult to quantify, but more importantly in lung cancer, we're studying a group of patients, especially metastatic lung cancer who do poorly as a group and who die early, who don't come back for therapy, who go on to hospice care and are lost to follow-up. So you have built into the nature of the disease itself a dropout rate that you don't see with other conditions and other diseases. So when a group takes on quality of life, they need to do that knowing that they're really going to have to go after that group of patients who are still alive from the disease to have any kind of numbers available.

Next slide. Well, you need to clearly understand that symptom control and quality of life are not the same thing. Symptom control is disease and treatment specific.

Quality of life is a much more global measure that in many ways includes symptom control but is not solely symptom control.

You will hear about two measures today, the FACT-L and the EORTC Lung Cancer Scales. They're both well studied, validated instruments, not made up for these trials that get at both concepts and they include both disease specific and generic issues related to quality of life. Most importantly, the patient takes these and the patient fills them out, they're not filled out by staff.

Where were we in the early 1990's when the studies you're about to hear about were put together? We had available to us any one of several cisplatin-containing regimens. Etoposide-cis, Vinblastine-cis, CAP, cyclophosphamide, adriamycin and platinum, Vindesine-cisplatin and even some who would have argued at that point in time, particularly in SWAG(?) with Dave Gandara's(?) work, that platinum alone in this country was an adequate treatment for this disease.

We in particular pointed out in ECOG and then in several other areas that mitomycin containing regimens, which had been popularized in New York, were not as effective and in fact had a shorter one-year survival than

any of the other regimens.

All of these effective regimens had about a 20 to 25 percent response rate when tested in cooperative groups. They were always higher in single institution studies. They had one year survivals, this is for the effective regimens now, ranging from 18 to 25 percent. The mitomycin velban(?) platinum regimen was 12 percent in two consecutive trials.

In ECOG, a large analysis of over 900 patients, we felt that the best of our regimens was etoposide-cisplatin with a 25 percent one year survival. Was it significantly different than all of the others? No. There was really no difference between most of these regimens, but of the regimens we tested in the group, that was the best regimen for us. We describe it as the best of a modest lot.

The results, however, for etoposide and cisplatin was a standard in this disease in the early nineties and were very reproducible. They were reproducible across several ECOG trials and they were also reproducible across trials in the United States, Europe and Japan. The combination is relatively easy to administer in the community setting and it's readily combined safely with radiotherapy, a critical need in this disease.

Well, why all the excitement about Taxol? We were

the first group to have Taxol on a cooperative group basis. I believe I actually put the first patient on the ECOG trial for that, a woman with metastatic non-small cell with bone metastases who went on to receive 11 months of Taxol and to live for four and a half years on this particular trial. A 20 percent response rate for a single agent in metastatic non-small cell lung cancer confirmed at another institution with an even more impressive 40 percent one year survival in both of these studies convinced all of us taking care of patients with non-small cell lung cancer that this was truly a new era in both responsiveness and benefit for the patients. It was also helpful that this drug is very easy to combine with both cisplatin and carboplatin.

You can see in the ECOG randomized trial here, this is a phase II randomized trial, so you will see an absence of P values here, but I think it is, as we used to say in calculus, intuitively obvious to the casual observer that there's a benefit both in median and one-year survival for the Taxol arm compared to the other phase two agents.

Therefore in ECOG, a comparison of Taxol and cisplatin was an obvious next choice to compare to our ECOG standard of etoposide and cisplatin. At the urging of the NCI, we added a second arm looking at a dose effect

question. Then we took on, under Dave Sela's(?) leadership, this very difficult task of measuring quality of life on a longitudinal basis across literally hundreds of hospitals and institutions that make up ECOG this difficult to obtain quality of life data, and did, as you will see, a really spectacular job of that.

Next slide. Well, while we were waiting for this study to be completed, to be reported, to be analyzed, chewed over a lot of things were happening in non-small cell. First of all, there were multiple phase II studies of Taxol in combination with either cisplatin or carboplatin that were conducted and showed even more striking response rates and more striking one-year survival than we had seen with the single agent.

Also, during this period of time, and starting about in 1995 at ASCO and the international lung cancer meetings, a whole series of new active compounds, several of which you've heard about here, denorabangim(?), sidobene, docetaxel, all of these compounds were identified, tested as single agents and then also combined with cisplatin or carboplatin. All of these various permutations are now being tested in phase III trials.

In fact, as we have moved forward beyond the

results of the studies that you will see presented today, we have found in each of the groups in the United States and in Europe that the control regimen, the standard of care that we apply today when we design a study is either Taxol/cisplatin or Taxol/carboplatin. You can see here each of the four major groups in the United States and Europe who are conducting studies in advanced metastatic non-small cell have a Taxol/cis or a Taxol/carbo arm as the standard therapy.

Well, we have not solved the problem of metastatic non-small cell lung cancer. As you've seen today, we've made progress with that. You heard patient presentations, you've also seen now the data that brings that forward. I think personally and professionally that Taxol has made a significant difference and a significant change in the outlook for patients with non-small cell lung cancer. Thank you.

I would now like to introduce Dr. Phil Bonomi, a dear friend and colleague from Rush-Presbyterian who will give you the results of the ECOG trial. Phil.

DR. BONOMI: Good morning. I would like to start by reviewing the strategy that ECOG has employed over the last 20 years in the treatment of non-small cell lung

cancer. Starting in the late 1970's through the middle 1980's, our policy was to test regimens which had shown promising response rates in single institution studies. Unfortunately, the relatively high response rates were not confirmed and none of the regimens appeared superior with respect to survival with the exception, as Dr. Ruckdeschel has already pointed out, that etoposide/cisplatin produced the highest one-year survival rate, 25 percent. That regimen was retained as a reference regimen in a number of subsequent ECOG trials.

Having looked at all of these results, out of 10 years worth of work, we were somewhat discouraged and felt that the maximum benefit had been reached with the currently available drugs.

So at this point, we decided to switch our philosophy -- next slide please -- and we wanted to focus on drug discovery. Eight consecutive drugs were tested and none of them gave a response rate higher than five percent. Then Taxol came along, and in our analysis gave a 21 percent response rate and a 40 percent one-year survival. Virtually identical results were achieved by M.D. Anderson investigators. So at this point, we decided to test Taxol and platinum in a phase III trial.

The design of the trial is shown here. Each of the regimens had the same dose of cisplatin, 75 milligrams per square meter. Each was repeated every three weeks. We moved from dose finding studies that we could combine 135 milligrams per square meter of Taxol over 24 hours at that dose of platinum with acceptable toxicity. Dr. Rowinsky(?) and his colleagues at Hopkins showed that we could even use 250 milligrams per square meter over 24 hours if GCSF were included.

Again, the reference regimen was etoposide/cisplatin picked because it was the best one-year survival, picked because we thought it was the hardest one to beat and picked because it was widely used in the community.

Patients were randomized or stratified by symptomatic versus non-symptomatic, stage IV versus locally advanced, measurable versus evaluable and whether they had lost weight or not.

The main objectives were to compare survival, tumor response and safety. A secondary objective was to compare quality of life. We expected a median survival for the control of about six months. The study was sized to detect a 50 percent increase in either Taxol arm versus

control with 90 percent power.

Eligibility criteria, basically it was ambulatory, locally or advanced or metastatic non-small cell lung cancer patients who had not previously been treated.

The patients were seen at regular intervals. Tumor measurements were done at regular intervals. Treatment was discontinued for disease progression or excessive toxicity. Also, we defined progression of disease if a patient started a new therapy, if a patient got radiation because of painful bone metastases or an obstructed bronchus, that was considered progression, whether we showed objective increase in the measurements. So any change to new therapy was also included as an event and indicated progression.

As Dr. Ruckdeschel has pointed out, the FACT-L instrument was used in this study. It was administered at baseline, week six, 12 and 25 and was completed by the patients. There was periodic review by the ECOG data monitoring committee. In fact, it stipulated in the protocol that it would be done after every 116 deaths. At the first meeting of the data monitoring committee, the recommendation was that survival on the control arm would be compared to survival on the combined Taxol arms if there was

no difference between survival in the Taxol arms.

This study was first presented at ASCO in 1996 and was published in the ASCO proceedings in 1996.

In April of 1995, Bristol-Myers Squibb outlined to the FDA an analytical plan. This was one year before ECOG released the data to Bristol-Myers Squibb. They in this plan, all patients that were randomized were to be included. We were to compare each Taxol arm to control. The objectives were to compare time to progression and also to show the survival was at least as good in the Taxol regimen as the control, and also to compare quality of life.

This was a large study. It accrued very rapidly, 16 months, 600 patients for 34 ECOG sites, 200 patients per arm. With the last follow-up in January of 1997, 85 percent of the patients had either died or progressed.

Patient characteristics were well balanced across the three treatment regimens. A little more than a third were women, a little more than two-thirds were symptomatic but ambulatory, around a third had lost more than five percent of their usual body weight. Most of them, about 80 percent, were stage IV. The majority had visceral metastases and most of them had measurable disease.

This slide shows the responses, 26 percent for

lower dose Taxol, 30 percent for higher dose Taxol, 14 percent for the control. Comparing the Taxol low dose to control, there's a significant difference in favor of Taxol at .003. High dose also significant, less than .001.

This slide shows the time to progression for the lower dose Taxol arm. You can see that the curve breaks and then stays above the control arm out to about 15 months. Median time to progression 3.6 months on Taxol, 2.7 months on the control.

The high dose, same thing, the curve breaks early and the Taxol stays above the control out to about 15 months. A 4.3 median time to progression on Taxol, 2.7 on the control.

When we looked at survival, this is the lower dose Taxol versus the control, median 9.3 months versus 7.4. Again, fairly early on there's a break, and then it stays above the control arm out to around two years. The hazard ratio is 1.181 which translates into a 15 percent reduction in the risk of death for patients treated with Taxol.

At the high dose, again, the curve breaks early on and stays above for the Taxol treated patients. Median survival of 10 months on Taxol, 7.4 on the control. A hazard ratio of 1.207, translates to a 17 percent reduction

in the risk of death for patients treated with Taxol.

Next slide. This compares the two different doses of Taxol. You can see these curves were basically superimposable, no significant difference between them, 9.3 and 10 months were the median survivals.

Then this is the pooled or combined Taxol arms compared to control for survival. Keep in mind, the data monitoring committee in ECOG said we were going to do this if there was no difference in the Taxol regimens. You saw from the previous slide there was no difference in the Taxol regimens.

Again, it breaks early and it stays above out to beyond two years in favor of the Taxol arms. In this, the logrank P value was .049.

When we look at the survival rates here, and this was discussed yesterday and you heard it again today from Dr. Ruckdeschel, if we have patients who get just supportive care, we would expect a 10 to 15 percent one-year survival. In this study, 32, 36 and 40 percent, again the Taxol arms are higher and consistent with the other survival results. All the points on the curve, that's another thing we talked about, even getting out to one year, it's a little bit higher for the Taxol regimens. The same thing for two

years, 15 and 12 percent versus 11. Again, these aren't big differences, but the Taxol regimens are a little bit higher.

What does this mean to an individual patient? I guess it's easy to be nihilistic when you talk about lung cancer, but what does it mean? Well, it could mean, this difference could mean the difference between seeing a grandchild born or seeing a child graduate from college, medical school or whatever. These are the things that Dr. Ruckdeschel and other physicians who take care of, myself, take care of lung cancer patients, this is what we hear from the patients. These are their goals, the patients' goals.

Next slide. The treatment, we can see that there is a median of five courses on Taxol, the lower dose, four courses on high dose, four courses on etoposide/cisplatin. Amazingly, some of the patients got 15 and 16 courses of treatment.

Next slide. This slide summarizes severe hematologic toxicity. The things that are highlighted in yellow are statistically significantly different. The Fisher's exact test was used to compare the toxicities. What we see is there's a significantly higher rate of grade IV neutropenia on Taxol versus the control, but the important thing is there is no significant difference in the

infections, 11 to 10 percent. Patients on Taxol, the counts go down. They come up quickly. The duration of the granulocytopenia is the thing that determines this. That did not turn out to be an important factor. There was a little more thrombocytopenia on the control arm compared to Taxol.

Non-hematologic toxicity, again this is severe non-hematologic toxicity grades III and IV. We see there's no difference in hypersensitivity reactions, cardiovascular, neurosensory or arthralgias and myalgias.

If we look at hematologic toxicity for the high dose Taxol, there's a little more grade IV leukopenia on high dose Taxol, but again no difference in granulocytopenia. Keep in mind that these patients got GCSF. No difference in infections, and no difference in thrombocytopenia.

Severe non-hematologic toxicity, it's higher for hypersensitivity reactions on high dose Taxol, four percent versus one. No difference in cardiovascular. This seems like nothing now, but when this study came out that was a big concern. Was Taxol going to have a lot of cardiac toxicity? We didn't see it.

Neurosensory was more, a more severe neurosensory

on high dose Taxol. More arthralgias and myalgias on the high dose Taxol.

This slide serves as a summary of adverse events. How many patients died within 30 days of their last treatment. We see there is no significant difference across the three regimens. It's nine to 12 percent. No difference in the adverse events which occur within one month of the last treatment.

Next slide. As Dr. Ruckdeschel has already pointed out, we felt that including quality of life was very, very important in this study. We had made one attempt to do quality of life measurements in previous ECOG studies and we didn't do very well. We weren't able to get the patients to continue to fill their records out. As Dr. Ruckdeschel pointed out, these patients are very sick. When they are sick and they don't feel well, they don't feel like filling out forms.

At any rate, a major effort was made by the physicians, the nurses, the data managers in ECOG. They tried to get the patients to fill out this FACT-L questionnaire which was developed by Dr. David Sela. Twenty-eight questions focused on general quality of life issues and nine questions, a lung module, focused on lung

cancer symptoms. This instrument had been validated, and again it's important to point out the doctors and the nurses weren't telling the patients what to do, the patients were filling out how they felt, could they go out, could they work, what could they do, could they have dinner with their family and so on and so forth.

How was this scored? Every question had five possible responses, zero to four, not at all or very much and so on. Each of those scores were added up for the subsets of questions, for instance physical well being, social well being and for the total score.

This really was a Herculean effort on the part of hundreds, maybe even thousands of people to get these things filled out. So you can see we had pretty good compliance, above 90 percent at baseline, around 70 percent at week six, 64 percent total for week 12 and 50 percent at week 25. This is of the patients, obviously, who survived.

This slide shows the comparisons, and keep in mind it's a longitudinal comparison. It isn't just one point, it's all the points on that six month curve. What we see is there' a significant reduction in lung cancer symptoms in favor of Taxol in this analysis. Virtually all of the other things, in fact all of the other things, there's no

significant difference. In none of the categories listed over here do we see that it comes out in favor of the control arm.

Next slide. This shows exactly what we saw in the last slide, but it shows it graphically. What we see, we have baseline, they start out with their score and then the Taxol stays at baseline at six weeks and actually goes above baseline at 12 weeks. Then, as you would expect in people with incurable disease, their quality of life is going to go down as their disease starts to progress. Whereas in the control it goes down right away and it stays below baseline, in the difference between these two curves, not just one point here or there, the entire curve again is in favor of Taxol and cisplatin in relieving lung cancer symptoms.

This just shows bar graphs to show that at six weeks significantly more people, or a higher number of people on Taxol had relief of their lung cancer symptoms. The same at 12 weeks and the same at 25 weeks, always consistently better relief of lung cancer symptoms for the patients treated with Taxol.

This shows some of the individual questions. I have been short of breath, tightness in my chest, I have been coughing, breathing is easy for me. We see again a

percentage of people who think that those things are better for them is higher for Taxol versus the control.

Next slide. We looked at the same type of longitudinal comparisons for high dose Taxol. We see there's a trend for better emotional well being on high dose Taxol compared to control. All of the other parameters there's no significant difference. We see that never did etoposide/cisplatin come out to be better than Taxol.

In summary, based on these results, ECOG has concluded that in advanced non-small cell lung cancer, Taxol/cisplatin provides greater efficacy and clinical benefit compared with etoposide/cisplatin as documented by increased survival, increased response rate, increased time to progression, acceptable and comparable toxicity and improved lung cancer symptom score.

In light of this study, Taxol/cisplatin has and should replace etoposide/cisplatin as a standard therapy for non-small cell lung caner. It has become the reference regimen for the current ECOG phase III trial. Thank you very much.

I would like to introduce Dr. Giaccone who will present the results of the EORTC study.

DR. GIACCONE: Good morning. The Study 08925 was

a EORTC study that compared Taxol/cisplatin to our center regimen of teniposide and cisplatin. You may wonder why in Europe we would use teniposide instead of etoposide. The question is in fact that we like to build up -- next slide please -- like to build up our experience on randomized trials. In fact we selected the standard arm of teniposide/cisplatin based on the results of our previous phase III study that showed that a combination of teniposide/cisplatin yielded superior results in terms of response rate, progression-free survival and survival compared to teniposide alone. These data have been published about two years ago.

Next. In the present multicenter study, we compared to arms, the cisplatin/teniposide arm and the Taxol/cisplatin arm. The study was conducted by the EORTC Lung Cancer Cooperative Group. It was designed as a phase II study leading to a phase III trail.

The patients received either Taxol at a dose of 175 milligrams per square meter over three hours, plus cisplatin 80 milligrams per square meter or teniposide and cisplatin. Note that the cisplatin dose was the same in both arms. Stratification factors are the usual ones that you hear in randomized phase III trials.

The phase II part of the study was performed in order to ensure that the study arm has sufficient activity and tolerability to be further evaluated in a full fledged phase III trial. Remember when we started this study, there was not that much data on the combination of platinum/Taxol.

The primary phase III objective, when we moved into the phase III trial, were to compare survival between the two arms. The secondary objectives were to compare response rate, time to progression, safety and quality of life. In fact, this time we also felt that quality of life was important and we added it to the phase three part of the study.

The study was sized to detect a three month increase in median survival.

This protocol applied our usual eligibility criteria, which are rather similar to the ones you heard about the ECOG study, with the exception of the performance status. In fact, we also included some patients with a performance status of two.

The phase II analysis demonstrated after 80 patients had been evaluated sufficient activity and adequate safety to expand the study into a phase III trial. At the time of the expansion, as I said to you before, we added

quality of life as a new study objective. Clinical and tumor evaluations were performed at regular time intervals.

Between August 1993 and February 1996, a total of 332 patients were randomized by 19 EORTC institutions. There were in fact 166 patients randomized in each arm. And the data presented today represents patient follow-up through February 1997, about a year ago.

Overall, pretreatment characteristics were well balanced between treatment arms. We had about 70 percent of the patients male, about two-thirds had some impairment in performance status and nearly one-third had lost five percent of more in their body weight during the three months prior to study start. Only about one-third of patients had local advanced disease. As we noted in this analysis, there were however significantly more patients in the Taxol/cisplatin arm with visceral metastasis. This was not controlled in fact by the stratification. The vast majority of the patients had measurable disease in both arms.

Here you can see on this slide the clinical response. We had in total 320 patients that were evaluable for response and the overall response rate was 36 percent in the Taxol/cisplatin arm. This was statistically superior to the overall response rate of 25 percent that we observed in

the teniposide/cisplatin arm with a P value of .031.

On this slide you can see the time to progression curves. At the time of this analysis, more than three quarters of patients had progressed or died. As in the ECOG study, the start of another therapy was considered as an event for the 10 percent of patients in whom progression had not been previously documented.

The median time to progression of 4.6 months was observed in the Taxol/cisplatin arm. This was of course, similar to the 4.7 months observed in the teniposide arm, as you can see in this slide.

At the time of the survival analysis, the majority of patients had died. The median survival was similar in both treatment arms with almost complete overlapping of the survival curves as you can clearly see on this slide. Median survival was 9.5 months in the Taxol/cisplatin arm and 9.9 months in the teniposide/cisplatin arm.

The treatment duration was comparable in the two treatment arms. In fact, a median of five treatment courses were administered to patients in each arm.

On this slide you can see the hematologic toxicity, the severe hematologic toxicity. For each safety parameter, the incidence of severe events is compared

between arms, and the differences, the significant differences I mean are highlighted in yellow. Overall, teniposide/cisplatin resulted in more severe hematologic toxicity than did Taxol/cisplatin. Particularly noteworthy is the incidence of severe neutropenia observed in more than two-thirds of patients treated with teniposide/cisplatin compared to less than one-third treated with Taxol/cisplatin. Moreover, febrile neutropenia was also significantly more common in the teniposide/cisplatin arm, observed in more than one-third of patients in contrast to five percent of Taxol/cisplatin treated patients.

On this slide you can see the non-hematologic toxicity. As you can see here, the incidence of severe non-hematologic toxicity was generally low in both arms, probably exception made for nausea and vomiting, which was however comparable between the two arms. The Taxol/cisplatin did, however, cause more peripheral neuropathy.

Overall, nine percent of patients died within 30 days of last therapy. There was no difference between the two arms.

The EORTC quality of life questionnaire C30, core questionnaire, and the lung cancer module 13 were added as a

phase III study objective with the protocol amendment. Two-thirds of the patients randomized after the initiation of this amendment participated in the quality of life evaluation. Using this instrument, the patient self assesses five functional scales, a global health status and multiple symptom scales. With the lung module, disease related symptoms are evaluated in 13 single or multi-item questions. As with the FACT-L evaluation used by the ECOG study, also this has been validated in the EORTC, also this instrument.

In this slide we show the comparisons between arms for the functional scale scores in the quality of life questionnaire. In four scales, those in yellow in fact, the comparison significantly favors Taxol/cisplatin, namely physical functioning which includes questions related to performing daily tasks and simple exercise, role functioning, social functioning and global health status which encompass overall physical condition and quality of life. In none of this course was the comparison in favor of the teniposide arm.

In addition, for the symptom of fatigue, the comparison significantly favored Taxol/cisplatin and a borderline advantage existed for the symptoms of dyspnea,

hemoptysis, loss of appetite and diarrhea, as you can see on the left column. Teniposide/cisplatin was only significantly favored for peripheral neuropathy. For all other quality of life symptom scores, there was no significant difference favoring either arm as shown in the middle column.

So in summary, the EORTC has concluded that in advanced non-small cell lung cancer, Taxol/cisplatin provides greater clinical benefit as compared to teniposide/cisplatin. Taxol/cisplatin produces an increased response rate and improvements in most of the quality of life functional scales. An acceptable safety profile was also observed with comparable time to progression and survival.

In light of this study, Taxol/cisplatin has in fact replaced teniposide/cisplatin in our group and is the new reference regimen in the current EORTC phase III trials for advanced non-small cell lung cancer. Thank you.

I would like now to ask Karen Ferrante to continue.

DR. FERRANTE: Thank you. I will describe the results from a third large randomized phase III trial. BMS-208 was a multicenter international study that compared

Taxol/cisplatin to high dose cisplatin. In this study, patients were randomized to either Taxol at 175 milligrams per meter squared administered over three hours, followed by cisplatin at 80 milligrams per meter squared, the same dose and schedule you just heard utilized in the EORTC study, or to high dose cisplatin administered at a more aggressive dose of 100 milligrams per meter squared given every three weeks. Stratification factors are listed here.

The primary study objective was to compare survival between the two treatment arms. Secondary objectives included a comparison of tumor response, time to progression, safety and quality of life. The sample size was calculated to detect a 50 percent increase in one year survival.

Next. The protocol applied typical eligibility criteria. Stage IIIA patients were ineligible and a Karnofsky performance status of 60 or better was required.

Next. Clinical evaluations, as well as quality of life assessments were to be performed at regular time intervals on study. In total, 414 patients, 207 in each arm, were randomized by 35 sites between January of 1995 and April of 1996. The six major accruing institutions randomized approximately 40 percent of all patients. The

data presented today represents patient follow-up through July of 1997.

Overall, pretreatment characteristics were well balanced between the treatment arms. Eighty percent of the patients were male, the vast majority had some impairment in their performance status, and about one-third had lost five percent or more of their body weight in the six months prior to study start. Seventy percent of the patients had stage IV disease, just under one-half had visceral metastasis and the great majority had measurable disease.

In total, 387 patients with measurable disease were evaluable for clinical response. The overall response rate of 26 percent observed in the Taxol/cisplatin arm was significantly superior to the overall response rate of 17 percent with high dose cisplatin with a P of .028.

Next. At the time of this analysis, more than 80 percent of the patients had progressed or died. Time to progression is presented here as it was in the other two studies, considering the start of secondary therapy as an event for the 10 to 15 percent of patients in whom progression had not previously been documented. The median time to progression of 4.1 months in the Taxol/cisplatin arm was significantly superior to the median time of 2.7 months

with high dose cisplatin with a P of .026.

Next. At the time of the survival analysis, the majority of patients had died. The median survival was similar in both treatment arms, 8.1 months for Taxol/cisplatin and 8.6 months for high dose cisplatin.

The treatment duration is summarized on this slide. It is particularly noteworthy that patients in the high dose cisplatin arm received significantly fewer treatment courses than did those in the Taxol/cisplatin arm with a median of three compared to five.

In terms of hematologic toxicity, there was more severe neutropenia in patients treated with Taxol/cisplatin, however this was associated with the complication of febrile neutropenia in only four percent of Taxol/cisplatin patients. More importantly, there was no difference between treatment arms in the incidence of severe infection.

Non-hematologic toxicity is summarized here. With the exception of nausea and vomiting, the incidence of severe non-hematologic toxicity was five percent or less in both treatment arms and there were no differences between treatment arms in the incidence for any of these toxicities.

Next. Overall, less than 10 percent of patients died within 30 days of last study therapy. There were no

differences between arms.

The quality of life scale used in the other two studies was also used here. In terms of longitudinal comparisons between treatment arms, there was a borderline significant advantage in favor of Taxol/cisplatin for physical functioning. There were no differences, or no significant differences between arms for any of the other functional scales.

In addition, nausea and vomiting, loss of appetite and constipation were significantly improved in patients treated with Taxol/cisplatin, whereas high dose cisplatin was perceived as advantageous for both hair loss and peripheral neuropathy.

In summary, this multicenter international study demonstrates that Taxol/cisplatin provides greater clinical benefit compared to high dose cisplatin. Taxol/cisplatin produced an increased response rate, a prolonged time to progression, as well as improved physical functioning. An acceptable safety profile was observed and survival was comparable between treatment arms.

Dr. Benjamin Winograd will now present our concluding remarks.

DR. WINOGRAD: We have presented today three large

randomized studies that have evaluated Taxol/cisplatin in the treatment of advanced non-small cell lung cancer. The first study was conducted by the ECOG, the second by the EORTC and the third was a multicenter multinational study. Final results from all three studies demonstrate that Taxol/cisplatin provides greater clinical benefit than cisplatin-containing control therapy. Survival with Taxol/cisplatin is at least as good as cisplatin-containing control therapy, if not better as suggested by ECOG.

Next slide. Clinical response rates for Taxol/cisplatin were consistently between 26 percent and 36 percent. In all cases, the response rate for Taxol/cisplatin was significantly higher than for the respective control therapy.

According to our preplanned analysis, time to progression included all randomized patients and considered patients who died or received secondary therapy prior to documented progression as having progressed. The median time to disease progression for Taxol/cisplatin consistently ranged from 3.6 to 4.6 months. In three of the four comparisons, this was significantly longer than the respective control therapy.

In this rapidly progressive disease, more than 80

percent of all patients across the study, so this pools the patients from the two arms together, had progressed at the time of these analyses. Another five to 10 patients across all studies were alive without progression. The remaining 10 to 15 percent of patients have received subsequent therapy prior to documentation of a progression. Many of these patients were taken off study for toxicity reasons and can thus be considered to have failed the therapy.

Alternatively, we also analyzed time to progression in these three studies by censoring these 10 percent of patients at start of their subsequent therapy. Using this alternative analysis, the median time to progression for Taxol/cisplatin again ranged very consistently between 4.3 and 5.1 months. This again was consistently longer than the respective control therapy.

Next. The three studies confirmed that Taxol/cisplatin has an acceptable safety profile as compared to the respective cisplatin-containing control. It may be noted that in the ECOG study, Taxol/cisplatin was better tolerated than the high dose Taxol/cisplatin arm. The Taxol/cisplatin combination has been extensively utilized for the treatment of non-small cell lung cancer.

All three randomized studies prospectively used

quality of life instruments that were patient self-administered and validated instruments. Each instrument utilized a specific lung cancer module and quality of life was assessed at multiple time points in all of the studies.

It is particularly noteworthy that in the ECOG study patients on the Taxol/cisplatin arm perceived a significant improvement of their lung cancer symptoms as compared to patients on the control arm.

As with the FACT-L instrument in the previous slide, the areas of borderline or significant difference in patient perception between Taxol/cisplatin and the respective control are summarized here for the EORTC quality of life instrument. Physical functioning was improved for Taxol/cisplatin in both of the European studies. There were additional functional improvements in the EORTC study.

For the symptom scales, again, there were multiple perceived advantages for the Taxol/cisplatin therapy in both of the studies. Only hair loss and peripheral neuropathy of any grade were perceived as worsened to control therapy.

In summary, Taxol/cisplatin provides greater clinical benefit than standard cisplatin-containing therapy. Taxol is safe and effective therapy for patients with non-small cell lung cancer. Our conclusion is that Taxol is

indicated for the treatment of non-small cell lung cancer. Thank you.

Agenda Item: Questions from the Committee

DR. DUTCHER: Thank you very much. We are now going to see if there are any questions from the members of the committee for the sponsor.

DR. SCHILSKY: I have a few questions. I guess maybe I would like to start off by asking Phil Bonomi some questions about the ECOG study. Most of my questions, Phil, relate to some of the issues with respect to toxicity. Could you tell us a little bit further about how infection was defined? Is that bacteriologically documented infection or is that episodes of febrile neutropenia or how is it defined?

DR. BONOMI: Actually that was both infection documentation -- can you hear me okay -- and temperature above 101 in the presence of granulocytopenia. So both of those were lumped together on that slide.

DR. SCHILSKY: So that one slide that showed infection rates being the same, I guess as I recall in the various arms, that included episodes of febrile neutropenia in there.

DR. BONOMI: Yes, it did.

DR. SCHILSKY: Did you collect any data on rates of hospitalization for toxic events in that study?

DR. BONOMI: No, we didn't.

DR. SCHILSKY: So you have no data on that. Any data on the requirement for platelet transfusion?

DR. BONOMI: We don't have that either, but it was relatively low in the regimens. We don't have that data.

DR. SCHILSKY: And on the slide that you showed with hematologic toxicity, anemia was not listed. Do you have any data on rates of anemia?

DR. BONOMI: Yes, we do. There is about 20 percent grade III anemia and it's across the three regimens. It's not different.

DR. SCHILSKY: Not different, okay. If I could just ask another couple questions. I have a couple of questions about the other two studies. Both of those studies we're told that the majority of patients in both of those studies had measurable disease. That was described to us as being both uni-dimensionally and bi-dimensionally measurable. So I'm curious to know how many patients had uni-dimensional disease and how many had bi-dimensional disease.

DR. CANETTA: It was an extremely small proportion

of the measurable patients that only had one measurable diameter, five percent.

DR. SCHILSKY: Those patients were included in the response assessments?

DR. CANETTA: Those patients were included as measurable in the response assessment.

DR. SCHILSKY: And what definition of response was used for those patients?

DR. CANETTA: More than 50 percent reduction in the diameter.

DR. SCHILSKY: In the single measurement. Okay.

DR. CANETTA: Maintained for four weeks, obviously.

DR. SCHILSKY: And how were those responses verified in those studies?

DR. CANETTA: We took individual measurements of the lesions. These were reviewed by BMS physicians.

DR. SCHILSKY: So you took measurements of the lesions off case report forms?

DR. CANETTA: They were recorded prospectively in the case report forms, lesion by lesion.

DR. SCHILSKY: So basically what you did was just to be sure that the math added up okay by multiplying it out

again.

DR. CANETTA: We took into consideration also non-measurable lesions that were listed in the case report form. We made sure there was no progression in those lesions.

DR. SCHILSKY: You didn't review any of the x-rays or anything?

DR. CANETTA: For these particular studies, no, we did not.

DR. WINOGRAD: In fact, what you have to do is you have to split the three studies because obviously ECOG has their procedure on how they review and evaluate responses. EORTC has their procedure on how they do that. For our multicenter study, we prospectively monitored the study and at the point of the monitoring we reviewed the data as it came on the case report forms. Then for all three studies after that first level, we reviewed the data as it was in the database and for the ECOG and the EORTC study we communicated with the respective groups if there were any discrepancies that we thought should be evaluated differently. We did the same type of review for our sponsored study where we went back to the investigator and reviewed things that were not entirely clear.

DR. CANETTA: Perhaps Dr. Giaccone wants to

comment on the EORTC procedure.

DR. GIACCONE: Yes, for the EORTC, we had an independent review of radiological responses within our group from independent physicians. So in fact we had a higher response rate than was mentioned here.

DR. SCHILSKY: Maybe I could ask one other question, I'm sorry, about the ECOG study. You showed us that very nice curve on the change in lung cancer symptoms from baseline. As I understand it, that curve was for the patients on the low dose Taxol/cisplatin arm. Do you have a similar curve for the patients on the high dose arm?

DR. CANETTA: No, we don't have such a curve, but when you look at the way the P values were calculated, these are the statistical representation of what that analysis means. That curve was shown to illustrate the methodology that was using in analyzing quality of life and to illustrate the fact that the entire interval for which we had information available was taken into consideration and not individual data points.

DR. SCHILSKY: I think there's a comment in the submission about the fact that the patients on the high dose arm actually had a consistent worsening of their quality of life over the initial six weeks or so of the evaluation.

DR. BONOMI: No, Rich, we actually in ECOG, as you know, quality of life can be analyzed a number of ways, but one of the things that was analyzed in ECOG, two things, one a longitudinal look at the quality of life over the entire six months. No difference for either the Taxol versus the platinum, they're exactly superimposable similar curves. But maybe more importantly is we've defined a thing we call quality of life response in ECOG which means you have to improve by five units in a score of quality of life.

We looked at one of the things that Dr. Sela(?) has identified, he calls it trial outcome index. Trial outcome index is the thing that best depicts the physical component of quality of life, how they're feeling and what they can do, functional capacity. In fact, the percent of responders was higher and consistent both in the high dose and the Taxol at the six week time point, 20 percent versus 10 percent on the control arm. It did not reach statistical significance, but it was higher and consistent with higher frequency than the TOI score for both high and low dose Taxol.

DR. CANETTA: If you're interested we can show the TOI analysis done by ECOG.

DR. DUTCHER: Thank you, let's go on. Dr. Albain.

DR. ALBAIN: Yes, thank you. I have a question similar to one that was raised this morning earlier during the ovarian session pertaining to the wording of the indication. It's stated in several places that there is a request for approval or indication in combination with the platinum compound. With that in mind, many of us are aware that you have completed a very important trial in this country this year submitted to the ASCO meetings, it's actually referred to in some of our materials. Could you make a comment regarding that? This is a trial of Taxol/carboplatin versus etoposide/cisplatin. There's a lot of rumors on the street about what's going to be presented. Am I describing your trial correctly?

DR. CANETTA: There are several trials that are going on. You have seen the four that have been presented by Dr. Ruckdeschel. There are two additional trials that have been completed for accrual. One was done in this country to compare Taxol and carboplatin versus etoposide and cisplatin. That trial, to the best of my knowledge, had not matured a sufficient number of events to warrant a final analysis. There is a second study done in Europe that compares carboplatin and Taxol versus cisplatin and Taxol. The trial has accrued about 600 patients. It has been

submitted to the ASCO meeting. However, what has been submitted to the ASCO meeting is only preliminary results because not enough follow-up has occurred for that trial.

If I can comment to the indication, again, I think it should be seen in the same context as we framed the indication for the ovarian cancer. At this moment, the three pivotal studies have used cisplatin. In our recommendation dosage, what we worded this recommendation is as follows. Taxol be administered over three hours at a dosage of 175 milligrams per square meter followed by a platinum compound, meaning cisplatin. Then we said should a 24-hour infusion of Taxol be selected, then the dosage should be 135 milligrams per meter.

Basically again, our approach was to provide all of the data and both choices to the physician and to the patient to choose from. We could have worded it the other way around, recommended 135 24 hours, should the three hours be preferred, 175 should be the dosage.

DR. ALBAIN: If I may follow up, so the information that many of us had heard that there is no survival advantage to carbo/Taxol over cis/etoposide is not ready for publication at this stage?

DR. CANETTA: I don't think that this information

is really accurate. I haven't seen these results. Again, I've been told that not enough events have occurred so we would not have assessed these results.

DR. ALBAIN: A second question pertaining to your completed trials, was there not a European trial looking at best supportive care versus Taxol? Actually we have some material in our printed that there so far is no difference. Could you comment regarding that study?

DR. CANETTA: Yes, that is correct. Actually, we can show some data. You're to keep in consideration, and again we go back to this morning's presentation, we don't have yet mature data for this comparison of single agent Taxol given at 200 milligrams per square meter over three hours versus best supportive care. We did provide to the agency upon request of the agency whatever information is available to us, but there are a few caveats concerning this data.

This is the study design. It encompassed stage IIIB and stage IV. It was stratified by these parameters and also performance status zero and one and two. This is the study we referred to as study two to four.

Next. We can proceed quickly. Okay, like I said, in this trial, there's accrued a total of 157 patients.

There are still -- 49 patients are still alive, but as you can see, the follow-up has not been fully completed.

Can we move to the next slide. This is the survival data as they stand at this moment. Again, I have to caution you about the number of censored observation that appear early in the curve. These are by no means mature results. Again, we provided these results to the agency upon the agency request. At this moment, there is a median survival of 6.4 months for patients receiving single agent Taxol. There is a median survival of 4.6 months for patients receiving best supportive care. The P value stands at .07. Again, we do not consider these data to be mature enough to draw any conclusion. We made the point about that to the agency. We plan to complete a full update of this data within the next three months, three to six months I should say.

I should also say that this trial was performed in the United Kingdom and in Canada. I think we have a slide about who the investigators were. The leading investigator was Dr. Thatcher in Manchester. Dr. Thatcher did perform one of the original phase II trials of Taxol as a single agent at a dosage of 200 milligrams per square meter over three hours. A group of British investigators and one

Canadian investigator participated in this trial. It's difficult in today's reality to be able to sustain a best supportive care choice in designing the trial.

DR. ALBAIN: I also would like to ask Dr. Bonomi a few questions, Phil. There seems to be a little bit of difference in how the pooling information is being presented. You specified that it was in the protocol up front as a prospective plan, that you intended to pool the two arms, you did not.

DR. BONOMI: No, it's not in the protocol, Kathy, it was at one of the first data monitoring committee meetings, every 116 deaths they said this is what we're going to do. It probably should have been put in the protocol but it was not put in the protocol. Why not? Probably because this is the difference between probably a cooperative group and regulatory bodies and we were not thinking that way. The statisticians agreed that this was okay to do. In fact, a manuscript which will be sent off soon is going to be basically saying that too.

DR. ALBAIN: Your survival P value was a .04 something I believe.

DR. BONOMI: Zero four nine.

DR. ALBAIN: Zero four nine, which actually has

gone up a bit from when you originally presented it at ASCO.

DR. BONOMI: That's correct.

DR. ALBAIN: Is that type one error the correct type one error for that comparison?

DR. BONOMI: I guess I would probably have to ask our statisticians to comment about that.

DR. JOHNSON: One comment about that. I know I'm not allowed to vote, but I'm allowed to speak --

[Laughter.]

-- which is exactly like my house, being married for 30 years and having a 20-year old daughter. I'm lucky if I can speak is right.

This study was actually the power, this has a much higher power of detecting smaller differences. The beta error here is not 10 percent, it's five percent in this study, which is something that's unusual, very unusual for a cooperative group trial, it needs to be pointed out. Of course, I would be showing my bias if I said this is probably the best trial I've ever heard presented at FDA, the ECOG trial --

[Laughter.]

DR. DUTCHER: He said humbly.

DR. JOHNSON: -- which is a true statement. I

think it's worth pointing out, I mean again, there's some very important issues in my view about the data that we've heard over the past two days on lung cancer, because in reality what we've heard is eight randomized controlled trials from two different sponsors which are amazingly consistent, which shows that this is a lethal disease that people who don't get treated die in four months. That's what -- and in fact, we just saw yet another trial. I don't know how many times we have to prove that you die of lung cancer before people recognize that you die of lung cancer.

What Bristol-Myers has shown this morning is three randomized trials, one of which I think is conclusively positive with survival data and I think properly analyzed. The second two trials, however, I think are interesting because they don't show a survival benefit, but if you look at the data from these eight randomized trials, four of which compared a single agent to a doublet with either a vinca-alkaloid or a podophyllotoxin, and four of which compared a platinum-containing regimen to one of these newer doublets, what you see is in these trials the single agent gives amazingly consistent survival data, 7.6, 7.1, 6.6 and 6.0. The sole exception to that is the single agent study, high dose platinum showed, where there was an 8.6 month

median survival. That's an outlier compared to the other trials we saw.

For the doublets, the platinum vincas or the platinum podophyllotoxin, the four trials in which such an arm was contained, the median survivals were 7.2, 7.4, 7.6, 7.4 with the exception of the EORTC trial where it was 9.9, a huge outlier and inconsistent with the previous experience of that same cooperative group in the same population of patients using the exact same regimen where their median survival had been 7.4. What's happened in my view is Bristol has had amazingly bad luck with two trials. Yet the time to progression benefit in all three trials favored the experimental arm in this.

There are a lot of data to look at here, and I think as we pointed out in the ovarian data, a shift of a patient or two here or there makes a difference in a P value of .115 to .048, which we all worship at that particular altar. I think those are some of the issues that need to be considered.

DR. CANETTA: If I may add one thing. I wanted to point out the fact that the high dose cisplatin study that we presented in fact used a more aggressive approach than the ones that have been presented during this committee

yesterday. It was every three weeks and given really in a much more aggressive way.

DR. ALBAIN: I would still wonder if Bristol could answer my question, which was for them to comment on the type one error on the pooling.

DR. CANETTA: This is Dr. Beltangady from the statistical department of Bristol.

DR. BELTANGADY: This did receive a lot of attention while the study was ongoing, and as part of the planned analysis that ECOG conducted. We didn't have access to any of this data before, so I had a lot of discussions recently and even about a year ago when we got access to this data and these data were presented with the ECOG statisticians. They feel that the message is that there is no problem in concluding that the Taxol with the two arms combined, the data suggests that there is improved survival. That's going to be part of the main message that was at ASCO and they are also going to be saying the same thing in a manuscript.

DR. ALBAIN: But my question specifically, I'm sorry to belabor this, is the .05 or the .0125. It seems to have to do with a number of additional -- I'm not a statistician so I may be misspeaking -- but the number of

additional analyses you do in addition to the planned analyses.

DR. BELTANGADY: I think that question is well put and in the protocol specifies that these comparisons will be done at .0125. That is related to the number of comparisons that will be done in the analysis. So in a strict technical sense, one could say that this would be considered a post-hoc analysis. That was not written into the protocol. The only difference here is that it was preplanned from the time there were about 115 or 116 events that were seen by the data monitoring committee.

DR. DUTCHER: Grant, you wanted to make a comment.

DR. WILLIAMS: I have a similar kind of technical question regarding time to progression. Depending on which analysis you do, you have various numbers of trials that are positive from a strict statistical sense. I believe the first analysis you did is probably biased in favor of Taxol, that is when you crossover to a new therapy you call it a failure. Well, especially in the study that had only cisplatin as a control arm, the physicians are going to be perhaps thinking their patient could receive Taxol, I presume that was one of the options. And at the earliest time when there might have been any sign of progression,

they might have crossed over to Taxol. I don't believe there would have been a similar bias in the other direction.

So I believe that analysis might be biased in favor of Taxol, however I think the other analysis where you called that an event, you called it a censor there, I think that could be biased against Taxol. So I don't believe either one is right, there isn't a right way to do it, but I do believe there's probably bias in that analysis.

DR. CANETTA: I can show you three slides, the ones that are without preplanned analysis and the two graphs with the confidence intervals. I think that what is important to point out is that we submitted our planned analysis in April of 1995 as it was stated by Dr. Bonomi. We had not received a single piece of information from the data monitoring committee of ECOG. There was full control over the data by the DMC and we hadn't seen, nor had we known anything about this trial at all. This is what we filed with the agency back in April of 1995.

Now, the reason why we decided to do the analysis this way, considering an event, the fact that the patient switches to another therapy, again we didn't know the way the data were going, we had no access to the data. We thought that in this disease, this is not ovarian cancer,

this is rapidly progressive disease and normally if the patient abandons treatment, it's because the treatment is salient to provide the appropriate benefit to the patient. We thought that that was the most appropriate way to analyze the data.

If we can show the next slide, with the confidence intervals, this is the analysis that we did considering an event. As you can see, there is a certain consistency.

Now, one can do the analysis the other way, and in fact we did the analysis the other way as well and we provided in the filing, and I can show the same graphs with confidence intervals. I think that this is done considering when there is a switch of therapy, not an event but censoring the patient at that level. But as you can see, there is no substantial difference between the ultimate outcome of the data. We can show you also the time to progression curves for this particular analysis. If you want, we can show them to you, you can see that the Taxol arm is always on the top. It's true, the P value is not less than .25. It is .05 in fact, .05 or .04 I should say in that particular comparison. We didn't paint it in yellow. It's .08 in the last study.

I think what is important to point out, I don't

think it is important to argue about the P value, it's important to look at the consistency of the data and the fact that overall there was no indication whatsoever that the Taxol-containing treatment would provide an inferior type of effect. I think that's the important notation.

DR. SWAIN: I had a question about study 165. You said there were in one of the slides, there were about 22 patients that died within 30 days of therapy that were possibly drug related deaths on the Taxol arm. Could you describe those to us?

DR. BONOMI: Yes. There were a number of patients, for instance, who died midway between a cycle, just dropped dead, presumably a cardiac event. For the long time the statisticians had been telling me, you clinicians aren't as smart as you think you are. We think that's not a treatment related death, but because it happened while they were in between the treatments, we listed anything that could possibly be treatment related as treatment related.

DR. SWAIN: Were there any that were definitely treatment related, neutropenia, fever?

DR. BONOMI: I didn't think there were any that were definitely treatment related, other than the infections. We definitely had deaths due to infections, no

question about that.

DR. SWAIN: Actually there were nine then due to neutropenia on the high dose arm?

DR. BONOMI: Right.

DR. CANETTA: This might not necessarily be neutropenia, only it's any severe infection in the way ECOG has collected the data.

DR. SWAIN: Okay. I have a general question. I don't treat lung cancer patients, so bear with me here, and maybe Jack could answer this. You mentioned in your presentation that patients with IIIB disease are getting radiation, there's a survival benefit with radiation. I guess none of the patients in any of these studies that had IIIB disease got radiation as part of their primary therapy. Why didn't they? Was it timing of study results or what?

DR. BONOMI: In fact, we've changed the current protocol very appropriately. The IIIB patients who are allowed are only those with pleural effusion. I think most of us believe that if you have IIIB disease that radiation and chemo provide a benefit over either one alone, even though there is so much data with radiation and chemo against chemo alone. We don't know exactly how many of the patients got radiation in the previous study, we did not

actually collect that information.

DR. SWAIN: Couldn't that affect your survival outcome?

DR. BONOMI: I guess it could, but I don't think it probably did. It was only 20 percent of the patients. Again, I don't know that all of them got radiation therapy, so I don't know -- we have some data?

DR. CANETTA: In fact, we do have the numbers. It's about 18 to 20 percent in each one of the three arms of the ECOG study that had gotten some form of prior radiation therapy. That doesn't necessarily mean the primary tumor. It may mean a metastatic localization. These numbers for the other two studies amounted to less than 10 percent. So less than 10 percent in the other two studies prior radiation. Equally, I think the numbers if I remember correctly for ECOG is, bear with me, 18, 20 percent across the arms. In the other two studies it was something like nine and 10 or 11 and 10.

DR. RUCKDESCHEL: Sandy, your question was I think did they get radiation after their chemotherapy, was that your concern?

DR. SWAIN: As part of their primary therapy.

DR. RUCKDESCHEL: None of them had radiation

afterwards. We were in a switch during that, so if they were on the ECOG study with IIIB disease, they couldn't get radiation as part of their primary treatment. It was a chemo only study.

DR. SWAIN: But they could have had primary radiotherapy before the chemotherapy?

DR. RUCKDESCHEL: Yes, and they would have had to document progression before they could do that. They couldn't be treated with radiation and then with no further interval change go on to chemotherapy. They had to have a lesion outside the radiation field or documented progression.

DR. SWAIN: Okay. I have another simple question.

DR. CANETTA: I'm sorry, and the numbers are here just to prove that my memory is bad.

DR. SWAIN: Another simple question is what constitutes visceral disease with lung cancer patients, metastatic visceral disease?

DR. RUCKDESCHEL: Liver, bone, brain. We did not include brain metastases patients on any of the ECOG trials.

DR. SWAIN: You count bone as visceral disease?

DR. RUCKDESCHEL: Yes. Very different than breast. Bone is, in fact, bone and liver metastases are

the worst prognostic factors, aside from cutaneous metastases for non-small cell

DR. SWAIN: Do you have the numbers for your study and for the ECOG study, how many patients had liver disease versus bone disease? I think you had 50 some percent of patients had visceral metastases.

DR. BONOMI: I don't know if we have it broken down by those specific sites, Renzo, do we have that? I don't know.

DR. CANETTA: Overall, in the ECOG study, just counting percent of patients, there were 57 percent in the low dose Taxol/cisplatin arm, 58 percent in the high dose cisplatin arm and 63 percent in the etoposide/cisplatin arm that had visceral disease. I think we have the numbers broken down.

This is not zero(?) on visceral disease, it's any localization, but you can figure this one out. As you can see, there was a higher proportion in the Taxol/cisplatin arm for liver involvement versus the high dose Taxol/cisplatin arm and 21 percent in etoposide. There was no significant difference in the distribution across --

DR. DUTCHER: Dr. Albain.

DR. ALBAIN: Just to follow up on Dr. Swain's

question. In the wording of the indication for not candidates for potentially curative surgery and/or radiation therapy. going back to what Dr. Bonomi and Dr. Ruckdeschel just said, I think the tendency here is to exclude patients potentially candidates for curative chemo/radiotherapy with IIIA and IIIB disease from the stage IV pleural effusion. Could you clarify what type of patient you are seeking the indication in?

DR. CANETTA: Basically we can talk only of the patients that were constituting the base for our pivotal trials. These were patients who had stage IV disease. Patients who had stage IIIB disease that were not amenable to a combined modality approach, I think in today here, we would not recommend this type of treatment to be used alone in treatment with stage IIIA or with stage IIIB. I think the state of the art is going faster than we are and showing that a combined modality approach should be recommended.

DR. DUTCHER: Dr. Margolin.

DR. MARGOLIN: That was basically my question. I don't recall how many patients you had with stage IIIB that we would now funnel off to chemo-radiotherapy either on trial or routinely. I mean the numbers are not going to be big enough for any P values to be significant, but it would

be reassuring to know that the kind of patients we would be treating now with this regimen all have the same at least favorable trend with the new --

DR. CANETTA: We can show you the ECOG data of efficacy split by disease stage just as an example. I can tell you that consistently with what has been shown in other forums, including this one yesterday morning, the stage IIIA are doing better than the stage IV and that is expected.

I also wanted to point out the fact that we had the stage IIIA and IIIB patients who relapsed after an attempt of local or regional control. These patients were entered in the trial.

This slide depicts the survival data for the ECOG study. This is for the low dose Taxol arm. The overall hazard ratio is on the top and you have the stage IIIB in the middle and the stage IV at the bottom. Obviously, there were no stage IIIA in this particular trial. We can show the high dose next, but that again goes along with what I said.

Here you have the median, okay? This is the high dose, and again the stage IIIB seemed to fare better than the stage IV.

DR. ALBAIN: Just to follow up with Dr. Bonomi.

Phil, did you not say that some of those IIIBs would no longer be on your current generation trial though?

DR. BONOMI: Yes, that's true.

DR. SWAIN: In the EORTC study, did the increase in the global health status correlate with response at all?

DR. CANETTA: We did attempt to correlate improvement of symptoms with the quality of life analysis. We do have an analysis that compares non-responders versus responders. Can we show the ECOG data?

DR. SWAIN: But you don't have it for the EORTC data where there was clearly a benefit in global health status? No?

DR. CANETTA: Phil.

DR. BONOMI: Dr. Sela when he did his presentation at ASCO last year, he showed -- he may not have shown it at that presentation -- but he did some analyses and he showed that responders had significantly higher quality of life scores compared to non-responders.

DR. CANETTA: Okay, this is the EORTC quality of life results taken over time after 24 weeks. The numbers are small in this trial, however, there seems to be a better outcome for the responders. Again, that goes along with the fact that there is an overall improvement of physical

functioning in patients whose tumor is shrinking.

DR. SWAIN: And that was true for the global health status also?

DR. BONOMI: Do we have the global health? In Dr. Sela's analyses, it was both the TOI and the total quality of life was higher for patients who had response versus non-responders.

DR. CANETTA: This is what it shows for the global health status in the EORTC trial.

DR. SWAIN: So it actually isn't better than at 18 or 24 weeks?

DR. CANETTA: Only at the beginning. Again, the numbers are small.

DR. DUTCHER: Dr. Simon.

DR SIMON: Could you clarify the quality of life analyses? First, I have I guess two kinds of questions. One, was the same kind of analysis used on all three trials except I guess the ECOG questionnaires were different than on the other two trials?

DR. CANETTA: The instruments were different, however, the type of analysis was consistent across the three trials. Dr. Beltangady may want to comment on the fact that the approach was the same despite the fact that

questionnaires were different.

DR. BELTANGADY: Yes, I think the approach in all these three studies that was used for statistical analysis was using the nonparametric test.

DR. SIMON: Could you summarize, I'm getting a little bit lost in all of the subscores and everything, could you summarize the results for these three trials with regard to quality of life just for the overall scores for symptoms and the overall scores for functional status? Although let me say when I looked at your symptoms for the non-ECOG trials, a lot of those didn't look like lung cancer symptoms. They were sort of toxicities of treatment. I guess what I would really like to know is if we could look at overall lung cancer symptoms and overall functional status, what statistical significance do we have in each of these three trials?

DR. CANETTA: Before we address that statistically, let me point out two factors that I believe are important. What you have seen in our presentation is the evaluation of each individual subscore. So you have the complete picture. In many instances, there was no difference between the two treatments. We highlighted where a difference existed, and you will see that in yellow in our

type of things, but that is the totality of the data collected.

The type of analysis encompasses all of the data collected in each patient over time. As a clinician, before we talk about statistics, I would say that it probably is difficult to expect to see an improvement in each one of these domains that are being addressed by different type of questions, because again, this is patient self assessed. It's not the physician that tells the patient what is important, it's what the patient perceives as being important for his or her own life. People and patients might have different perspectives.

However, I think what is remarkable is the type of consistency that we observed and the fact that very rarely was any of the subscore in favor of the control arm and very often were these type of questionnaires showing an advantage for the Taxol therapy. But again, this is a clinical response and I would like also to give you the statistical one.

DR. SIMON: What I'm trying to get at, I'm not expected subscore by subscore to get consistency across trials. That's why I'm trying to get away a little bit from the subscores. The problem with looking at all the

subscores is you have so many statistical tests going on that when this one is positive here and that one is positive there you're a little bit worried, are these just sort of random results from the results of lots of scores.

Now, the fact that you have enough statistically significance in some of these studies suggests that that's probably not the case. I just wanted to confirm that to myself that if you didn't look at the overall, for example, functional status in the ECOG study, do you have statistical significance say in comparing, for example, the standard dose Taxol arm to the control arm?

I wonder whether you have the overall results for functional status and for lung cancer symptoms?

DR. BELTANGADY: Let me answer that. All scoring for both the FACT-L instrument that was used for ECOG and for the EORTC C30 instrument that was used in the other study, it was done according to the manuals that have been put together and recommended by the developers of those instruments. The total score is only defined for FACT-L instrument. To answer the question, on the FACT-L total score, we showed on the slide that Dr. Bonomi presented, there was no difference on the total score.

The lung cancer symptom total score for the low

dose. Lung cancer symptoms is an added module to the FACT-L. It's separately analyzable and analyzed according to the manual.

The EORTC, however, does not specify a total score. They recommend, in fact, analysis in each of the separate domains of physical functioning. The symptom scales or the symptom scores, symptoms actually were a separate addition for the lung cancer module. So again, there is no specific total score defined.

DR. WILLIAMS: Regarding quality of life, I wonder if you would address the whole issue of whether one should look seriously at quality of life comparisons when the control arms for the other studies besides ECOG are somewhat non-standard. Some of these changes just could be due to toxicities of a non-standard arm.

DR. CANETTA: I'm not sure I understand the question. I think my answer would be these questionnaires are the tools that were available to us and to everybody in our area. These happen to be validated, happen to have the specific modules for lung cancer, which we believed was an important factor in this type of evaluation. I think more importantly, these are patient self assessed.

Other than giving the patient the opportunity to

reach a certain type of conclusion about his or her own quality of life, I think then we would be back to normal toxicity scales that we used.

DR. WILLIAMS: Let me clarify. I think we should keep in mind that these changes could be due to toxicity of the control arm rather than the benefit of your therapy, especially when the control arm might consist of something that's maybe not standard in the U.S. perhaps.

DR. RUCKDESCHEL: I think at the time these studies were designed, one could argue that in Europe, teniposide/cis was as good as VP/cis. One could hardly say there's a big difference. High dose cisplatin as a single agent was really SWOG's(?), almost their choice for a period of time. Dave Gandara(?) had a lot of data that he thought as a single agent, and they went on to massive doses of it.

So, I think those were all legitimate comparative regimens at the time. ECOG had its own because it had its own data for doing that.

DR. CANETTA: And I would point also out to the fact that perhaps the committee might consider that counter-intuitive. I think the fact that in both of the European studies the patient perceived a neurotoxicity to favor the control arm, I think gives us some quality assurance of the

fact that there is again an assessment that is subjective because it encompasses all of the grades of toxicity, but is important to the patient. When you take that in the context of the whole picture, I think you're more reassured of the fact that the patient is an objective observer of his or her own treatment.

Within the context of the fact that it's true, both of the European studies had aggressive controls, like I pointed out before, 100 milligrams per square meter of cisplatin every three weeks is aggressive therapy. The teniposide regimen did produce important bone marrow toxicity. It's interesting to point out too the fact that the prior study of the EORTC even used a higher dosage of teniposide. What was used in this particular trial cut down the dosages of teniposide by 20 milligrams per square meter on each of the three days the teniposide was given.

DR. SIMON: Do you have any explanation for why the EORTC study did not come up with a difference in time to progression, even though it did come up with a difference in response rate and some differences in quality of life?

DR. CANETTA: I mean, one can put it down as a joke and say that it's a good European active control. The reality is again, that particular control arm was pushed to

toxicity. It was fairly aggressive treatment.

But the second reality that I hope was not missed is the fact that the curves and the median for time to progression in the EORTC study in the Taxol arm is very consistent with whatever has been observed in the other comparisons. To me, that tells me that there is something going on in the control arm more than in the Taxol arm. That's a matter of interpretation.

DR. DUTCHER: Now, looking out for our quality of life, we're going to stop at this point. We will have questions with the FDA presentation. We're going to take a lunch break at this point and we will try to get back by 1:30 if we can. If not, it will be a minute or two after that. Thank you.

[Whereupon at 12:40 p.m., the meeting recessed for lunch, to reconvene at 1:30 p.m.]

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

DR. DUTCHER: All right. We are going to go ahead and proceed with the FDA presentation. Dr. Chico

Agenda Item: FDA Presentation

DR. CHICO: Good afternoon, ladies and gentlemen. I will be presenting the FDA review of the clinical trials on the NDA supplement 20-262 for Taxol in patients with non-small cell lung cancer.

Before I proceed, I would like to acknowledge the members of the FDA review team.

This application seeks approval to market Taxol in the United States for the treatment of patients with non-small cell lung cancer who are not candidates for potentially curative surgery and/or radiotherapy. There are two proposed dosing schedules. One is a 24-hour schedule and the other is a three-hour infusion schedule in combination with a platinum compound given every three weeks.

In February of 1990, the Oncologic Drugs Advisory Committee led by Dr. Daniel Ivey(?) discussed issues concerning efficacy endpoints that would be critical in the design of clinical trials and evaluation of new drugs in the treatment of non-small cell lung cancer. A report written

by Dr. Anthony Morgo(?) at the FDA summarized the recommendations by the committee regarding the role of chemotherapy in various treatment settings and the evaluation of various clinical endpoints that may serve as surrogates for survival.

First, it was the opinion of the committee that it appears appropriate to include randomized control arms in clinical trials consisting of different drug combinations and/or best supportive care untreated arm. Since there is a trend toward combining the most active drugs, it was believed that studies should be designed to establish the contribution of each of the components, as well as that of the new agent.

Since standard chemotherapy for non-small cell lung cancer at that time had not been thoroughly established, it was also the committee's opinion that in order for a new drug to be approvable, it must prove to be superior to the control. Once an effective drug regimen is established, such a regimen could be used as a control for evaluation for a new drug, in which case the drug may be approvable if it proves to be equivalent or better than the control arm.

Tumor response rate was not considered an

appropriate surrogate for survival or quality of life, unless it significantly increased the range of 65 to 85 percent with complete response rates increased to 15 to 30 percent. Response duration and time to tumor progression were also not considered appropriate surrogate endpoints.

Other endpoints such as improvement in inter-thoracic symptoms and quality of life may be valuable in determining the overall beneficial impact for new therapy and may in fact be regarded as sufficient endpoints for approval.

In November 1994, the applicant met with the agency proposing to submit data on two ECOG studies using the 24-hour infusion schedule of Taxol. The first study is Study 129 which is a phase II trial and Study 165, the three-arm trial, that was included in the final submission.

In June of 1997, the applicant held a teleconference with the FDA proposing to submit data on three studies. Study 165, which is the three-arm, 24-hour infusion schedule study which was a phase III trial, and studies 103 and 20, which are both three-hour infusion schedule studies in combination with cisplatin and are both phase III randomized trials. These three trials would be supported by single agent phase II trials.

Study 165 is a three-arm trial by ECOG with 135 milligrams per meter square of Taxol given as a 24-hour infusion followed by 75 milligrams per meter squared of cisplatin. The second arm is the high dose Taxol arm, which used 250 milligrams per meter squared of Taxol in combination with 75 of cisplatin. Taxol is given in both arms as a 24-hour infusion. The high dose Taxol arm GCSF follows the therapy. They're both given every three weeks.

Based on phase III trial results showing high one-year survival rates, cisplatin and etoposide was selected as the reference regimen. Seventy-five milligrams per meter squared of cisplatin was given over one hour and 100 of etoposide over 45 minutes on days one, two and three.

In study 103, patients were either given Taxol with cisplatin as a three-hour infusion. The Taxol dose is 175 milligrams per meter squared in combination with 80 of cisplatin. The teniposide/cisplatin regimen was chosen by EORTC based on superior response and survival over single agent teniposide. That is the control arm for Study 103.

Patients enrolled in Study 208 received a higher dose of cisplatin, labeled as high dose cisplatin, which is 100 milligrams per meter squared every three weeks. The experimental arm is again the combination of Taxol/cisplatin

at a dose of 175 of Taxol and 80 of cisplatin.

Survival is the primary efficacy endpoint for the three studies. Time to tumor progression, response rates, quality of life and evaluation of tolerability were other endpoints.

Patients characteristics were well balanced between treatment arms in the three studies. Characteristics identified to have major tumor response and survival implications are listed in the table above, however patients were also well balanced according to other factors such as gender, by therapies, histology and extent of disease.

In all the studies, a majority of the patients have stage IV disease. However, also a majority had good performance status and minimal weight loss prior to randomization.

There were proportionately more patients who had favorable pretreatment characteristics in Study 103 compared to 208. These two studies are the three-hour infusion schedule studies of Taxol. In Study 103, 62 percent of patients had stage IV disease, while 70 percent had stage IV disease in Study 208. Also, in 103, approximately 90 percent of patients have ECOG performance status of zero to

one, while only 82 percent of patients had Karnofsky performance status of 82.

Seventy-one percent of the patients in Study 103 had weight loss less than five percent, compared to only 52 percent of patients in Study 208.

Since the primary efficacy endpoint of the three studies is survival, I will be discussing the results of the analyses in each study separately.

Survival was calculated from the day of randomization to death or to the last date a patient was known to be alive. At the time the database was closed, 541 of 599 patients, or 90 percent were dead. Analysis of survival by the applicant and the FDA both agree. Median survival was 9.3 in the Taxol/cisplatin arm, 10 months in the high dose Taxol arm and 7.4 months in the cisplatin/etoposide arm with logrank test P values not showing statistically significant differences between the Taxol-containing arms and the cisplatin/etoposide arm at an alpha level of .0125. Hazard ratios for cisplatin/etoposide versus Taxol/cisplatin is 1.18 with 95 percent confidence interval between .9 and 1.55. Between cisplatin/etoposide and high dose Taxol, the P value is .08 with a hazard ratio of 1.21 with 95 percent confidence intervals of .92 to 1.58.

Survival comparisons for the three treatment groups and hazard ratios utilized pretreatment prognostic factors used for stratification. In each of the subsets, the relative comparisons of the Taxol arms to the cisplatin/etoposide arm were consistent with the overall results.

In Study 103, 248 of the 313 patients, or 75 percent were dead during the time of analyses. The median survival for patients enrolled in the Taxol/cisplatin arm was 9.5 months and 9.9 months in the teniposide/cisplatin arm. This comparison has a P value of .80 with a hazard ratio of 1.03 and 95 percent confidence intervals of .8 to 1.33. The difference is not statistically significant.

In Study 208, 81 percent of the patients were dead at the time of analysis. The median survival of patients in the Taxol/cisplatin arm is 8.1 months compared to 8.6 months in the high dose cisplatin arm with a P value of .86 and hazard ratio of .98, 95 percent confidence intervals of .79 to 1.22.

In summary, an adjusted analyses of survival showed no statistically significant differences between the Taxol-containing combinations and control arms in Studies 165, 103 and 208.

Time to tumor progression was defined as the period from date of randomization until first documentation of tumor progression or date of death for patients without such documentation. At the time of analyses, 77 to 87 percent of the patients have been assigned a progression date. Due to multiple comparisons in Study 165, a significance level of .0125 was assigned. A statistically significant difference in time to tumor progression was seen between the cisplatin/etoposide arm and the high dose Taxol arm with a P value of .004. However, due to significant toxicity in this arm, the applicant did not choose the high dose Taxol regimen for consideration in this application.

When patients were considered progressed in the first day of secondary therapy instead of being censored, significant differences were also seen favoring Taxol/cisplatin in Study 165 and Study 208. However, the accuracy of predicting tumor progression using the first day of secondary therapy is questionable.

Time to tumor progression is significantly longer in the high dose Taxol arm in Study 165, but this regimen is not included as the proposed regimen in the labeling. Therefore, there is no statistically significant differences between Taxol arms and control for the treatment regimens

proposed by the applicant.

This table is a comparison of tumor response analyses by the applicant and the FDA. Although there were differences in opinion in a number of patients, Fisher's exact test showed significant differences in favor of the Taxol arms in all the three studies. There is overall agreement between the applicant and the FDA in the tumor response analyses. However, as was touched on yesterday, results of prior clinical trials in non-small cell lung cancer have shown that response rates do not always correlate with survival. In fact, an inverse correlation has been seen in some trials. Therefore, tumor response rate is probably not a good measure of clinical benefit in this disease.

For the pivotal trials 165, 103 and 208, there are no statistically significant differences in survival and time to tumor progression for the Taxol treatment arms being proposed and the corresponding control arms. Tumor response rates were significantly in favor of the Taxol combination arms in the three studies.

Quality of life assessment in this disease could play a major role in evaluating the merits of the particular treatment since it may directly translate to clinical

benefit. However, the quality of life analyses had some weaknesses in methodology, problems with dropouts and missing data and subscale profiles that overlapped with toxicity.

For Study 165, the sponsor compared quality of life across treatment arms by examining median change at each time point to baseline and found no statistical differences in five of the six subscales. However, using the significance level of .0125 for multiple comparisons, the FDA reviewer found no statistically significant difference in lung cancer symptoms which was the subscale reported by the applicant as positive in favor of the Taxol arms. Longitudinal analyses of three subscales by the FDA showed no difference in lung cancer specific symptoms, functional well-being and physical functioning. Therefore, in Study 165, no statistically significant differences were seen between treatment arms.

In Study 103, the sponsor reported significant differences in six subscales favoring Taxol/cisplatin. However, in this study, missing data is a major problem. Data was collected at baseline from 100 patients, 50 in each arm, which was decreased to a total of 45 patients in both arms by week 18 of testing. Such a number may not

accurately reflect quality of life for the whole population. Longitudinal analyses by the FDA, however, showed a statistically significant difference favoring the Taxol/cisplatin arm with respect to physical functioning.

In Study 208, quality of life was collected in more patients and the follow-up was better. The FDA agrees with the longitudinal analysis done by the applicant which showed improvement in physical functioning, improvement in symptom profile such as nausea and vomiting, loss of appetite and constipation in favor of Taxol/cisplatin. However, for symptom profiles such as hair loss and peripheral neuropathy, the quality of life tests were in favor of the high dose cisplatin arm.

Since chemotherapy in this disease is not curative, the effect of treatment and efficacy should be weighed against the potential for toxicity. The FDA safety analysis includes deaths within 30 days of last treatment, dose reductions, dose delays, hematologic and non-hematologic toxicity.

Deaths were caused by treatment related toxicity, disease progression and its complications and other medical conditions. In Study 165, 60 patients have died within 30 days of last treatment dose. Toxicity from treatment was

related to five percent and six percent of the Taxol arms versus two percent of patients in the cisplatin/etoposide arm. However, using Fisher's test, there is no statistically significant differences between death due to toxicity between the Taxol arms and the cisplatin/etoposide arm.

In Study 103, more patients died within 30 days of treatment in the teniposide/cisplatin arm, 11 percent versus six percent. However, the proportion of patients dying from drug related toxicity was similar in both arms.

In Study 208, more patients died from the high dose cisplatin arm compared to the Taxol/cisplatin arm, but the deaths were mostly due to progressive disease.

Therefore, there is no significant findings favoring either experimental or control arms regarding 30 day deaths.

The NDA submission did not include an analysis of dose reductions for Study 165. The figures were obtained from queries created from the electronic database. Data regarding dose reduction for Studies 103 and 208 in this table were obtained from the sponsor's analysis.

With the 24-hour infusion of Taxol in Study 165, the dose was reduced to 29 percent of the courses in the

Taxol/cisplatin arm and 23 percent of the courses in the high dose Taxol arm. Note however, that the dose of etoposide was decreased in 20 percent of the courses in the control arm. In contrast, the three-hour infusion schedules of Taxol, only three percent of the courses were decreased in both Taxol/cisplatin arms in Studies 103 and 208.

In all the studies, there were less dose delays in the Taxol arms. In Study 165, 30 percent of the cisplatin/etoposide courses were delayed compared to only 14 and 13 percent in the Taxol arms. Treatment delays were mostly due to hematologic toxicity in both experimental and control arms in all the studies. This may mean that although the hematologic toxicities were more profound in the Taxol combinations and resulted in more dose reductions, the cycle length of three weeks allowed sufficient time for recovery of blood counts.

The following table summarizes the incidence of severe hematologic toxicity. Seventy-four percent of the patients in the Taxol/cisplatin arm had significantly more grade IV neutropenia compared to the control arm. However, the incidence of fever, neutropenia in Study 165 was not available nor can be queried from the electronic database. In Study 103, teniposide/cisplatin caused significantly more

hematologic toxicities, namely grade IV neutropenia, more patients with fever and neutropenia, thrombocytopenia and anemia. In contrast, in Study 208, there were more patients who had severe neutropenia and significantly more patients with fever and neutropenia in the Taxol/cisplatin arm compared to the high dose cisplatin arm.

In Study 165, significantly more patients experienced all grades of arthralgia and myalgia in both Taxol arms. However, in the high dose Taxol arm alone, there were more patients who had more severe hypersensitivity reactions, more neurosensory events and all grades of arthralgia and myalgia, more severe arthralgia and myalgia.

As expected, patients in the Taxol/cisplatin arm of Study 103 experienced more severe neurosensory events, arthralgia and myalgia. In Study 208, more patients in the Taxol/cisplatin arm had more severe hypersensitivity reactions, alopecia and all grades of arthralgia and myalgia.

Again, in continuation of non-hematologic toxicities for Study 165, more patients enrolled in the Taxol/cisplatin arm had all grades of diarrhea, and more patients in the high dose Taxol arm also had all grades of

diarrhea, more mucositis and more patients were off treatment due to toxicity in both arms compared to the control arms.

In Study 208, more patients enrolled in the Taxol/cisplatin had all grades of diarrhea, while those patients who were enrolled in the high dose cisplatin arm had more severe ototoxicity compared to the Taxol/cisplatin arm. Data from the supplemental application contains important information for more than 1,300 patients from three randomized phase III studies. Patients enrolled in the three pivotal trials were carefully selected and balanced according to pretreatment characteristics that are known to have major impact on prognosis. The volume of experience gathered from these trials provides a large amount of evidence regarding the effect of Taxol in combination with cisplatin for the treatment of non-small cell lung cancer as compared to three treatment regimens, two with cisplatin in combination with pedophylotoxins(?), etoposide and teniposide which were expected to be minimally cross reactive and having significant activity in disease and one in comparison to single agent cisplatin given at higher dose. These studies also provide a large amount of efficacy and safety data using the different doses and

infusion schedules of Taxol in non-small cell lung cancer.

In summary, Study 165 provided vital information on the use of 24-hour infusion schedule of Taxol in 599 patients through a randomized study comparing Taxol in combination with cisplatin to a commonly used regimen known to have good activity and safety profile in this disease. The study has shown that patients treated with 175 milligrams per meter squared or 200 milligrams per meter squared of Taxol as a 24-hour infusion have the advantage of higher tumor response rates compared to cisplatin/etoposide. A significant improvement in time to tumor progression was seen in the high dose Taxol arm, but the regimen was not proposed for consideration.

On the other hand, the Taxol combination arms did not show superior survival nor a clear advantage in quality of life. The treatment was also less tolerated with more severe neutropenia, arthralgia, myalgia and diarrhea.

Study 103 and 208 both provided information on the use of the three-hour infusion schedule of Taxol. Study 103 enrolled 332 patients in a randomized trial comparing Taxol in combination with cisplatin to a regimen more commonly used in Europe but was chosen on the basis of providing a response and survival advantage in studies of single agent

teniposide. Superior response rates, better tolerance and an improvement in physical functioning was experienced by patients treated with Taxol/cisplatin. However, no survival advantage was shown and the reliability of the quality of life test results is in question.

Study 208 compared Taxol in combination with cisplatin to a higher dose of cisplatin alone. The use of unequal doses of cisplatin makes the determination of Taxol's contribution to the combination difficult. Like Studies 165 and 103, the response rates were higher, but a survival advantage was not shown by the Taxol combination. Quality of life in terms of physical functioning and improvement of symptom profiles such as nausea, vomiting, loss of appetite and constipation were in favor of the Taxol/cisplatin arm. However, the quality of life symptom profiles favored the control arm with respect to alopecia and neurosensory events.

Summarizing the overall efficacy results from the three trials, there were no statistically significant differences in survival and time to tumor progression between the Taxol treatment arms being proposed and the corresponding control arms. Tumor response rates favored the Taxol combination arms in all three studies.

Longitudinal analyses of quality of life by the FDA showed no difference between the six subscales in Study 165 and statistically significant differences favoring the Taxol/cisplatin arm with respect to physical functioning in Studies 103 and 208. The symptom scales also favored Taxol/cisplatin with respect to nausea and vomiting, loss of appetite and constipation, but favored cisplatin with respect to alopecia and peripheral neuropathy in Study 208. A major problem with the quality of life analysis specifically for Study 103 was missing data.

In Study 165, patients experienced more severe non-hematologic toxicities in the Taxol arms. There were also more severe neutropenia in the Taxol/cisplatin arm but there was no data regarding fever and neutropenia.

The teniposide/cisplatin arm in Study 103 resulted in more hematologic toxicity including fever and neutropenia. The Taxol/cisplatin arm resulted in more severe neurosensory events, arthralgia and myalgia.

In Study 208, in addition to grade IV neutropenia, fever and neutropenia, more patients experienced diarrhea, hypersensitivity reactions, alopecia, arthralgia and myalgia in the Taxol/cisplatin arm while more patients experienced more severe ototoxicity in the cisplatin arm.

For a drug to be approved for this indication, it is important that a favorable ratio of benefit to risk be established. Efficacy could have been demonstrated by a significant increment in survival and/or by convincing superiority in response rates, time to progression and a believable increment in quality of life. Aside from a clear demonstration of an advantage in efficacy, the treatment being considered should also demonstrate a tolerable toxicity profile.

In the controlled study submitted to the NDA, Taxol given as a 24-hour or three-hour infusion in combination with cisplatin did not provide evidence of an improvement in survival nor time to tumor progression for the regimens being proposed in the labeling. The treatment, however, showed high response rates with an improvement in the number of quality of life subscales. There were no significant differences in quality of life for patients treated in Study 165. Patients enrolled in the Taxol/cisplatin arm in Study 103 showed better physical functioning but the quality of life test had a large amount of missing data. Patients enrolled in the Taxol/cisplatin arm in Study 208 had better physical functioning and symptom profiles such as nausea and vomiting, loss of appetite,

constipation, but worse profiles with respect to alopecia and neuropathy.

Finally, patients enrolled in the Taxol/cisplatin arm of Study 165 had significantly more grade IV neutropenia, diarrhea, arthralgia and myalgia of all grades compared to cisplatin/etoposide. For Study 208, patients enrolled in the Taxol/cisplatin arm experienced significantly more severe neutropenia, fever/neutropenia and non-hematologic toxicities. Patients enrolled in the Taxol arm in Study 103 had significantly more severe neurosensory events, arthralgia and myalgia but less severe hematologic toxicities.

With the above issues at hand, the recommendation for this NDA supplement should depend primarily on whether one considers the results of the studies adequate to support the considerations for approval in this indication. One must then consider, in view of the documented toxicity of Taxol in this setting, whether the overall therapeutic ratio of Taxol in combination with cisplatin was acceptable in these trials in patients with non-small cell lung cancer who are not eligible for potentially curative surgery or radiotherapy. Thank you.

I will be happy to take any questions.

We would like to just have a few words from our biostatistician to just explain what we did with the quality of life analysis because there might be some question about it.

DR. SMITH: David Smith, statistical reviewer, FDA. I would like to explain our rationale for forming our own quality of life analysis as opposed to accepting the sponsor's. There are two main reasons that we performed our own quality of life analysis, as Dr. Chico mentioned.

The first reason is that the sponsor's analysis, even though it's a non-parametric analysis, it depends on the assumption that dropout of the patients is not confounded with the treatment arm, therefore you don't have differential rates of dropout. The sponsor assumed that there is no difference in dropout between the Taxol arm and the control arm.

Our exploratory analysis determined that there was a difference, that dropout is confounded with the treatment arm. So we had to, the conclusions were difficult to make, the sponsor's conclusions are difficult to interpret in the presence of that differential dropout, so we tried to tailor our analysis to reflect that confounding problem.

The reason that we performed our own analysis is

the issue that I believe Dr. Simon mentioned earlier. When you have a large number of quality of life subscales, or any endpoints in general, on the average about five percent of those are going to be significant just due to chance alone. So we tried to narrow the scope of our quality of life analysis so we don't have that multiplicity problem. Thank you.

Agenda Item: Questions from the Committee

DR. DUTCHER: Dr. Albain.

DR. ALBAIN: I had a few left over questions for the sponsors. May I ask those that were hanging at the break?

DR. DUTCHER: Why don't we deal with the FDA first and then we can see if there's something he can answer for you, then we can ask them to supplement the information.

DR. ALBAIN: Okay. I would like to know when the survival analysis will be available for the two trials, best supportive care versus Taxol and carbo/taxol versus cis/etoposide, approximately when do you anticipate that first analysis available?

DR. DUTCHER: I think we need to deal with these data first and then we can go -- you can answer it, sure, answer the question.

DR. ALBAIN: I just didn't know procedurally because I had my hand up before.

DR. DUTCHER: I know, but we ran out of time. We have to deal with the data that we're dealing with for the application right now. If we can get an answer, I suggest we get an answer since you asked the question, but let's --

DR. CANETTA: For the best supportive care, we plan an analysis within the next six months. We are updating these results and actually we plan to be there earlier than that.

For the second trial, which is a trial that was performed by Al(?), you asked a subsidiary. Again, the only thing that I know is that a number of events had not yet occurred that was projected to occur during the first quarter of 1998. So it should have occurred by now.

DR. ALBAIN: Could you make a comment about the pooled survival analysis that was in your written materials that was not on your slides. In particular, I'm interested in the one and two year survivals and the confidence intervals using the .0125 alpha level.

DR. CHICO: Regarding the pooling of the survival analysis, I believe there are two issues here. One is a strictly statistical issue, which is the alpha level that

they used here is .0125. So really, if you look at what they've established, you can say that really there's no significant differences. But on the other hand, if you look at the clinical impact of pooling the survival data, it's something that's not very clear because these are two different regimens. One is a higher dose of Taxol and one is a much lower dose. So I don't know how that will impact clinically if you pool the two survival data. Despite the fact that there is no statistically significant differences between the two Taxol arms if you compare them.

DR. ALBAIN: With those disclaimers, what are the one and two year survivals for the pooled arm?

DR. CHICO: I don't have it offhand. For the survival analyses, we agreed with the analysis that was done by the applicant, except for the pooling of the survival data.

DR. ALBAIN: Are those data not available anywhere, the percent one and two year survivals?

DR. WILLIAMS: Are you wanting the confidence intervals of the difference between the two arms?

DR. ALBAIN: No, just the percent, just the simple percent.

DR. WILLIAMS: Perhaps the sponsor can come up

with it easier than we can.

DR. BONOMI: For the pooled arms, it's 39 percent for one year and 14 percent for two years.

DR. ALBAIN: Phil, and in the cis/etoposide?

DR. BONOMI: It's 32 percent for one year and 11 for the --

DR. ALBAIN: Thank you.

DR. SIMON: I was going to ask a question, but maybe this would be a point to give my view of this pooling versus non-pooling issue on the survival curves. I think, well first of all, in terms of multiple comparison corrections, statisticians are -- there's a lot of controversy on the role of multiple comparison corrections, whether you should divide your .05 by the number of comparisons you're making or not. There's a lot of statisticians who feel, for example, this study here, the ECOG study you had two Taxol arms, one control arms.

Some statisticians would take the point of view if these were two different studies, nobody would say well you should divide your .05 by two, even though they are two studies of Taxol/platinum. So why should you do -- because they decided to do it as one study, which is strengthening the information, why should you penalize the analysis of

that study by multiple comparison corrections. Other statisticians feel differently about it. So there's really no right and wrong point of view on it.

Similarly on pooling or not, I think you can take two perspectives. You can say well, these were two different regimens, one could have been effective on survival, the other not, so why should you pool? Other people might say, well they're both Taxol/platinum arms and somehow the information should reinforce each other rather than be viewed completely separately. So again, I don't think there's a black and white point of view.

My own viewpoint is that for the ECOG study viewed in isolation, I believe that there probably is a survival effect for those two arms, just because it's so concordant with what you're seeing in terms of time to progression and response rate. But I guess I would -- I don't know what the overall medical significance of that would be because we have the benefit of two other large randomized trials before us. There really was not any evidence of a survival difference in those two trials. But for the ECOG trial by itself, I would tend to come down believing that there's probably some small survival benefit to cisplatin and Taxol.

I guess the presentation that was given by the FDA

it seems to me has been based on a very rigid statistical multiple comparison point of view, in which lots of statistically significant differences have disappeared because of multiple comparison corrections. For example, even time to progression in the ECOG study for the 135 milligram dose I think had a P value of .03 or .02 or something like that, the conclusion was that there's no statistically significant difference in time to progression. Well, I think it's a gross over simplification to say we apply a multiple comparison correction, it doesn't meet our cutoff and therefore there's no statistically significant differences as if that means that they're equivalent. I just don't think that that's the right interpretation.

But the question I was going to ask was could you say more about your analysis of quality of life, because there are also statistically significant differences that disappeared. I want to find out whether they disappeared because of a relatively rigid imposition of multiple comparison adjustments or for some other reason because it was a different kind of analysis.

DR. SMITH: Suppose I have the perspective of the far end of the spectrum in which -- since I don't have the clinical, as a statistician, I don't have the clinical

background that whenever I make multiple comparisons I have to be very, my personal point of view is to be very rigid about the P value cutoffs and not get sloppy about what's significant and what's not. The rule is, as we're trained as statisticians, if you split up your alpha for a certain cutoff and it fails to show significance, then there's no significance. But it's good to know that there are experts who aren't as rigid as I am. It's comforting I guess I should say.

For the quality of life analysis question that you asked, there are two separate analyses, one from the sponsor and one from ours. Some of the differences that disappeared there, as you say, could be just from the differences in analysis. Since conclusions about quality of life are difficult to make just because patients don't comply as well as you would like, we tried to do an analysis that was robust against those problems. So perhaps by trading robustness against flexibility, we determined that our analysis became -- well, that's the reason why some of those quality of life endpoints disappeared. Is that clear?

DR. KOUTOUKOS: Let me make some comments too about this. My name is Tony Koutoukos. I'm a statistical reviewer too. I would like to I guess for the Study 165,

even the sponsor used the [word lost] method to find the statistically significant result for the lung cancer symptom subscale. We did, I guess, as Dr. Smith mentioned before, to see how the missing data came from in the study. So did we have missing data at random or not? We found that the data were not missing at random. We did our own longitudinal analysis similar to what Dr. Takeuchi did yesterday and we did find actually again for the lung cancer symptom subscale that there was a statistically -- well, I guess the P value was about what the sponsor reported using their analysis.

I guess the appearance of a statistical significance is because of the multiple comparisons, but the original protocol specified alpha level was .0125. Now, for the rest of the studies, I think we found very similar results to what the sponsor did. Specifically, for Study 103, there was only one I think P value that was three percent. This was on physical functioning. So you can say that this is statistically significant based on the factors but again, there they were at least six subscales, so you still have to proceed with caution, is this real or not.

I think we agree for Study 208, we agree with most of what the sponsor found.

DR. TEMPLE: I have some questions about the multiplicity correction too, but I guess I'm astonished to see the question almost dismissed by Rich. I think it's often hard to say what the correction should be, but if someone does 10 studies of something and one of them manages to skip the considerable(?) -- I'm entitled to wonder whether that was a chance occurrence and how exactly the correction that I grant to you is debatable and people engage in controversy, but there is some -- you can do this with simulations or other ways -- there is some penalty, some increased likelihood of chance giving a result.

But having said that, I wonder where the sponsor got his alpha of .125 which seems by any standard an extreme correction if you're only making two comparisons, especially when they're both compared with the same control group. We've been telling people in that situation that .35 ought to be enough because they're not independent comparisons and there's really only two of them.

In addition, I just want to throw this out really to you and to Rich, if you win on both of your groups that seems to have something to do with something. After all, the two groups that were compared with the control, both for time to progression now, both were nominally significant

.05. That seems different from one of them being significant at .05 and the other having a .5 or one or something like that. Of course, our corrections never clearly take those matters into account. They don't account for leaners which seems to me we usually over correct for multiplicity, not that I don't think you should pay attention to it, but I do think we tend to over correct and tend to maybe dismiss things that are closer than they seem if you just stick with the original correction.

DR. SIMON: First of all, on the quality of life I wasn't saying there shouldn't be a correction. What I was objecting to was just a statement that there were no statistically significant this and there were no statistically significant that without any details of what kind of corrections were made or anything.

In terms of, I think there are, I'm accurate in what I say, there are some people who believe in terms of for example the time to progression, if you have two experimental regimens and a control regimen, there are many statisticians who would probably take the position that you shouldn't do a multiple comparison correction. There are lots of ways of doing multiple comparison corrections. For example, the way I tend to do it is not the way people are

doing it here. I will do an overall test of homogeneity of say the three groups with regard to the endpoint of say time to progression. If I find that there's evidence at the .05 level that the outcomes of the three groups are significantly heterogeneous, then I will say okay, now I've dismissed that homogeneity hypothesis and I will then go in in a situation like this and do the two comparisons to the control group at a nominal .05 for each of them. That's a different way of trying to control.

DR. TEMPLE: I was mostly interested in the time to progression. That testing at .125 and doing nothing else seems very conservative let's say. It seems closer to being -- I guess in a lot of situations, not particularly here, but in numerous discussions we've had on three group studies in the cardiorenal, we've been telling people if you're comparing it to the same control and if there's only two groups and you're not planning to throw the groups together, something like .3, .35 ought to be your critical value. Well, that's a lot closer to .05. You might feel better about it if that was your idea, but the .0125 is quite an extreme I would have thought, even if you do believe there's correction necessary.

DR. KOUTOUKOS: I think the sponsor could correct

me about this, when the protocol was designed, the main comparison of the study was the high dose Taxol with the low dose. So they were using .025 for this comparison. So there were two more comparisons now, the low dose versus the control and the high dose versus the control. So this [word lost] the .025 level in half for .0125. Am I right? That's I think what the protocol said.

DR. TEMPLE: So they weren't comparing it with platinum/etoposide at all?

DR. KOUTOUKOS: Well, this was -- I guess --

DR. BELTANGADY: I will try to answer that. The protocol as it was developed by ECOG specified that there would be three comparisons done, high dose Taxol to low dose Taxol and then each of the Taxol arms to etoposide/cisplatin arm. The P value was in the protocol divided as Tony just mentioned in three portions. I believe that is what is being used as the alpha level in the review that was done.

When we had a discussion with the agency some time late December of 1994, I think we had a discussion about something along the same lines that you were saying that this thing is too rigid and propose a criteria to do the Taxol comparison, one each with the etoposide/cisplatin. That's what we used as the preplanned analysis criteria to

demonstrate that the two primary comparisons which are Taxol each arm to the control.

So our position is that the .0125, even though that is what is written in the protocol when it was designed by ECOG, is somewhat different from our position.

DR. TEMPLE: So what did you propose when you came to us with that suggestion as a critical value?

DR. BELTANGADY: We took [word lost] .025.

DR. TEMPLE: Okay. I've always thought that was too extreme if it's with the same comparative group, a little over done because they're not completely --

DR. BELTANGADY: It was a bit more liberal than the .0125, but again your point is well taken.

DR. KOUTOUKOS: I guess one more question that I have. Could I ask Dr. Simon about his comment on doing a global test on the three arms. How would you do this on the time to event endpoint? Because usually if you have means, you can do --

DR. SIMON: No, you could do a logrank test with more than two treatment groups.

DR. JOHNSON: I won't make any comments about the statistics. I heard bodies falling out there.

Actually I'm going to ask some questions of the

FDA that do have to do with statistics, because I don't understand statistics very well. The thing that was striking to me, as Chairman of the Lung Committee for ECOG, and probably more so than anyone in this room other than Dr. Bonomi having looked at these data from every angle that I know to look at it, I have to tell you I was surprised to see the alleged differences in toxicity. I'm only now looking at Study 165 that the FDA found. I heard I will characterize them as criticisms about the multiple number of analyses, the quality of life issues and how if you look at 10 different things, you're bound to find something that's statistically significantly different. That I understand. That's about all I understand about statistics, but I understand that.

It seems to me that in the toxicity analysis that has been done, that's essentially what the FDA did here. For example, if you look at hematologic toxicity, you look at grade IV toxicity, which okay that's very important, but typically clinically we think about grade III/IV toxicity and tend to lump those things together. You saw a modest difference there that's not probably clinically relevant.

In some of the other non-hematologic toxicities, when you looked at the grade III/IV, there weren't

differences, but when you look at the I through IV, there were differences, which you now ascribe to being "different". I don't know that many of us really think of grade I/II toxicities as being something that we find clinically relevant. It's often a laboratory value or something of that nature, which doesn't translate into a clinically meaningful difference in toxicity that most patients find, or for that matter physicians find very important.

A good example is mucositis that you've listed here as being absolutely no different when you look at grade III/IV, but then you characterize a grade I through IV where you get a P .005 showing that the high dose treatment is worse. I'm just wondering how many analyses were done before we came up with the ones that you have in the color boxes? That's really what I want to know.

DR. CHICO: Let me just correct you by saying that the toxicity is not my analysis. This was derived totally from the data that was supplied to us by the sponsor. So that means that I didn't do anything --

[Laughter.]

DR. JOHNSON: Then you didn't do your job. No, I'm very serious about this, because if all you did was

recapitulate the sponsor's data to us and their analysis, then we didn't need your presentation.

DR. WILLIAMS: I can guarantee you he didn't do that, since I secondarily reviewed it and I don't think we ever do that Dr. Johnson.

DR. JOHNSON: Then let's talk about was an analysis done in the manner in which I asked. I think that's a very important question because in my view, there is no toxicity difference between these three regimens based on my analysis of this. I assure you that I have looked at these data very, very carefully, so I want to know why you're showing these kinds of differences. We didn't see this yesterday in a similar presentation.

DR. CHICO: This was just actually from the sponsor. I mean this was the part of the data that was submitted in the NDA. I made notes of which severe toxicities were more evident in the treatment arms and didn't make my own analysis. It's --

DR. JOHNSON: I guess I'm wondering then why you didn't show this in other areas, why you didn't show the whole spectrum of toxicities that we normally look at, that's what I'm asking.

DR. CHICO: Because in the other toxicities there

were no differences. I only showed toxicities where there were differences between the treatment arms.

DR. SCHILSKY: I think a lot of my questions have been brought out already, but I want to discuss a little bit further the time to progression data in the 165 study. I'm not going to discuss statistics either, but I am confused about just the differences in the absolute numbers. In the sponsor's presentation for the Taxol low dose cisplatin arm, they had a median time to progression of 3.6 months. In your analysis, the median time to progression is 4.3 months. Could you just describe what the difference is that led to that -- how was the analysis done differently?

DR. CHICO: I noticed the same differences too, as the sponsor was doing their presentation. Looking back, if you look at the protocols and how time to tumor progression was defined, the events that were counted were those patients who had documented progression or those who died before documentation of such. However, the data when the sponsor was discussing their data on each of the studies, I believe they presented the results of the secondary analysis where secondary therapy was counted as an event and not censored. I believe they also had one slide where they presented all the time to progression dates in the three

studies which were more consistent with the primary analysis.

DR. SCHILSKY: Could we also just discuss a little bit further the issue of when there's a change in therapy whether that should be counted as progression or whether that patient should be censored, because usually when there's a change in therapy, there's a reason for that. The reason is either in most cases that the tumor is growing so therapy is not working or the patient is having some unacceptable toxicity that it's felt by the doctor or the patient that they can't continue with that particular treatment.

It would seem to me that in either of those cases, it's reasonable to consider that the patient has progressed in the sense that they're no longer able to tolerate that particular therapy. So are you concerned about counting that as progression versus censoring the patient or --

DR. CHICO: Actually, I don't have a definite take on that because it could either go both directions. The secondary therapy may antedate or be way beyond the actual date of progression. So I'm not saying that first or secondary therapy should either be counted as an event or censored. It's a problem.

DR. WILLIAMS: You don't really think toxicity should be counted as progression though? That means you have the most toxic drug, you have the one --

DR. SCHILSKY: Right, but I guess what I'm saying is that when there's a change in therapy that there usually are clinically two reasons for changing the therapy. One is that the disease has grown and the other is that the patient can't tolerate the treatment. Maybe I misspoke.

DR. DUTCHER: The third is go to transplant.

DR. SCHILSKY: Okay, well so I was just puzzled by the fact that you actually had a longer median time to progression than what the sponsor presented and yet you didn't characterize that as being a significant difference, whereas the sponsor did. I guess that gets back to the statistics again and how we're dividing the P value.

I also wanted to just talk for a moment again about the pooling of the survival data in that particular study because clinically it seems to me that if the two Taxol-containing arms are not different, and this is a point because it may be that the study isn't really powered to determine whether they're different or not and that's a potential confounder. But if they're not different, then one could imagine that there's no dose response relationship

for Taxol on this schedule in this disease. Maybe there's a threshold effect and that if you get to 135 per meter squared on a 24-hour schedule you get an effect and increasing the dose beyond that doesn't give you any further effect.

So, it would seem to me that if all those hypotheses are true, that it would be perfectly reasonable to pool the survival data.

DR. CHICO: Again, when Dr. Albain asked me about it, I must say that I didn't have any definite feelings for or against pooling. I'm just stating that it's potentially problematic if you try to interpret it in a clinical sense, because these are two different treatment regimens.

DR. SCHILSKY: I think it's actually pretty easy to interpret it in a clinical sense.

DR. WILLIAMS: Dr. Schilsky, if you consider that one of these regimens is not tolerable, is basically a drug treatment you would recommend to nobody, I can see why someone might have a problem with accepting that data to support the more tolerable regimen. You're saying there's an unacceptably regimen, yet, I'm going to accept the efficacy data from it. If that is the position, then I can see why there would be trouble pooling.

DR. SCHILSKY: I guess I'm not convinced that that particular regimen is unacceptably tolerable. It seems to me that one of the reasons that the decision was made not to pursue that regimen was because the additional expense and complexity of adding an hematopoietic growth factor to the therapy, not necessarily because if you do so that the therapy is unacceptable medically. It may be economically unacceptable.

DR. DUTCHER: Dr. Albain.

DR. ALBAIN: And actually, one could argue it the other way too. In fact, if we had those toxic deaths in the high dose arm, if anything you might be weakening the lower dose arm and strengthening your sense of being comfortable with there being a true survival benefit here.

DR. TEMPLE: One could believe that the high dose regimen strengthens the evidence on the low dose regimen, because for example it shows that there might be some correspondence with response rate and outcome, even without believing you should just go on them together. I think that's what Rich was saying before. That seems also true. Responses aren't really discontinuous usually, you can sort of think that they bear on each other.

DR. DUTCHER: Could I ask our consultants to

comment about the one-year survival in view of the data that was used to -- the rationale that was used to bring Taxol into the combination was a one year survival between 35 and 40 percent and the one year survival for the two arms of each of these studies, either arm appears to be in that range.

DR. ALBAIN: That's actually why I was pushing ahead with those two year figures. I think one way to bring all of this together is to think that -- to look at globally where were we with the second generation regimens, which really I think the cisplatin alone, cisplatin/etoposide, high dose cisplatin may all fall in the same category. What we could expect with those is almost never seeing a two-year survival, perhaps up to five percent.

[Fire alarm and brief recess.]

DR. DUTCHER: Dr. Albain, you want to continue?

DR. ALBAIN: Right. Just backing up a bit, how to put this in perspective in terms of the similarity of the percent one year survivals that are being noted across these various arms in the context of the lung cancer literature. I think looking at the two-year percents that we just heard here indicate that cisplatin plus Taxol are in the very same ball park as cisplatin plus gemcitabine and cisplatin plus

capecitabine(?). These are two very large randomized trials, as everyone knows who has been here since yesterday morning, show a survival benefit compared with cisplatin alone.

What I was saying at the fire alarm was that cisplatin plus etoposide, carboplatin alone, they're probably all pretty much similar in terms of what the second generation trial showed. That is three, four, five percent, two-year survival, 11, 15, maybe up to 20 percent one-year survival, but nothing like this. I think if you look at these so-called third generation doublets, they're all falling out very similarly in terms of what we're seeing at two years.

That one-year percent is going to be a little more impacted by how many IIIA and IIIB patients are in the particular trial. The SWOG trial had very few, where some of these that we've heard had a significant percentage on up to 20 percent. So I think that might shift what you're seeing as the one-year percent.

DR. SWAIN: I just had a quick question. I noticed in the 165 study that about half the patients on the high dose Taxol arm come off because of toxicity. Was that because more of those patients had more treatment for a

longer period of time? I know they were not limited to six cycles, whereas they may have been in the other studies.

DR. CHICO: Yes, more patients in the high dose Taxol arm in 165 came off because of toxicity compared to the other arms. The median number of courses received by patients in this arm was five cycles compared to six in both cisplatin and the low dose Taxol. So I really couldn't say much whether they were treated longer or not.

DR. SWAIN: Does the sponsor have any comment on that?

DR. BONOMI: One of the things I had asked was to see if we could find out how many patients had six cycles, seven, eight. All I can tell you is from my review of the data, the people when they went off, generally especially in the high dose regimen, they would get out to the sixth cycle and then neurotoxicity would start to be a problem. We saw in the data that there was significantly more neurotoxicity. So I think going off treatment for toxicity, my gut feeling, although I don't have the actual data to back it, that that is -- I guess if we go to seven and eight courses, it's fairly similar, maybe a little bit lower in the platinum 16(?), 27 versus 21 versus 17, 21 versus 11 and 11, so fairly similar.

DR. DUTCHER: Thank you. Dr. Schilsky.

DR. SCHILSKY: Phil, can I just ask you one other question? I know obviously there are ongoing and planned ECOG studies in lung cancer. I suppose I could ask David this, but I will ask you this. Is this the regimen that is now being considered the standard in ongoing or planned ECOG trials, 135 over 24 hours?

DR. BONOMI: It's the reference regimen for the current trial which is a four arm regimen, Taxol at 135 over 24 hours and Taxol as a three-hour infusion, 225 plus carbo, gemcitabine/platinum, Taxol(?)/platinum. So four arms and it's been our policy in ECOG always to retain what we think was the best arm from the previous study and carry it forward.

DR. SCHILSKY: Do you have any sense from your knowledge of the lung cancer literature about whether there's any relationship between the Taxol schedule used in combination with platinum and outcome. In other words, is the 24-hour regimen, how does that compare to a three-hour schedule?

DR. BONOMI: Some of the things that suggest that they are fairly comparable in terms of response rate, but that's an important question for an ECOG trial, even though

it's combined with carbo rather than cisplatin at three hours, 225 versus 135.

Maybe I will make comment about the dose to pick up on what was said earlier. I think 250 milligrams per square meter, we were trying to see if dose would be better, actually in virtually all the lung cancer studies where dose has been tested, it never turns out positive in non-small cell. In this trial, we did not present the data, but we actually collected serum for getting steady state Taxol levels. We collected that in half of the Taxol patients, about 100 with the high dose and 100 with the low dose. We were able to get threefold in the serum steady state Taxol level but that did not translate into any improvement in survival. It translated into more neurotoxicity. So we're pretty convinced efficacy wise they're similar. Toxicity-wise, the higher dose is worse.

If I could maybe make one other comment, in the three hour thing, 175, 225, that's one of the questions that isn't answered yet.

DR. DUTCHER: Thank you very much, thanks a lot. Well, we should proceed then with discussion of the questions. Are there any other comments or discussion issues that the committee wants to bring forward?

DR. ALBAIN: Could I just ask a procedural question? In terms of the wording that's here versus the wording that was sort of agreed to in the discussion in terms of clarifying this as cisplatin, clarifying this as the non-potentially curable stage III patients. How does one approach the vote with the wording on paper a bit different?

DR. DUTCHER: As we get to each question, we can suggest modifications.

Agenda Item: Committee Discussion and Vote

DR. DUTCHER: All right. Three randomized, prospective, multicenter clinical trials in more than 1,300 patients compared Taxol in combination with cisplatin to cisplatin/etoposide in Study 165, cisplatin/teniposide in Study 103, and a higher dose of cisplatin alone in Study 208. You can all review the table for a moment, if you don't have it memorized by now.

The Taxol combination arms in the three trials showed superior response rates compared to the control arms. We have different interpretations of the significance of the time to tumor progression. In this analysis, there was no statistically significant difference in overall survival between the treatment arms in any of the studies.

The Taxol combination arms were more toxic than cisplatin/etoposide in 165 compared to a higher dose of cisplatin in 208. In Study 103, the teniposide/cisplatin had significantly more hematologic toxicities while the Taxol/cisplatin arm had more arthralgia/myalgia and neurosensory events. You have the table of the safety results.

Does anybody want to make any comments about those before we go on to the questions?

Okay. The indication sought by the applicant is for the treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy. The applicant's recommendation is that Taxol be administered over three hours at a dose of 175 milligrams per meter squared followed by a platinum compound given every three weeks. Should a 24-hour infusion of Taxol be selected for combination with a platinum compound, the recommended dose of Taxol should be 135 milligrams per meter squared every three weeks.

Dr. Schilsky.

DR. SCHILSKY: Just I guess a procedural question which is whether you would be willing to have us vote on questions two and four before questions one and three?

DR. DUTCHER: We can do that. Okay, do you want to start with two? Does anybody want to change that paragraph? DR. ALBAIN: Yes.

DR. DUTCHER: Yes, you want to put in cisplatin instead of a platinum compound.

DR. ALBAIN: Yes.

DR. DUTCHER: How do other people on the committee feel about that?

DR. TEMPLE: The paragraph is what's being requested. The opening paragraph.

DR. WILLIAMS: The paragraphs within each number have just cisplatin anyway. This is just what the company is asking.

DR. DUTCHER: So we will go to the questions

DR. WILLIAMS: The paragraph reflects what was requested.

DR. ALBAIN: What about the type of patient for which this indication -- your wording in the questions is identical to the paragraph, whereas in the discussion this morning it was further clarified to include state IV and those patients ont appropriate for combined modality curative intense chemo/radiation.

DR. DUTCHER: So how would you word it?

DR. ALBAIN: Potentially curative -- can you not put the stage groupings in it?

DR. JOHNSON: No, we've had these discussions previously and personally I'm willing to go with whatever the committee says since I can't comment about it, I mean vote on it, but we've had these discussions before about trying to restrict based on performance status, trying to restrict based on other things. What we've heard from our patient advocates in general, and I think from several of the physicians, is that there needs to be some room for judgment here. Candidly, I think patients who are not candidates for potentially curative surgery and/or radiotherapy covers the concept of multimodality. That's my perspective and I think that's an adequate description of who we're talking about.

DR. ALBAIN: Most IIIB patients are not cured by radiation, however, there is a finite cure rate with chemo/radiation.

DR. JOHNSON: But it says and/or and I think that it leaves room for multimodality treatment. That's what I'm saying. I think the operative word is curative, and I think physicians who deal with this population generally feel pretty comfortable making that decision, I think.

Certainly again, if a patient of mine were to say this doesn't make you --

DR. DUTCHER: It doesn't preclude giving combined modalities.

DR. JOHNSON: Right.

DR. DUTCHER: The way it's stated.

DR. JOHNSON: That's my point.

DR. ALBAIN: I think perhaps the way it's stated would allow cisplatin and Taxol at these doses to be given with radiotherapy, depending on how you interpret it.

DR. JOHNSON: Some people will do that.

DR. DUTCHER: That can be discussed I think subsequent to our decision about the questions. I think that the FDA gets the sense of the committee and the cautions that need to be put in place and they work with the sponsor to define that.

All right, number two then. Does Study 165 serve as an adequate and well controlled trial demonstrating the efficacy and safety of 135 milligrams per meter squared of Taxol as a 24-hour Taxol infusion in combination with cisplatin for the treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy?

Dr. Schilsky, do you want to -- since you suggested we start here, start here?

DR. SCHILSKY: Okay. Well, I would answer this yes and I am persuaded that there is a modest survival advantage. I'm not particularly concerned about the pooling of the two arms to demonstrate that more definitively. I'm also persuaded that there is some quality of life advantage for this therapy. It was interesting to me that in the bar graphs that the sponsor showed that there was a progressive decrement in each of the parameters displayed for the platinum/etoposide arm over time, whereas there was relative stability in the Taxol/platinum arm indicating that there was at least at better preservation of some quality of life for patients receiving that treatment.

So, I guess I've been persuaded that there is clear clinical benefit associated with platinum and Taxol given as was done in this particular study. So I would move that the answer to this be yes.

DR. DUTCHER: Dr. Albain.

DR. ALBAIN: I would also move that it be yes, in addition based upon the fact that this doublet falls right where the other new third generation doublets are in terms of intermediate long-term survival and giving another option

for patients that we didn't have five years ago.

DR. DUTCHER: Other comments? All those who would vote yes to question two, please raise your hand, those who may vote?

[Show of hands.]

One, two, three, four, five, six. Six out of six and Dr. Krook votes yes. Dr. Margolin votes no. So seven yes, one no.

DR. TEMPLE: Dr. Dutcher, can the committee members say a little more about what they believe has been shown? Dr. Schilsky was very clear. He thought a survival advantage was probable. Could others say further? These things have precedential(?) value if it's response rate people are responding to or time to progression or what, it would help us to know.

DR. SWAIN: I was responding to the time to progression, which I'm more convinced of. I do disagree with the quality of life. I'm not so convinced about that at all because of the dropouts. Also, there were a lot more patients who discontinued because of toxicity. So my vote was really based on response rate and time to progression.

DR. TEMPLE: This study is actually relatively weak on the quality of life. It's the other studies that

are stronger.

DR. SWAIN: Right.

DR. DUTCHER: I think I was persuaded by the time to progression and the one-year survival.

DR. JOHNSON: Since I didn't vote, I guess it doesn't matter what I think, but I think the data are absolutely clear that there's a survival advantage in my mind. I will grant you that from a P value it's rather weak, but I agree with Kathy's comments vis a vis it's stacking up with every other data that we've seen, including the presentation we heard yesterday.

But I would completely differ with Dr. Temple's comment vis a vis quality of life. In fact, these are the strongest data, so strong that ASCO chose it as a plenary session last year. So it wasn't data that experts in the field of quality of life felt was weak. I think the TOI clearly correlates with outcome in this study. Those data may not have been presented as strongly at this presentation as perhaps we think they ought to have been, but from the standpoint of quality of life data, I will assure you that you will never find as much data from a lung cancer study as was identified and collected in this study.

So, from an independent body, different from the

sponsors, different from the FDA, different from myself who has a vested interest in this study, that's my conflict clearly, the quality of life data were perceived as being superb, enough to be a plenary session presentation. I think that speaks for itself.

DR. DUTCHER: Dr. Simon.

DR. SIMON: I don't think anything is clear.

[Laughter.]

For me it's a close call, but I believe there is probably for this study some small survival benefit, although I would like to have seen a stronger statistical -- I think everyone would have liked to have seen a stronger statistical demonstration of it without having to get in statistical controversies of technical points.

I believe that, and the quality of life, I think there probably is some quality of life benefit, although I think that to me it's not clear. So I think it's a tough call, but I would come down on the side of voting for the --

DR. DELAP: Just for my precedential kind of precedent for subsequent applications viewpoint, I would like to know what some people think about the quality of the survival finding. I would like to know really what the consensus of the panel was about whether this particular

study was indicative of a survival benefit.

DR. DUTCHER: Did or did not show a survival benefit based on --

DR. DELAP: Based on what you've seen. If you feel it's reasonable to pool the data and all that -- bottom line, do you feel that this study --

DR. DUTCHER: I think in this particular study it was reasonable to pool the data.

DR. DELAP: Okay. Do you then believe that there was a survival benefit shown?

DR. DUTCHER: Well, you know, I'm not a lung cancer doctor, so I had trouble thinking there's any survival benefit, but I think that the two arms, I think the data as it was presented in the ECOG analysis shows a survival benefit, yes. I believe it's there. I think it's small, but I think we talked about incremental steps.

DR. ALBAIN: You have to talk about a doubling of one and two-year survival here over what all of the second generation regimens show.

DR. TEMPLE: What about in this study?

DR. ALBAIN: In the ECOG trial alone.

DR. TEMPLE: What were the numbers at one year? I don't remember.

DR. ALBAIN: Approximately 39 percent for the pooled data and 14 percent in the cisplatin alone arms of some of the other trials --

DR. TEMPLE: No, no, in this study. I mean we have a study.

DR. ALBAIN: Fourteen percent versus platinum -- I'm sorry, I hope I'm quoting you right, Phil. Thirty-nine percent one year for the pooled, 14 percent one year for the control -- no, 14 percent two year, excuse me.

DR. TEMPLE: Let's do the comparisons.

DR. ALBAIN: Thirty-nine and 14 were one-year and two year.

DR. TEMPLE: Versus?

DR. ALBAIN: Thirty-two and 11.

DR. TEMPLE: Okay, so it's 39 to 32.

DR. JOHNSON: Yes, I think that that's the more fair and more data points are available at that point. What it shows is approximately -- this is where we differ, I think, in terms of our interpretation of these data. I'm looking at it as a clinician and I see that as an approximate 10 percent gain. If I look at it, as we talked about it yesterday when we were talking about gemcitabine, best supportive care 10 percent survival at one year,

platinum based chemotherapy 20 percent survival at one year.

You then take and subselect patients, which was what was done in the ECOG trial to zero and one performance status. You're going to incrementally drive up that one-year survival to approximately 25 to 30 percent with standard platinum chemotherapy. That's what every study will show if you subset analyze just that group of patients.

So, what we've done then is further increase this by eight, nine percent. As we pointed out by Dr. Ruckdeschel, that's 1,700 lives per percentage point per year. So again, that will drive a statistician nuts, Rich will pull his hair out doing this, but that in fact is what we're saying.

DR. TEMPLE: It's happened already.

[Laughter.]

DR. SIMON: I don't think that's a good way of looking at it. That might be a good way of looking at it when you're looking at a point on a survival curve where the curve is flat, but to look at one-year survival when some of the patients who are alive at one year are not going to be alive at 13 months I think is meaningless.

DR. JOHNSON: I accept what you're saying, but all survival curves eventually end up at the same spot. They

all do eventually. This is a disease where again, I think it's very important that when you're talking -- we talked about ovarian this morning, where you have survivals of three years or two years or a year with no treatment versus a disease where you have about an eight week to 16 week median survival with no treatment.

So the difference is, I mean the magnitude of the change is there. It's a clinically relevant change. As I said yesterday, you're not hitting home runs here. I think that's why you have to do this very carefully. If the only advantage that we're willing to accept is a year or more, that makes our job easy. I think we have to look at the total picture. Obviously, I'm biased, but I'm a lung cancer physician. That's what I believe. I believe that's what we've shown, or these data have shown.

DR. DELAP: I think that's excellent discussion for us and that's what I wanted just a sense of how people are looking at the survival results as they assess this study.

DR. DUTCHER: All right, let's go to question four.

DR. TEMPLE: Can I just have one more clarification? The thing that knocks your eyes out here is

the lung cancer symptom result particularly, because that's the one clear thing.

DR. JOHNSON: Sure, I mean I think the thing that really impresses you is if you can improve a patient's symptoms. Again, Dr. Ruckdeschel I felt gave a superb presentation, an overview of how we view lung cancer treatment. There's a nihilistic perspective and I will quickly tell you this story.

In Dublin this summer, where the Scottish physicians were presenting the fact that they don't treat lung cancer in the west of Scotland because it costs the Scottish government 37 million pounds a year to treat lung cancer so they don't treat it at all. Somebody stood up and said, well you know, my God, you spend that much on laxatives every year in Scotland. He says, yes, but laxatives work.

So there's this general perspective that there's no benefit to treatment in lung cancer. But as Dr. Ruckdeschel showed you, 70 percent of patients survive, symptoms improve with chemotherapy over no treatment. I do believe, and this goes back to the discussion we had yesterday vis a vis the breast cancer, you asked rhetorically and I answered no, I didn't hear the other

answer, but does response alone mean anything. I think the answer is no. But if response is correlated to something, survival hopefully, but symptom improvement, then yes. There are data that clearly show that response in lung cancer is associated with tumor related symptom improvement.

I think that was seen, perhaps not as cleanly as we would like to see in some of the studies we've done, but again, this wasn't a regulatory study that was undertaken, 165 wasn't. It was done as a part of a cooperative group trials that attempted to look at a quality of life issue, which is very difficult to do, but I think nevertheless was done.

So, yes, I think that's very important.

DR. DUTCHER: Just from a non-lung cancer person, but nevertheless treats solid tumors with an equally nihilistic outlook, renal cell, a lot of what we do is a plateau effect. If you can keep people on a plateau, no matter what the end of that plateau means, they live better and they function better. I think that's where the quality of life assessment, particularly for these teeny incremental improvements, becomes very important, because you don't want to spend the rest of whatever time it is in bed.

DR. JOHNSON: I think the other thing you asked

the other day about, which I think is a very important question, was time to progression, is that a valid endpoint. When you ask it that way, my answer would be no. But if you ask it time to progression, coupled with some other perceived benefit, then my answer to your question would be yes. I think, again, the GOG-132 trial is a perfect example of that. You would never have seen a survival difference. You would see a time to progression difference perhaps, but if that's coupled with some kind of clinical benefit that I as a clinician, and more importantly, a patient is understand, that is they're feeling better, then to me that's very important.

We've having a tough time measuring that. Again, I agree with everything Rich has said vis a vis looking at a curve. I don't want to look at just one point. You have to look at the whole curve, but I do think we are looking at the whole curve on these.

DR. TEMPLE: I guess the other thing that strikes me is that we lump a lot of stuff under quality of life assessments. The one thing that was most impressive here was the thing that was most closely related to what we really think people ought to pay attention to which is tumor specific symptoms.

DR. JOHNSON: Correct.

DR. TEMPLE: That's hardly surprising. You would expect that to do better than emotional status on the whole.

DR. JOHNSON: I come from the old school where if you're really concerned about the quality of life, you ask the patient and say are you feeling better. If they say yes, that pretty much answers the question for me, but I guess you have to learn how to measure that. I don't know maybe the patient rep would comment about that.

DR. DUTCHER: Actually, she would like to make a comment. Ms. Rosen.

MS. ROSEN: Thank you. Yes, I think that's very true. I'm on the other end of the spectrum here being a stage I by accident. I haven't had any chemo, so in a certain sense I'm in the same boat as everybody else because I really don't know what it's like to be a stage IIIB or a IV and what might be going on for me physically, emotionally and in every other sense. But from what I've read and listened to here, in a certain sense, I mean maybe small gains are okay, but where I'm coming from they're really not.

You're really not okay to be spending this much time and this much effort on a tiny little gain when we have

such a huge problem out there that's going unaddressed, or at least I haven't heard much about it in terms of high risk population, in terms of cure, in terms of spending our dollars and our time and effort and critical thinking skills on let's get this at an earlier stage. Let's not let it develop to stage IV. Let's have people have the chance, if they are going to be diagnosed, to be diagnosed early as they are now being diagnosed in other cancers.

I don't know if this is relevant to what we're discussing here, but I just feel compelled to have to share this point of view with you because that's my commitment, that's my goal, that's really why I'm here. These little gains in someone who is -- I mean life is valuable I guess at any stage, I can't deny that, but so much emphasis seems to be being placed here on two months more. Maybe to the fourth stage lung cancer patient two months more with a little better quality of life is a huge thing. But if you are really going to look at the whole picture, then we've got to look at stage I, II and IIIA and IIIB and look at the early stages and look at the occult stage, where I don't know if anybody is really looking. That's what I'm requesting. That's what I'm requesting going forward, more of the emphasis being placed there.

Not to be cynical, but I guess I am, I can't help considering that maybe what's going on here is the easier way out, the easier thing to study, the easier thing to approve or not approve, the less challenge and the more possible lowering of cost and profitability and gains for corporate America. I'm sorry to have to say that but that is also there for me and it's very present for me. I'm very scared and I need you guys to be concentrating on what can help me not get to stage IV. Thank you.

DR. DUTCHER: Okay, thank you. Well, unfortunately we still have to deal with what we've been talking about.

DR. TEMPLE: It's drug therapies that come to this committee and I don't think anybody doesn't agree that there are more important things to do for lung cancer than change two months. Our former commissioner probably struck the greatest blow yet for doing that because lung cancer is a failure of public policy in a large sense. So that's going on publicly and in Congress and everywhere else. Meanwhile, small increments are what we have to ask the committee to help us deal with.

MS. ROSEN: Today, yes.

DR. DUTCHER: But I will comment that some of the

people that went out for the fire drill went out with a cigarette from this group.

DR. JOHNSON: I also noticed that people grabbed important things, but no one took their briefing books with them when they went out.

[Laughter.]

DR. DUTCHER: Question number four. Should Taxol as a 24-hour infusion at 135 milligrams per meter squared in combination with cisplatin be approved for the treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy? So this is a question of approvability. Dr. Schilsky.

DR. SCHILSKY: Well, since I like to be internally consistent, I guess I would move the answer to this should be yes. It seems to me that if we accept the fact that Study 165 was a well controlled trial that demonstrates a clinical benefit for Taxol/cisplatin, then it should follow logically that that therapy should be approved for this indication.

DR. SIMON: Well, yesterday I voted no, because I wanted to see a second trial. Here we see a second trial, a third trial, which I don't feel confirmed the first trial,

so I plan to vote no.

DR. DUTCHER: All right. All those that feel that this is approvable, please raise your hand.

[Show of hands.]

One, two, three, four. Ms. Beamon voted yes and Dr. Krook voted no. Dr. Margolin abstained and Dr. Simon is voting no. So we have one, two, three, four, five yes, two no and one abstained.

Okay, so then we go on to the first and the third questions. Do Studies 103 and 208 serve as adequate and well controlled trials demonstrating the efficacy and safety of 175 milligrams per meter squared of Taxol as three-hour infusion in combination with cisplatin for the treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy? Dr. Albain.

DR. ALBAIN: Well, here we lose the proven survival benefit. Here we see, I think, equivalence in survival. Certainly the response rates, the one year survival, those are very much in keeping with what we saw in the 165 trial, but the rigor is not here for survival as it was for the study we just voted on.

DR. DUTCHER: Is that a no? Any other comments?

Are these adequate and well controlled trials demonstrating efficacy and safety? Dr. Schilsky?

DR. SCHILSKY: I guess I would say the answer to that is yes, no and yes.

DR. DUTCHER: They're adequate and well controlled.

DR. SIMON: I think they are adequate and well controlled. I'm not convinced that they demonstrate efficacy. I think these are two studies where in fact, if I remember this correctly, in the Taxol/cisplatin arm the survival is actually a little bit inferior to the control arm in both studies. There clearly is not an advantage in terms of time to progression. I actually think that the quality of life data in these studies is not nearly as good as it is in the ECOG study, so I guess I would agree with David and disagree with Dr. Temple on that.

So, despite the fact that I think the studies were well done, I don't think they've demonstrated a benefit for the Taxol containing regimen.

DR. DUTCHER: Which part of this question do you want answered, the adequate and well controlled or the demonstration of?

DR. TEMPLE: We actually think they're well

controlled studies, so the question is what they showed. Right? I'm not putting words in anybody's mouth am I?

DR. ALBAIN: Do you need the safety separated from the efficacy here?

DR. WILLIAMS: I think you can basically take the last question -- you really combined these into one question yes or no.

DR. TEMPLE: But you can focus on efficacy. The safety data is the whole database really.

DR. DUTCHER: All those who think these do demonstrate, Studies 103 and 208 demonstrate the efficacy in these randomized studies please raise your hand.

[Show of hands.]

One, two. Okay, all those who would say they do not?

[Show of hands.]

One, two, three, four, five. Dr. Krook and Dr. Margolin abstain and Ms. Beamon votes yes and no. Yes, she voted a yes. She wasn't here for the benefit of the discussion, but that's okay. So five no, one yes, two abstained.

Number three. Should Taxol as a three-hour infusion at 175 milligrams per meter squared in combination

with cisplatin be approved for the treatment of non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy? All those who would say yes, please raise your hand.

[Show of hands.]

All those who would say no. One, two, three, four, five. We have a yes from Beamon and Krook and an abstain from Margolin. So it seems that the less convincing data for the three-hour infusion, more convincing data for the 24-hour infusion. Dr. Schilsky.

DR. SCHILSKY: I just wanted to make a comment. I think that this is a very tough call. I think if you look across all of these studies, it actually doesn't strike me that there's a great deal of difference in the Taxol arms with respect to the outcome parameters. So that the three-hour arms in those two studies look pretty much like the 24-hour regimen in the ECOG study. In fact, all of these data look pretty similar to data that we've seen yesterday with Gemzar and in the past with phenoralbine(?). I think what that's telling us is that there are a variety of platinum based regimens that produce a reasonable outcome and probably a better outcome than chemotherapies that we've had available in the past.

I think the reason that I was not able to vote for approval for the three-hour regimen is because I don't think these particular trials actually demonstrated benefit, although it seems to me that in the grand universe of things that the outcomes with the three-hour therapy are probably not terribly different from the 24-hour regimen.

DR. DUTCHER: I think we also have to think that perhaps moving as fast as this field is, the control arms that have been used here are perhaps a bit better than the control arms that have been used in other previous studies, so we're comparing a tougher set of studies. Yes.

DR. ALBAIN: Also, I think very soon we will have the answer to this. ECOG is asking this very question in their ongoing trial about the three versus 24 and we will also have the carbo/Taxol data also very soon to help sort this out further.

DR. DUTCHER: Okay. Thank you all very much. See you in June.

[Whereupon at 3:27 p.m., the meeting was adjourned.]