FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

SIXTY-THIRD MEETING

OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE

8:07 a.m.

Thursday, September 16, 1999

Kennedy Ballroom
Holiday Inn

8777 Georgia Avenue
Silver Spring, Maryland

ATTENDEES

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ATTENDEES (Continued)

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SANDRA ZOOK-FISCHLER - for Evacet
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ON BEHALF OF BRISTOL-MYERS SQUIBB:

STEVEN BENNER, M.D., M.H.S.
RENZO CANETTA, M.D.
JAMES CARMICHAEL, M.D., PH.D.
ROBERT DIASIO, M.D.
JOHN MACDONALD, M.D.
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ON BEHALF OF THE LIPOSOME COMPANY:

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STEVE PIANTADOSI, M.D., PH.D.

JAMES SPEYER, M.D.
ERIC WINER, M.D.

ATTENDEES (Continued)

ALSO PRESENT:

DR. MICHAEL COHEN
LAURENCE F. DASPIT
LAURA MEEKER
MARGARET VOLPE
MARISSA WEISS, M.D.

C O N T E N T S - MORNING SESSION

NDA 21-053, UFT (tegafur and uracil) CAPSULES
BRISTOL-MYERS SQUIBB COMPANY
Indicated with leucovorin calcium tablets for the
First-line Treatment of Metastatic Colorectal Cancer

C O N T E N T S - AFTERNOON SESSION

NDA 50-772 EVACET (doxorubicin HCl liposome injection)
THE LIPOSOME COMPANY, INC.
Indicated for the first-line Treatment of
Metastatic Breast Cancer
in Combination with Cyclophosphamide

COMMITTEE DISCUSSION AND VOTE 282

P R O C E E D I N G S

(8:07 a.m.)

DR. SCHILSKY: Good morning, everyone. If people can please be seated, we'd like to begin the meeting today. Welcome to the 63rd meeting of the Oncologic Drugs Advisory Committee. I am not sure if this is the first meeting that has ever occurred during a hurricane, but it must be one of the few.

Karen Somers has a few opening remarks before we have introductions.

DR. TEMPLETON-SOMERS: We have some new members to welcome to the committee, and Dr. Schilsky is our new Chair, in case you hadn't noticed already. The new members who are already present are Dr. Douglas Blayney and Dr. Jody Pelusi, who is our new Consumer Representative, and Dr. Scott Lippman, who is over here. In addition, Dr. David Kelsen will be arriving late. He was having trouble getting a plane from New York and will be coming by train this morning, but he should be here by around 9:00.

DR. SCHILSKY: Thanks, Karen.

I think we'll go around the table and ask each

of the committee members to introduce themselves, and why don't we start with one of the experienced members. Dr. Raghavan.

DR. RAGHAVAN: I'm Derek Raghavan, medical oncologist, USC.

DR. LAMBORN: Kathleen Lamborn, biostatistician, UCSF.

MS. FORMAN: Sallie Forman, Patient Representative.

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

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

DR. SCHILSKY: I'm Rich Schilsky. I'm a medical oncologist with the University of Chicago.

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

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

DR. DAVID JOHNSON: And I'm Dave Johnson, medical oncologist at Vanderbilt University.

DR. PELUSI: And I'm Jody Pelusi. I'm a nurse practitioner in oncology in Arizona.

DR. KROOK: Jim Krook. I'm a medical oncologist from Duluth. When Karen asked me to come back to ODAC, she said there was a drought. She said, bring water.

(Laughter.)

DR. KROOK: I brought it. Don't complain.

(Laughter.)

DR. TEMPLETON-SOMERS: Dr. Krook does not know moderation.

(Laughter.)

DR. BLAYNEY: I'm Doug Blayney. I'm a medical oncologist from Pomona, California. And when I joined, they told me all the meetings were going to be in California.

(Laughter.)

DR. WHITE: Robert White, FDA, oncology.

DR. JOHN JOHNSON: John Johnson, clinical team leader, oncology.

DR. JUSTICE: Bob Justice, acting Division

Director, oncology.

DR. BEHRMAN: Rachel Behrman, Deputy Office Director, FDA.

DR. SCHILSKY: Thank you.

Karen has a conflict of interest statement.

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

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

In accordance with 18 U.S.C. 208(b)(3), full waivers have been granted to Drs. Douglas Blayney, David Johnson, David Kelsen, Scott Lippman, Kim Margolin, Richard Schilsky, James Krook, and Kathleen Lamborn which permit

them to participate in all official matters concerning UFT.

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

In addition, we would like to disclose for the record that Drs. Johnson, Lippman, and Schilsky have interests which do not constitute financial interests within the meaning of 18 U.S.C. 208(a), but which could create the appearance of a conflict. The agency has determined, notwithstanding these interests, that the interests of the government in their participation outweighs the concern that the integrity of the agency's programs and operations may be questioned.

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

With respect to all other participants, we ask in the interest fairness that they address any current or

previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. SCHILSKY: Thank you, Karen.

We have two people listed on the agenda for the open public hearing. Is Michael Cohen here? Please come to a microphone and state your name and affiliation and whether you've received any financial support from any sponsor.

DR. COHEN: Since I'm a pharmacist and not an electronic engineer, I'll start here. My name is Michael Cohen. As I said, I am a pharmacist and I head an organization called the Institute for Safe Medication Practices. It's an independent, nonprofit organization. The United States Pharmacopeia operates the medication errors reporting program in cooperation with our organization. We're also FDA Med Watch partners.

We publish reports of medication errors that we receive from practitioners from around the country, and these are published in various journals and newsletters, including Oncology Times. We have an ongoing feature in

Oncology Times.

We also have our own publication called the ISMP Medication Safety Alert, which is faxed or e-mailed to hospitals around the country and other practice sites every two weeks. The reason I mention that is I'd like to disclose that Bristol-Myers Oncology does help to sponsor that for some of the hospital organizations, so that it is available to them.

My comments are related to the potential for medication errors with the product that you're about to discuss. Through the years, we have had some reports from practitioners of confusion when prescriptions are written for the drug leucovorin calcium with the product Leukeran, and that concerns us because the drug that you're about to approve, UFT, apparently will be prescribed with leucovorin calcium.

We also have occasional problems where the drug is referred to as folinic acid, and again we have had reports from practitioners where folic acid was administered instead.

About 25 percent of the reports that come to

USP and FDA of medication errors have to do with labeling and packaging. One of the things that we've always promoted, besides clear labeling and packaging obviously, is simplification. That certainly is promoted by human factors experts as well. I think it would be very important then to simplify things and instead of having to write two prescriptions for the drug and have a patient have to have two prescriptions filled, with the added possibility of confusion between leucovorin calcium and Leukeran, that the products be available and packaged together.

And those are my comments and I'd like you to consider them. Thank you very much.

DR. SCHILSKY: Thank you very much.

Is Laurence Daspit here? So, please come to the podium and state your name, affiliation, and whether you've received any financial support to be here.

MR. DASPIT: I have a brief prepared text with some notes.

My name is Laurence Daspit. I'm 54 years old, married with one son. I live in Spring, Texas. My wife

and I are here at the courtesy of Bristol-Myers Company which paid our airfare, transportation, and lodging.

Also by way of disclosure, in December of 1996, I did a brief marketing video, for which I received $200. That is the extent of any compensation to me from Bristol-Myers.

In May of 1995, I had surgery at M.D. Anderson Cancer Center to remove a cecal region -- cecal colon tumor. Excuse my medical terminology. I'm not a doctor. During the surgery, biopsies established that the disease had spread to my abdominal lymph nodes and liver. The surgeon opted not to remove the lesions from the liver. He did remove the abdominal lymph nodes.

After recovering from surgery, I had the opportunity to participate in a clinical trial of UFT with leucovorin. I began taking these medications in late June of 1995. I took UFT with leucovorin three times a day, as indicated, for 4 weeks followed by a week without medication. After two rounds of medication, CT-scans of my abdomen and pelvic region, x-rays, and blood labs indicated no evidence of disease.

Because the treatment was an oral medication, our family was able to travel to France in November of 1995 and take other extended vacations. The staff at M.D. Anderson arranged for the required weekly blood work to be done at local hospitals where we were vacationing. The results were faxed back to the research nurse in Houston.

I continued to take the oral medication until mid-October of 1997. I was on this therapy regimen for approximately 2 years and 3 months. During that entire time, I do not recall missing a single day of work because of medication side effects. I did miss time from work for scheduled diagnostic procedures.

Well into each 4-week cycle, usually in the third or fourth week, I often did experience moderate diarrhea. On the advice of the research nurse, who had monitored my therapy, I would skip doses as needed and use over-the-counter anti-diarrhea medication to control and restore normal bowel function.

Also well into each round, I did often experience bothersome but not debilitating fatigue.

In mid-October 1997, at the suggestion of the

oncologist who was treating me, I stopped taking the medication. I continue the schedule of diagnostic procedures, the CT-scans, the blood work, and the x-rays.

My most recent set of diagnostic procedures was in early May of this year. Those procedures revealed no evidence of disease.

I want to close by asking this panel to make this medication available to anyone who is diagnosed with metastatic colon cancer. Long before hearing no evidence of disease and long before understanding complete response, this medication let me work productively, enjoy leisure with my family and friends, and start a regular routine of physical exercise that has resulted in the best annual physicals I've had in my adult life. I'm asking you to please give others with this disease the same opportunity.

Thank you.

DR. SCHILSKY: Thank you.

Is there anyone else who wishes to make a statement before the committee?

(No response.)

DR. SCHILSKY: If not, we'll move on to the

sponsor's presentation. Dr. Canetta.

DR. CANETTA: Good morning. My name is Renzo Canetta. I'm with the Clinical Oncology Group at Bristol-Myers Squibb. We plan to present to you today the contents of our NDA for UFT capsules plus leucovorin tablets for the treatment of metastatic colorectal cancer.

This biomodulated treatment consists of UFT capsules that is a fixed combination of tegafur. Tegafur is a prodrug of fluorouracil and uracil which is an inhibitor of the catabolic pathway of 5-FU. And that contributes also to the increase of the levels of 5-FU when UFT is given.

The addition of leucovorin is meant to provide potentiation of the 5-FU effect. Altogether, this approach allows an efficient oral delivery of 5-FU, and that is coupled with a significant reduction of its side effects. That's resulting in an overall improvement of the therapeutic index for fluoropyrimidine therapy.

UFT was originally developed in Japan by the Taiho Pharmaceutical Company, and it was approved there in 1983. In that country, UFT has been widely adopted for the

treatment of several solid tumors, including metastatic colorectal cancer. You see listed here the countries where the drug has been approved after Japan, and these are the countries that approved the drug before the beginning of the pivotal trials that we'll be discussing today in the U.S.

The use of the drug in the U.S. and in Western Europe has been limited to clinical trials, and the only exception was Spain where the drug was approved in 1986. Following the approval in Spain, the drug has been generally given in conjunction with leucovorin as a treatment for metastatic colorectal cancer.

The Taiho Company began the clinical development of this compound in this country, and phase I and phase II were conducted under IND for the combination of UFT and leucovorin. In 1995, Bristol-Myers Squibb acquired the license to the compound.

Throughout the entire development of UFT and leucovorin, a series of meetings were held involving the sponsor and the FDA. As a result of these meetings, the registrational plan was developed with a stated goal to

demonstrate equivalence and efficacy as measured by survival in comparison with the standard of care of intravenous 5-FU and leucovorin. The definition of non-inferiority was included both in the study protocol and the analytical plan submitted as early as 1996 or 1997.

The NDA submission began in September 1998 before the number of events projected for the final survival analysis had occurred. And a number of events were projected to occur early in 1999, and that is when the rolling NDA procedure was completed.

During the review period, an update of the survival analysis was agreed upon with the FDA.

The NDA contains two prospectively randomized trials. As a matter of fact, the pivotal study is the largest randomized trial ever submitted to the FDA for registration of a drug for this indication.

We believe that these studies have conclusively demonstrated that oral UFT and leucovorin produce equivalent survival effects to the standard of care, 5-FU and leucovorin given intravenously. The oral UFT and leucovorin regimen is associated with clinically

significant safety advantages. These encompass myelosuppression, febrile neutropenia, infections, gastrointestinal symptoms, including both diarrhea and nausea and vomiting, mucositis and stomatitis, and the concomitant use of additional medications.

Thus, overall oral UFT and leucovorin represents an important therapeutic advance for the treatment of the disease.

This morning's presentation will consist of a review of the chemotherapy for metastatic colorectal cancer, which will be given by Dr. Jack MacDonald from New York. Dr. Bob Diasio from Birmingham, Alabama will present to you both the pharmacological and the clinical aspects of UFT development. His presentation will be followed by the reporting of the results of the two randomized phase III trials. Dr. Steve Benner from BMS will present the pivotal study 011 whose principal investigator was Dr. Richard Pazdur from the M.D. Anderson Cancer Center in Houston. Dr. James Carmichael from Nottingham Hospital in the United Kingdom will present the results of the confirmatory study 012. At the end I would add a few concluding remarks.

We are very pleased today to have with us as consultants both Dr. Steven Piantadosi from Johns Hopkins University and Dr. Barry Lembersky from the Allegheny General Hospital in Pittsburgh.

I'd like now to introduce Dr. John MacDonald from St. Vincent's Comprehensive Cancer Center in New York.

DR. MacDONALD: Thank you very much. Dr. Schilsky, committee members, ladies and gentlemen, good morning.

I will review the use of chemotherapy in advanced colorectal cancer. In this disease setting, intravenous 5-FU and leucovorin is the current standard of care.

Colorectal cancer is one of the leading causes of cancer mortality in the United States and throughout the world. By American Cancer Society estimates, over 129,000 new cases will be diagnosed in the United States in 1999. Each American has a 1 in 20 lifetime risk of developing colorectal cancer. This year the disease will result in an estimated 56,000 deaths in the United States alone. Of all the patients initially diagnosed with colorectal cancer,

slightly over half will develop metastatic disease sometime during the course of their illness. In the past, without therapy, survival for metastatic colorectal cancer has been well under 1 year, with many studies reporting survival of less than 6 months.

The results of these three randomized clinical trials comparing 5-FU/leucovorin based regimens to best supportive care are shown to highlight the impact of chemotherapy on survival. Throughout the literature, the 5-FU/leucovorin based chemotherapy has been shown to result in median survivals of close to 1 year. This survival benefit represents both the statistically significant and clinically meaningful impact of chemotherapy for patients with metastatic colorectal cancer.

Leucovorin modulated 5-FU regimens have emerged over time as the standard initial treatment for metastatic colorectal cancer. A meta-analysis showed statistically significant increases in response rates for 5-FU/leucovorin regimens compared to 5-FU alone. But at the time of this meta-analysis, improved response rates did not translate into a statistically significant improvement in median

survival.

The studies included in the meta-analysis used a variety of 5-FU/leucovorin doses and schedules. The studies which used a daily times 5 schedule administered 5-FU at doses ranging from 370 to 400 milligrams per meter squared per day. Several additional studies, not available at the time of the meta-analysis, however, have demonstrated the beneficial effect of adding leucovorin to 5-FU in prolonging survival.

In the metastatic setting, 5-FU in combination with leucovorin is the current standard of treatment. In fact, 5-FU was approved in the U.S. in combination with leucovorin to prolong survival in the palliative treatment of patients with advanced colorectal cancer. In the U.S., schedules developed at the Mayo Clinic and Roswell Park Cancer Institute are approved, but only the Mayo Clinic regimen is widely approved throughout the world. In clinical practice, 5-FU/leucovorin has been the accepted standard for first-line treatment of metastatic colorectal cancer.

While different schedules have continued to be

used and debated, all of these included biomodulation of 5-FU with the exception of continuous, uninterrupted 5-FU infusions. This approach is not approved, however, and requires placement of a central venous catheter.

5-FU, combined with leucovorin, has also served as the backbone for new experimental drug regimens being evaluated in the treatment of metastatic colorectal cancer.

Among the leucovorin modulated 5-FU regimens, which have gained widespread acceptance, the regimen developed at the Mayo Clinic has been extensively studied through the North Central Cancer Treatment Group. This regimen in most of its iterations employs a bolus 5-FU given at a dose of 425 milligrams per meter squared for 5 consecutive days. This is accompanied by intravenous leucovorin at a dose of 20 milligrams per meter squared per day, also administered for 5 days. As approved, the regimen is given at 4-week intervals for the first two cycles and then repeated at intervals of every 4 to 5 weeks.

This regimen has continued up to the present time to serve as an internationally accepted comparator arm

for phase III trials in advanced colorectal cancer. Approximately two-thirds of the recently reported phase III trials have used the Mayo Clinic regimen as the comparator arm. While proponents for other 5-FU regimens certainly exist, there's no question that the Mayo Clinic regimen is an accepted standard in clinical practice, as well as an internationally approved and recognized comparator arm for clinical trials.

Dr. Robert Diasio, Professor of Medicine, Chairman of Pharmacology at the University of Alabama at Birmingham, will now review for you the development of UFT and the results of phase I and phase II studies performed in the U.S. to develop the UFT/leucovorin regimen.

DR. DIASIO: Thank you, Jack. Good morning.

As we all know, 5-FU remains the backbone of treatment for metastatic colorectal cancer. While the debate has continued for decades regarding the optimal schedule for administration of 5-FU, 5-FU modulated by leucovorin is now the standard in clinical practice and the basis for experimental combination regimens.

This morning I will describe for you the

initial development of UFT and how, when combined with leucovorin, it was developed as a fluoropyrimidine regimen with distinct advantages over IV 5-FU and leucovorin.

UFT is a combination of tegafur, a 5-FU prodrug, and uracil. Unlike 5-FU, tegafur is consistently well absorbed orally. The uracil component, of course, has no antitumor activity by itself. In combination with tegafur, however, uracil slows the breakdown of 5-FU. Animal experiments, later confirmed by human studies, establish the 4 to 1 molar ratio as optimal in producing high tumor exposure to 5-FU with much lower concentrations in normal tissue.

Following oral administration of UFT, tegafur is converted to 5-FU. The uracil component of UFT competes with 5-FU at the level of DPD. The inhibition of DPD by uracil is reversible.

Tegafur was first synthesized in 1967 as a 5-FU prodrug in an effort to improve upon 5-FU. Tegafur was tested in the U.S. using both IV and oral regimens. These studies did not demonstrate any efficacy advantage compared with 5-FU. In addition, with the high doses of tegafur

needed to achieve therapeutic levels of 5-FU, unique tegafur associated toxicities were noted; in particular, CNS side effects were observed.

Oral tegafur was studied in the treatment of metastatic colorectal cancer in the early 1980s. Six randomized trials compared tegafur given t.i.d. for 21 days versus IV 5-FU. In these studies, the tegafur treatment was not associated with an improvement in survival compared to 5-FU, and the results appeared inferior to the results of recent UFT/leucovorin trials. The tegafur treatment was associated with significant toxicity, however, with over 33 percent of the courses being associated with CNS toxicity and 54 percent of the courses with nausea. Based on this low therapeutic index, development of tegafur alone was discontinued within the U.S.

Due to the interest in Japan in oral therapy, development of tegafur continued there in combination with uracil as UFT. The uracil component allowed the oral combination to achieve therapeutic levels of 5-FU in man without the toxicities associated with high levels of tegafur. UFT has been widely used in Japan as chemotherapy

for the treatment of several solid tumors. The Japanese regimen was specifically developed to minimize toxicity and uses UFT alone at doses of 300 to 600 milligrams per day given twice daily, or t.i.d. In Japan, this regimen has been successful as an active antitumor regimen with minimal associated side effects.

The clinical experience in Japan with UFT supports the conclusion that the drug is extremely safe. UFT has been marketed in Japan for over 15 years. In addition to clinical trials, post-marketing surveillance now includes over 20,000 patients treated.

For UFT given, according to the Japanese label, the most common adverse events, considering all grades, are myelosuppression, anorexia, nausea, and diarrhea. The occurrence of severe toxicity was very uncommon. With this extensive clinical experience, the toxicity profile associated with UFT has been extremely well described.

In the U.S., UFT has been studied in combination with oral leucovorin to improve fluoropyrimidine treatment for colorectal cancer. As many of us know, leucovorin calcium stabilizes the complex of

FdUMP with thymidylate synthase improving efficacy.

The following clinical studies were performed in the U.S. to develop the UFT and leucovorin regimen and are contained within the FDA. The clinical pharmacology of UFT plus leucovorin was evaluated in eight studies which enrolled a total of 110 patients. These clinical pharmacology studies demonstrated rapid absorption of both tegafur and uracil. Following each oral dose of UFT, a peak in plasma 5-FU concentration occurs and there is no significant accumulation of plasma 5-FU with repeated dosing. Consequently, repeated oral dosing with UFT produces a repeated peak and trough pattern.

Initially a series of phase I studies using oral UFT combined with oral leucovorin were performed. The UFT dose was divided into three doses per day. These trials may be divided into those with low dose, or 15 milligrams per day, and high dose, or 150 milligrams per day, of leucovorin, also divided into three doses per day, given together with UFT.

Among all of these phase I studies, the maximum tolerated UFT dose with either low dose or high dose

leucovorin, using a 14-day schedule as opposed to a 28-day schedule, was 350 milligrams per meter squared. In all of these studies, toxicities were very consistent, and the dose-limiting toxicity for all studies was diarrhea.

The phase I experience suggested that no dose intensification could be achieved by using a shorter dosing period. So, a 28-day schedule followed by 1 week of rest was chosen for the phase II studies.

In the phase II trials, both high and low dose leucovorin schedules were taken forward. The phase II studies were performed in previously untreated patients with metastatic colorectal cancer. In the M.D. Anderson Cancer Center trial, the initial dose of 350 milligrams per meter squared was not well tolerated. The dose was, therefore, decreased to 300 milligrams per meter squared per day in combination with high dose leucovorin.

Ultimately, from the phase II experience, this cohort -- that is, those patients treated with high dose leucovorin and 300 milligrams per meter squared per day of UFT -- achieved the best results. In this study, significant antitumor activity was observed, based on a

response rate of 44 percent, and the regimen maintained an excellent safety profile.

In this next slide, the safety experience for the phase II studies is shown based on the UFT dose. Those patients treated with a UFT dose of 350 milligrams per meter squared per day and either high or low dose leucovorin experienced an unacceptable incidence of severe toxicities, as you can see, including diarrhea, which occurred in 33 percent of the patients treated.

The difference in the toxicities observed between the 350 milligram and the 300 milligram per meter squared dose is quite striking. Here the incidence of diarrhea decreased up to 13 percent with no case of grade 4 diarrhea being reported. When looking at all other toxicities as well, there was an obvious improvement in the safety profile associated with treatment at a dose of 300 milligrams per meter squared per day compared with those treated at the 350 milligrams per meter squared per day.

For the phase III trials, after consultation with the FDA, a leucovorin dose of 75 to 90 milligrams per day was chosen. Oral leucovorin is clearly demonstrated to

have saturable absorption. As shown by this data taken from Straw, a leucovorin dose of 25 to 30 milligrams will produce bioavailability of over 90 percent.

The phase I and phase II trials demonstrated that the UFT in combination with leucovorin was a highly active regimen which was associated with an excellent safety profile. This is the regimen taken forward for the phase III trials. Dr. Benner from Bristol-Myers Squibb will now describe for you the results of the pivotal phase III trial comparing the UFT/leucovorin regimen to bolus 5-FU and leucovorin.

DR. BENNER: Good morning.

The 011 study was designed to demonstrate the safety and efficacy of UFT combined with leucovorin. Patients in the study had metastatic colorectal cancer and following enrollment were stratified by these criteria: presence of a measurable lesion, performance status, prior adjuvant therapy, and institution. None of the patients in this trial had received prior systemic therapy for metastatic disease.

The patients were randomized to receive a

treatment with either UFT and leucovorin or 5-FU and leucovorin. The UFT regimen was given as follows: UFT at a dose of 300 milligrams per meter squared per day divided into three doses per day and given for 28 consecutive days. This was followed by 1 week of rest. At the same time patients took UFT, they also took leucovorin again for 28 days, followed by a week of rest. The total daily dose of leucovorin was initially 75 milligrams in the United States, but when the study was expanded to include sites in Canada and Europe, the total daily dose was increased there to 90 milligrams per day due to the worldwide availability of a 15 milligram leucovorin tablet.

The control regimen was intravenous 5-FU and leucovorin given at 425 milligrams per meter squared per day for 5 days, leucovorin at 20 milligrams per meter squared per day for 5 days, with cycles repeated every 4 weeks.

The study was designed to demonstrate equivalence and survival for UFT/leucovorin compared with 5-FU and leucovorin. At least 630 events were required per the protocol. A conclusion of statistical equivalence was

based on the lower bound of the 95.6 percent confidence interval exceeding 0.8 for the hazard ratio.

The criteria used for eligibility are straightforward and they're summarized here. The patient population enrolled in the study had metastatic colorectal cancer, had at least a 6-month interval from any prior adjuvant therapy, and had not received prior systemic therapy for metastatic disease. Patients had a performance status of less than or equal to 2 and adequate hematologic, renal, and hepatic laboratory tests. The protocol was approved by each institution's review board and all patients gave informed consent prior to participation.

This slide illustrates the accrual by country with the number of sites in each country shown in parentheses. This large study enrolled 816 patients, with the majority of patients being enrolled from centers in the United States. Initially the study had included only centers in the United States, but as it was intended to serve a global registrational purpose, it was expanded to include Canada and Europe. The 011 study is the largest registrational trial performed for this indication.

Patient characteristics at study entry are shown here. As would be expected in a very large trial, the two treatment arms were well balanced with regard to these characteristics.

About 60 percent of the patients enrolled were men.

Most of the patients had a performance status of 0 or 1.

The median age for patients enrolled in the study was 64 years, with a wide range in age in both of the treatment arms.

Most of the patients had not received prior adjuvant therapy.

89 percent of the UFT/leucovorin patients and 91 percent of the 5-FU/leucovorin patients had measurable disease at the time of study entry.

The liver was the most common site of metastatic disease, with 80 percent of the 5-FU/leucovorin patients and 79 percent of the UFT/leucovorin patients having liver metastases at study entry.

The two interim analyses and the per-protocol

final analysis were preplanned and discussed with the FDA. An O'Brien-Fleming adjustment was used for the significance level. The first interim analysis, performed with 237 events, was described in the analysis plan and served as the basis for discussions regarding the possibility of an accelerated filing. The analysis with 453 events was also described in the analysis plan and was performed just prior to the initiation of the rolling NDA. The survival analysis performed with 640 events is the protocol-defined final analysis which was submitted with the NDA.

In preparation for ODAC, the FDA had agreed that it would be helpful to update the survival analysis and this analysis was performed using a cutoff date of June 20, 1999. This analysis included 700 events. This updated survival analysis allowed mature data from the prospective clinical trial to add in the assessment of efficacy.

At the time of the NDA submission, 320 deaths had occurred in each of the treatment arms. With these 640 deaths reported, the median survival for UFT/leucovorin treated patients was 12.4 months and was 13.4 months in the

5-FU and leucovorin group. The hazard ratio for survival 5-FU/leucovorin to UFT/leucovorin was 0.93 with a 95.6 percent confidence interval extending from 0.79 to 1.1.

Use of the 95.6 percent confidence interval resulted from the statistical penalty applied as a result of the previous planned interim analysis. Consistent results were obtained following a preplanned analysis adjusted for potential prognostic factors.

For the updated analysis, an additional 60 deaths had occurred since the time of the final protocol analysis. There were 351 deaths in the 5-FU and leucovorin arm and 349 deaths in the UFT/leucovorin arm. The median survival was 12.4 months for UFT/leucovorin and 13.4 months for 5-FU/leucovorin. The hazard ratio for 5-FU/leucovorin to UFT/leucovorin is 0.96, with a 95.6 percent confidence interval extending from 0.83 to 1.13. In the updated survival analysis, there was no change in the median survival, but the confidence interval for the hazard ratio shifted further upwards supporting the conclusion of equivalence.

The most mature survival curve from the June

1999 analysis is shown here. In these curves, the UFT is shown in yellow and 5-FU/leucovorin is shown in white. With this follow-up period, the survival curve now appears quite mature with few censored events occurring prior to the median. It is apparent from these curves that the results of the 011 trial, now reported with 700 events, clearly demonstrates equivalence in survival for UFT/leucovorin compared with 5-FU/leucovorin.

Results from a multivariate stratified Cox model are shown here. Among the covariates, only age was a statistically significant factor and gender was of borderline significance. The hazard ratios within the subsets, defined by age and by gender, were consistent with the equivalence of UFT/leucovorin to 5-FU/leucovorin.

707 of the 816 patients were observed to have developed progressive disease. The median time to progression for UFT/leucovorin treated patients was 3.5 months and was 3.8 months for the 5-FU/leucovorin treated patients. This finding was statistically different. The clinical interpretation of this 9-day difference in time to progression, in the setting of unequal time to

reassessment, is difficult, however.

Efficacy results for the secondary endpoint of response rate are summarized here for all randomized patients. There was no statistical difference in response rates in the two treatment arms and there was no difference between the two treatment arms and the percentage of patients achieving a complete response.

Comparing the two treatments, there are clear differences in hematologic toxicity. The incidence of both leukopenia and neutropenia, whether "any," CTC grades 1 through 4, or "severe," CTC grades 3 and 4, were highly statistically different favoring the UFT and leucovorin treatment group. The incidence of severe neutropenia, for example, was only 1 percent in the UFT/leucovorin treated patients compared with 56 percent in the 5-FU/leucovorin treated patients. Throughout the presentation of the toxicity data, the worst toxicity reported is shown for each patient, regardless of any assessment of drug causality, and it includes all courses of treatment.

The difference between the two treatments in the incidence of myelosuppression translated into a

clinically important benefit, none of the patients in the UFT/leucovorin treatment arm experienced febrile neutropenia compared with 13 percent of those patients treated with 5-FU and leucovorin, a highly statistically significant finding.

For infections there was also a lower incidence for both any infection and severe infections favoring UFT/leucovorin.

In the phase I trials, the dose-limiting toxicity for UFT and leucovorin was diarrhea, but as can be seen here, the incidence of diarrhea was no worse for the UFT/leucovorin treated patients than for those patients receiving 5-FU/leucovorin. In fact, the incidence of any diarrhea was statistically lower for the UFT/leucovorin patients compared with the 5-FU/leucovorin patients. The percentage of severe diarrhea was slightly higher for UFT/leucovorin, but this was not a statistically significant difference.

There was no significant difference between the two treatment arms in the incidence of severe nausea and vomiting, although patients on UFT/leucovorin were less

likely to have any nausea and vomiting than those patients receiving 5-FU/leucovorin. This occurred despite the fact that patients receiving UFT/leucovorin were much less likely to have received concomitant antiemetics.

Here the percentage of days with diarrhea is shown for both any toxicity on the top and severe toxicity here with the percentage of days across and the percentage of patients, the 0 grade favoring UFT/leucovorin. And when you look across the percentage of days, there was actually a statistically shorter duration of any diarrhea favoring UFT/leucovorin, and there was no statistical difference when you looked at the percentage of days with severe diarrhea.

Among these important safety advantages for UFT/leucovorin compared with 5-FU/leucovorin is the marked reduction in stomatitis/mucositis. There was a three-fold reduction in the occurrence of any stomatitis/mucositis favoring UFT/leucovorin treatment. For more severe toxicities, as you know, grade 3 toxicity means patients are unable to eat because of pain and grade 4 means that patients require parenteral or enteral support to maintain

their fluids. You can see that there was a difference from only 1 percent of the UFT/leucovorin treated patients having severe stomatitis/mucositis to 19 percent of the 5-FU/leucovorin treated patients. These findings were both clinically and statistically highly significant.

Comparing another toxicity commonly associated with fluoropyrimidine regimens, it is clear that the incidence of hand-foot syndrome was low in both of the treatment groups with only 2 percent observed in the UFT/leucovorin arm. This was actually statistically lower than seen with the IV 5-FU/leucovorin treatment.

There as no difference between the two treatment groups in the occurrence of elevated liver function with the exception of hyperbilirubinemia. UFT/leucovorin patients were more likely to have an increase in bilirubin, whether any or severe, than patients receiving 5-FU/leucovorin. This finding was isolated and there was no difference between the groups in reports of hepatomegaly or liver failure. With the interruption of UFT and leucovorin, the elevation in bilirubin declined. This laboratory finding of an increased occurrence of

hyperbilirubinemia due to the UFT/leucovorin was the only case in this study where the toxicity appeared worse for UFT/leucovorin than it did for 5-FU/leucovorin.

In this slide, the use of concomitant medications during treatment is summarized. As previously shown, the patients in the UFT/leucovorin arm enjoyed a favorable toxicity profile, and this toxicity profile corresponded to a marked reduction in the use of concomitant medications which was statistically significant for systemic anti-infectives, growth factors, antiemetics, and specifically for 5HT3 blockers.

Patients were highly compliant with the UFT and leucovorin oral outpatient regimen. This summary of UFT compliance, taken from patient diaries of treatment and including all courses of treatment, shows that at least 89 percent of the patients treated with UFT took at least 90 percent of the prescribed dose.

This slide describes the percentage of patients with dose reductions. As you can see here, at the start of course 2, the majority of UFT/leucovorin patients were able to continue the treatment as initially planned, but there

was a significant percentage, 43 percent for cycle 2, 56 percent at cycle 3, in the 5-FU/leucovorin treated patients who required a dose reduction.

This looks specifically at dose delays, and you can see that across the two treatment arms, they look somewhat similar suggesting that despite the 28-day continuous treatment, that the patients were able to resume the UFT/leucovorin regimen on time as planned, although apparently some of the patients with 5-FU/leucovorin required delays despite the long interval off of treatment.

The dose intensity and relative dose intensity of 5-FU and tegafur as received by patients in the study is shown here. The patients in this study received 93 percent of the planned tegafur dose.

This very large study, which enrolled 816 patients and in which 700 patients had been followed until the time of death, demonstrates clearly that as an initial treatment for metastatic colorectal cancer, UFT/leucovorin produces equivalent survival to 5-FU/leucovorin. While producing equivalent survival, this oral regimen is associated with significant safety advantages, including

reductions in severe myelosuppression, febrile neutropenia, infections, severe stomatitis and mucositis, as well as any stomatitis/mucositis, any diarrhea and nausea and vomiting, and the use of concomitant medications.

The second confirmatory phase III study was performed to support the 011 study and helped to serve as the basis for a global registration of UFT and leucovorin. This study, the 012 study, will now be described in detail by Dr. James Carmichael from Nottingham City Hospital.

DR. CARMICHAEL: Thank you. Good morning.

This study, the 012 study, was performed in a similar patient population to the 011 study. Patients were enrolled who had metastatic colorectal cancer and who had not received prior chemotherapy for metastatic disease. Patients were stratified by performance status, history of prior adjuvant therapy, and institution. Patients assigned by random allocation to the UFT/leucovorin treatment arm received the same regimen as those patients in the 011 study. For patients randomized to treatment with 5-FU/leucovorin, the doses were the same as in the 011 trial, but the interval of retreatment was 35 days rather

than 28 days so that the cycle lengths in the two treatment arms would be the same for the assessment of the primary endpoint of this trial, time to progression.

As shown here, the eligibility criteria were very similar in this study to the 011 study.

This slide illustrates the accrual to the study by country. The number of centers participating in each country are shown in parentheses. For the 012 study, in addition to accrual by sites in Canada, Western Europe, there were also sites in Poland, Australia, New Zealand, and Israel. The study had a total accrual of 380 patients up to July 1997.

Treatment arms were well balanced with regard to patient characteristics at baseline. In both treatment arms, the majority of patients were male, 67 percent and 64 percent, respectively. Most patients had an excellent performance status of 0 or 1, and the median age of participants was 61 and 62 years, respectively. As in study 011, there was a wide range in the age of patients at the time of enrollment, with a significant number of older patients being included in the trial.

23 percent of patients enrolled in each treatment arm had received prior adjuvant chemotherapy. Almost all of the patients, 97 percent in each arm, had measurable disease. As in study 011, most patients had liver metastases: 78 percent of the UFT and leucovorin treated patients and 77 percent on the 5-FU and leucovorin treated arm.

The efficacy results for survival at the time of submission of the new drug application are shown here. The median survival for patients treated with UFT/leucovorin was 12.3 months compared to 10.3 months for those patients treated with 5-FU/leucovorin. The hazard ratio of 5-FU/leucovorin to UFT/leucovorin was 1.16, with a 95 percent confidence interval extending from .93 to 1.46.

As in the 011 study following consultation with the FDA, the survival results for the 012 study were updated by determining the status of each patient as of June 20, 1999. At the time of submission of the NDA, 302 patient deaths had been observed, whereas for this analysis, a further 24 deaths had been observed. At this analysis, the median survival for the UFT/leucovorin

patients was 12.2 months compared with 10.3 months for the 5-FU/leucovorin treated patients. A hazard ratio of 5-FU/leucovorin to UFT/leucovorin was 1.14, with a 95 percent confidence interval ranging from .92 to 1.42.

Here the survival curves over time are shown with UFT/leucovorin shown in yellow. With 161 deaths in the UFT/leucovorin arm and 165 deaths in the 5-FU/leucovorin arm, the pattern of the curves look quite similar. It is also clear from examination of these curves that the curves are quite stable with very few censored events at early time points. These results are very supportive of the conclusion of equivalent survival as demonstrated in study 011.

This slide illustrates the curves for time to progression in the two treatment arms, which again appear very similar. At the time of this analysis, 320 of the 380 patients entered into the study had progressed. The median time to progression for the UFT and leucovorin treated patients was 3.4 months, compared to 3.3 months for the 5-FU/leucovorin treated patients. This difference was not statistically significantly different.

Results for the secondary endpoint of response rate are shown here. There were no statistically significant differences between the objective response rate seen for UFT/leucovorin and the 5-FU/leucovorin treated arms. There were, however, statistically significant reductions in the instance of leukopenia and neutropenia, both covering all grades of toxicity and, more importantly, severer grades 3 and 4 toxicities, favoring those patients treated with UFT/leucovorin compared to those patients treated with intravenous therapy. As in the 011 study, severe myelosuppression was uncommon in the UFT/leucovorin regimen.

The reduction in myelosuppression again led to a clinically significant outcome. Only 1 percent of the UFT/leucovorin patients experienced febrile neutropenia compared to 8 percent in patients treated with bolus 5-FU/leucovorin. For infection, there was a lower incidence overall for the UFT/leucovorin treated patients compared to the 5-FU/leucovorin arm, although no statistically significant difference was detected in the incidence of severe infection.

There were no significant differences in the incidence of the most common UFT/leucovorin associated toxicity, diarrhea. The percentages for any grade of diarrhea were lower amongst the UFT/leucovorin treated patients than for 5-FU/leucovorin treated patients. However, the percentage of patients experiencing severe diarrhea was higher for the UFT/leucovorin patients although neither of these differences achieved statistical significance.

The incidence of nausea and vomiting, either any grade or severe, was similar in the two treatment groups. The duration of GI toxicity, when it occurred, was similar between the two treatment arms.

One of the major safety advantages associated with the UFT/leucovorin regimen was the dramatic reduction in the incidence of stomatitis and mucositis. Despite the lower dose intensity of the 5-FU/leucovorin arm used in this study, stomatitis was still a major problem with this regimen. 55 percent of the 5-FU/leucovorin treated patients, compared to only 18 percent of the UFT/leucovorin treated patients, experienced some stomatitis or mucositis

during the course of their therapy. For severe symptoms of stomatitis or mucositis, which is an extremely painful and debilitating side effect, only 2 percent of the UFT/leucovorin, compared to 16 percent of the 5-FU/leucovorin treated patients, experienced this severe toxicity. Both of these findings were not only clinically but also highly statistically significant and these findings were consistent with those findings observed in study 011.

The incidence of hand-foot syndrome was extremely low in both treatment groups. There was no statistical difference between the two treatment arms.

The incidence of elevated liver function tests is illustrated here. There was no difference between the two treatment arms in the incidence of any or severe elevations in alkaline phosphatase or transaminases. The percentages of elevated bilirubin were higher for both categories, i.e., all grades or severe toxicities, for the UFT/leucovorin treated patients compared with the 5-FU/leucovorin arm. In this study, however, the findings did not reach statistical significance.

Overall the safety findings of the 012 study are consistent with the larger 011 study with the only trend towards worsening toxicity for the UFT/leucovorin treated patients being an isolated elevation in bilirubin levels.

This slide illustrates the percentage of patients receiving concomitant medications during the study. There were statistically significant reductions in the use of antiemetics, including 5HT3 blockers, for patients receiving UFT/leucovorin compared with the bolus intravenous arm. The use of anxiolytics was also lower amongst the UFT/leucovorin treated patients.

This slide shows the percentage of patients requiring dose reductions or a delay in retreatment. Patients were better able to tolerate the dosing regimen of 5-FU/leucovorin given in study 012 compared to study 011. In this study similar numbers of patients required dose reductions or dose delays in both treatment arms.

For example, UFT/leucovorin treated patients at course 4 required a dose modification in 38 percent of patients compared to 35 percent of patients on the

5-FU/leucovorin arm.

Nevertheless, even with the better tolerated 5-FU/leucovorin schedule used in the 012 study, significant safety advantages were again observed favoring the UFT/leucovorin compared with the bolus regimen.

The dose intensity of 5-FU and tegafur are shown here. The median 5-FU dose intensity of 418 milligrams per meter squared per week as delivered in this study compares to the 011 with a median dose intensity of 452 milligrams per meter squared per week, a reduction of only 8 percent. The median delivered dose intensity of tegafur is 1,542 milligrams per meter squared per week, which compares with 1,555 milligrams per meter squared per week in the 011 study. In this particular study, the 012 study, you can see that the relative delivered dose intensity was over 90 percent on both treatment arms.

The 012 study of 380 patients confirms the conclusion that, as an initial treatment for metastatic colorectal cancer, UFT/leucovorin produces equivalent survival to 5-FU/leucovorin. This equivalent efficacy is achieved with a regimen which results in significant

advantages in safety and in patient tolerability. These advantages include reductions in severe myelosuppression, febrile neutropenia, infection, stomatitis or mucositis, and less use of concomitant medication.

Dr. Renzo Canetta from the Bristol-Myers Squibb Pharmaceutical Research Institute will now make a few concluding remarks.

DR. CANETTA: Thank you, Jim.

As you've noticed by now, despite the differences of countless investigators and protocols, the consistency of the efficacy results obtained with oral UFT and leucovorin is quite striking. In both trials, the median survival exceeded 1 year, and the other efficacy endpoints were quite similar, thus supporting the predictability and the reliability of the efficacy effects of this compound.

For what we believe is the clinically most relevant efficacy endpoint -- and that is survival -- the hazard ratios of .96 and of 1.14 and the narrow variability of the confidence interval fully support the evidence that oral UFT and leucovorin is equivalent in effect to the

current standard of care of intravenous 5-FU and leucovorin.

Now, you've seen this slide before presented by Dr. MacDonald and we add the results of our two trials here. Now, it is important to point out that the evidence that supports equivalence is based upon a very large database. We are talking about almost 1,200 patients here, about the same size of several other the meta-analyses in the treatment of the disease.

Now, not only was the survival in the pivotal trial and the confirmatory trial comparable to the 5-FU and leucovorin arm, but it was also comparable to the 5-FU and leucovorin arm of all these trials that have been reported before. One thing that is important to point out is that all these trials that showed an advantage in survival for 5-FU and leucovorin in fact used a lower dosage than the one that was used for 5-FU and leucovorin in our pivotal trials. Here we used 425 milligrams per square meter. The Mayo clinic trial started with 370 milligrams per square meter, and only after the first time that patients were treated increased the dosage. This study used 370. These

two trials used 400 milligrams per square meter.

The other thing that appears from this trial is that UFT and leucovorin appears to provide survival that looks better than the 5-FU alone treatment using these historical controls.

The more aggressive dose regimen used in study 011 required in fact a rapid reduction of the dosage and delays in the treatment. That is, when you look at the delivered dose intensity, there isn't much difference between the two control arms of the two trials, and there is a mere 8 percent actual difference in dose intensity delivered between the two trials.

Now, the consistency of the results observed for efficacy is actually evident when you look at safety. No matter how intense was the 5-FU treatment delivered in the control arm, the UFT and leucovorin always came up with significantly reduced toxicity, and that is important for these categories that have clinical importance. This is not only lab test results and involves febrile neutropenia, severe infections, and severe mucositis across the two trials.

Now, the similarity of these findings is fairly remarkable, particularly if you keep in mind the fact that the vast majority of these investigators had no prior experience with UFT and leucovorin, and experience teaches us that one would expect that this profile would even be better as investigators gain more familiarity with the newer treatment.

Incidence of gastrointestinal toxicities both for diarrhea and nausea and vomiting was significantly lower for UFT and leucovorin in study 011. The elevations of bilirubin were significantly higher. However, the clinical impact of this observation was minimal. Only 1 patient -- and that patient was in study 011 -- discontinued the treatment because of bilirubin elevation. Only 1 patient in study 011 had elevated ALT values and only 1 patient in study 012 had elevated ALT values concomitantly with elevated bilirubin. 3 patients with elevated bilirubin also had elevated ALT values in this arm of this study.

The hand-foot syndrome with UFT and leucovorin was significantly reduced in study 011, and actually was

not observed at all in study 012.

In conclusion, what we believe is that oral UFT and oral leucovorin constitutes an important therapeutic advance in the treatment of metastatic colorectal cancer. Survival has been conclusively demonstrated to be equivalent to the standard of care in a large and well-conducted series of studies. The improvements in the safety profile for many toxicities are not only statistically significant, but are also clinically significant.

Finally, giving the option of an oral regimen constitutes an important alternative for the patients that are affected by this disease, and this is particularly true in view of the reliability and predictability of the effects of this treatment.

Thus, we propose that UFT capsules and leucovorin tablets be indicated for the treatment of first-line metastatic colorectal cancer, and we recommend the dosage of 300 milligrams per square meter divided in three daily doses for UFT accompanied by a dosage of 90 milligrams per day divided in three daily doses for

leucovorin, and the entire course to be repeated at intervals of 5 weeks.

Thank you for your attention. I would be happy to field the questions.

DR. SCHILSKY: Thank you very much.

Questions from the committee?

Let me start off with one question. I'm curious to know if there have been any comparative trials between tegafur and UFT that might help to discern the importance of the uracil to the combination.

DR. CANETTA: Dr. Benner will address this question.

DR. BENNER: There were some small randomized trials that were performed in Japan at the time that UFT was developed, but these studies were not specifically in metastatic colorectal cancer. There's one in breast cancer. And they tended to look in these small trials relatively similar.

The reason we don't think that that contribution needs to be further assessed now is because of the clear past experience with tegafur alone in this

country where the tegafur, when given as an oral regimen that produced survivals that appear worse than what we achieve now with 5-FU/leucovorin or with UFT/leucovorin in metastatic colorectal cancer, was associated with significant toxicities, so much so that the development of tegafur alone as an oral drug was abandoned in the U.S.

DR. SCHILSKY: Other questions? Dr. Johnson?

DR. DAVID JOHNSON: I have basically three questions. The first question has to do with the breakdown of data relative to prior adjuvant 5-FU therapy and how did that subset of patients fare as compared to those who had not received prior 5-FU.

The second question I have, while you look that up, has to do with second-line chemotherapy, and I'd like to know the subset analysis of those individuals who received second-line irinotecan and/or oxaliplatin.

And then the third question I have, while you look that one up, has to do with the mechanism of hyperbilirubinemia and what implications that has for drug-drug interactions and what sort of cautions we should be looking to in the package insert.

DR. BENNER: What we're looking for is a slide that will show you that the percentage of patients who received secondary chemotherapy in both the 011 and the 012 studies was actually very well balanced with regards to the percentage of patients receiving secondary chemotherapy. We do not know the specific types of secondary chemotherapy in the 011 study, but we do have that data for the 012 study.

What you can see, again, when you look specifically at the 012 study for the patients receiving secondary chemotherapy, that the regimens used were very similar within the two treatment arms so that the exposure to irinotecan and oxaliplatin actually look very well balanced across the two treatments.

DR. DAVID JOHNSON: Do you know in these 150 or so patients, from the point at which they were switched to their second treatment, what happened to these 150 patients?

DR. BENNER: Actually we'll ask Dr. Piantadosi to go through a landmark analysis.

DR. PIANTADOSI: Thank you. I'm Steve

Piantadosi from Johns Hopkins Oncology Center and a consultant to the sponsor on this drug.

We've looked very carefully at the effects of secondary chemotherapy not broken down by these particular drugs but any secondary chemotherapy, and I want to show you a couple of analyses that reflect on this that may be somewhat surprising.

The first slide is U12 which shows a proportional hazards model effect taking secondary chemotherapy as a time-dependent effect; that is, we model the effect of secondary chemotherapy when it occurred during the follow-up period and then its effect subsequently on the outcome of the patient with survival as the outcome here.

What you can see from this slide, first of all, is that the use of secondary chemotherapy has a hazard ratio estimate that's greater than 1, indicating that it is a risk factor for failure in these patients and that it's interaction with the treatment group is not significant either in terms of where the hazard ratio lies or the p value, indicating that this effect of secondary

chemotherapy, being an adverse risk factor, is the same in both treatment groups.

The next slide, U13, shows without the interaction, and since it was not significant, it was removed, supporting this as a risk factor. This seems backwards and so what we did were some additional exploratory analyses to try to understand why this would happen.

The next slide is U34 which shows a landmark analysis, stepping now away from the regressions but to a more traditional Kaplan-Meier approach. The treatment groups have been collapsed because the effect of secondary chemotherapy is the same in both treatment groups. What you see here is at each landmark time in 3-month intervals, we have taken those patients who received secondary chemotherapy at or before that time, so that it is a baseline risk factor with respect to this time, and looked at the subsequent outcome of those patients. And in this study, in 011, in all cases secondary chemotherapy is an adverse risk factor for outcome.

Now, there are a couple of different

interpretations of this, and the one that I favor is that when patients take a turn for the worse, it's evident clinically and they go on second line chemotherapy which probably has relatively little effect. Those patients who haven't taken a turn for the worse and don't need it are ultimately going to do better.

A second interpretation would be that second-line chemotherapy is in fact beneficial and that these patients would have done even worse had they not received it.

And, of course, a third interpretation is that they were doing marginally worse and that second-line chemotherapy is harmful.

But the point is, with respect to the empirical evidence in the data, it's a risk factor for adverse outcome.

DR. SCHILSKY: Don't you still have one question that still hasn't been answered?

DR. DAVID JOHNSON: Well, actually two, but I think Steve is going to the next one.

DR. BENNER: This is a slide that looks at your

first question with regards to the impact of prior adjuvant therapy. You can see that only a minority of the patients in the studies had received adjuvant chemotherapy and that the hazard ratios are very close.

So, these are the survival curves for the subset of patients that received prior adjuvant therapy.

Again, survival curves, UFT/leucovorin in yellow for patients who had not received prior adjuvant chemotherapy.

Now, Daryl Sonnichsen from BMS will address your question about the bilirubin.

DR. SONNICHSEN: Daryl Sonnichsen, clinical pharmacology.

With regards to your question about elevated bilirubins, we looked at possible pharmacological rationales for that. Preclinically in rats, the biliary excretion of tegafur and uracil is minimal. Tegafur and uracil metabolites accounted for about 3 percent and less than 1 percent of the radioactive dose that was excreted in the bile of rats. Of those metabolites that are excreted in the bile, tegafur and fluorureidoproprionic acid, or

FUPA, accounted for 90 percent of radioactivity.

In a study of 18 patients treated with UFT/leucovorin therapy, no associations between steady state pharmacokinetics and the incidence of course 1 elevation in bilirubin were noted, and I'll show you two figures following this to demonstrate that.

We did not come up with an apparent pharmacologic rationale for the development of this elevated bilirubin for this drug. What we know is that the tegafur and uracil do not appear to be substrates for transporters that may interfere with bilirubin at the level of the liver, unlike drugs such as protease inhibitors or cyclosporin. It does not have that pharmacology, so we wouldn't expect those.

Related to possible mechanisms of interactions, again we would expect that this is an isolated bilirubin. It did not have clinical sequelae. It would need to be monitored in those drugs more clearly in drugs that have a preponderance for bilirubin, but beyond that we don't have any further recommendations.

And can I just show the next two figures just

to show that in those patients with an elevated bilirubin in course 1, the AUCs for tegafur and plasma versus those that did not occur, the incidence, there was no apparent association.

And the next slide shows the same figure for 5-FU exposures. No apparent association.

DR. CANETTA: So, to summarize in a nutshell the three questions, the three answers would be the outcome in the patients who got adjuvant chemotherapy is equivalent in both subsets for whatever treatment was given.

For secondary chemotherapy, basically the same approach was used in both arms in both the trials. The 012 reflects the fact that oxaliplatin in study 011 were available in Europe. 011 we don't have the data. Obviously, oxaliplatin is not available in this country. But basically the investigators were equipoised and they proceeded in the same way whether the patient had been randomized to 5-FU/leucovorin or to UFT/leucovorin.

And finally, for the bilirubin, we don't know clearly the mechanism by which this elevation occurred, and yet what is important to say is that more than 80 percent

of the patients that had elevated bilirubin could continue to receive UFT/leucovorin and their value of bilirubin went back down. Of the 20 percent whose values did not go back, the vast majority had documented progressive disease in the liver, and it's difficult to separate out liver disease from these abnormalities.

The other thing, as I said before, elevation in liver enzymes did not seem to predict or accompany this type of bilirubin elevations.

DR. SCHILSKY: Dr. Krook.

DR. KROOK: I won't quite do what Dr. Johnson did. I think I have three questions also, but I'll try to do one at a time.

One of the things that was done with the study was a quality of life, and what we've seen here at least presented so far is toxicity, bilirubins, febrile neutropenia. What was the feeling of the people who were involved, the quality of life? Did the people who took the 5-FU/leucovorin have a poorer quality of life as far as they're concerned? At least I didn't see you present the quality of life.

DR. BENNER: For the 011 studies, the FLIC questionnaire was used as the subjective assessment of quality of life, and there were no statistical differences between the two treatment arms with regard to the scores on the FLIC questionnaire. This was despite the overwhelming safety advantages that I've shown you with regard to the CTC grading.

One possible explanation for that may be the fact that the FLIC questionnaire specifically addresses the quality of life for the patients in the 2 weeks preceding the questionnaire. You can see that those patients would have been 7 days from their last dose of UFT/leucovorin but would have been a much longer time, 22 days from their last dose of 5-FU, and it may be because of the IV regimen which causes severe toxicities associated with the nadir that the patients have recovered, and by the time the instrument was given, it was not able to detect the difference in quality of life.

DR. KROOK: What I think you're telling me, at least using that instrument, at least from the way it looks, there is not a difference in what the patient

perceives, although there's a difference in timing, and then we have to interpret that also. Okay?

DR. BENNER: That's correct. Using that instrument, there was no difference between the two arms.

DR. KROOK: And second is kind of a related question. The gentlemen at the open public hearing spoke how he was able to continue to do things. Were most of the people able to continue with their daily activities? And then the issue of the contribution of leucovorin. But the first one I think is, were most of the people able to continue their daily activities?

DR. BENNER: We'll pull up the figure.

DR. KROOK: I've got a comment. At least dealing with a lot of these people, it's nice that they can do their daily activities, do trips, but my perception is that either arm could perhaps do this.

DR. BENNER: So, this shows the time to the worsening performance status in the 011 study for the two treatment arms with the majority of patients starting out with a performance status of 0 or 1.

DR. KROOK: Now, they were measured at time of

evaluation, not --

DR. BENNER: This would have been reassessed at the start of each cycle.

DR. KROOK: Of each cycle, okay.

Following up on the chairperson's question, what is the advantage or disadvantage of leucovorin? We heard again from the open public hearing the gentleman who was a pharmacist say leucovorin is a potential mixup. Do you have any studies which suggest -- I saw what was presented -- the addition of leucovorin, perhaps the contribution with or without that? Obviously, if you have to take two pills, that's a problem, and all the things that were commented on.

DR. BENNER: When looking at the early preclinical experiment, the animal models suggested that animals that had been treated with UFT combined with leucovorin had a higher complete response rate than those treated with UFT alone. So, it was felt that because what we were trying to do was to replace 5-FU/leucovorin with another fluoropyrimidine and that for all fluoropyrimidine regimens used for metastatic colorectal cancer, leucovorin

is an important component with the exception of continuous, uninterrupted infusions, that given preclinical evidence that it added to the efficacy, as well as the existing clinical evidence for 5-FU and leucovorin, that it was most appropriate to develop it with leucovorin, and that the early results of the phase I and II studies showed response rates and a toxicity profile that suggested that the regimen had significant advantages.

DR. CANETTA: Yes. Dr. Carmichael wanted to make a comment on the daily quality of life. Since he's treated patients, I think it's appropriate for him to comment.

DR. CARMICHAEL: I think the issue that you were making was what was the impact on the daily life of people.

DR. KROOK: Right.

DR. CARMICHAEL: And what I would say is the majority of patients through most of the time, as you can see from the quality of life data, because the same in our study, the 012 study, there were no obvious differences in quality of life globally. But I think where it did make an

impact was in patients who had grade 2 or 3 stomatitis, and the number of days with stomatitis was substantially less in patients who were having the oral therapy. So, I think in a situation where you've got more mobility away from the clinic, as well as that you've got less days with quite a debilitating toxicity that does impact the quality of life, then that does have a significant impact for patients.

What we did see even more so in our study, the problem of interpretation, was the fact that we were out 30 days following the last 5-FU dose at the time of the quality of life assessment compared to only 7 days after UFT/leucovorin.

DR. SCHILSKY: Dr. Margolin.

DR. MARGOLIN: I have what I think is just one question, but it may be a little bit complex and it may be best left for the FDA reviewer. I'll let you decide Dr. Schilsky.

The question has to do with the study design and the choice of the type of 5-FU and leucovorin regimen, its toxicity, and the comparison of toxicities with the UFT/leucovorin. Presumably the agreement with the FDA in

the initial phase III study design was that showing equivalence or inferiority not lower than a certain level would be acceptable, but presumably that would also require a significant lowering of toxicities that must have been quantitated in some way and we haven't really heard that. We've just heard that the survivals were equivalent and that the toxicity was less in some systems for UFT and leucovorin. So, one of the questions is that and maybe that's best left to the FDA reviewer.

But the other question is the choice of the 5-FU and leucovorin regimen. The Roswell Park regimen is given once a week, usually 6 weeks out of every 8. That has been my experience and interpretation that one has a much better handle on patients when treating them that way because you assess them weekly. If you don't see them, you leave parameters for the nurses, and at the first sign of lowering of counts or mucous membrane toxicity, you have a chance to alter your therapy. And if you give 5 days in a row of therapy and then stop for 3 or 4 weeks, you are basically stuck with whatever toxicities you're going to see from those 5 days that are already gone. I would think

that we might see different outcomes here if the other regimen had been used, and I'd like the sponsor to address that.

DR. CANETTA: I'll take a quick shot at the questions starting from the second one, the choice of the so-called Mayo regimen as the control arm. Obviously we have dealt with the FDA, but we deal also with regulatory agencies around the world. And the reality is that the Roswell Park regimen is not approved outside of this country. Several countries only accept the Mayo Clinic regimen.

Honestly, we've been told that we could bias the trial against the control arm if we came in with a weekly type of regimen because the type of comments that we were presented was that the Mayo Clinic is short in time and then leaves the patient alone for a longer period of time. You can take it at face value.

The reality, though, is that we are doing a comparison of UFT/leucovorin versus the Roswell Park regimen. This has been done in the adjuvant setting. It's a very large trial by NASBP, and I should say adjuvant

setting for colon cancer. That trial has closed accrual with 1,600 patients. Obviously the results have not yet been publicly disclosed. I think that trial will give us a sense of what is the relative effect of UFT/leucovorin versus the Roswell Park.

I think also it will give us some sense of the effect of UFT/leucovorin on the liver function because we've been dealing here with patients that do not have up front a severe liver impairment or a liver impairment related to the disease.

Going back to the first question, the discussion all along with the FDA was on the .8 to lower boundaries. There was no established statistical goal for showing improvement in safety. Obviously the phase I and phase II program had been accurate at M.D. Anderson and other institutions to give us a sense that that would have offered safety advantages in addition of the convenience advantages. Again, once again, if we put that in the protocol, we would have been accused of being biased because everybody would say oral treatment may be better accepted by the patients than intravenous treatment. But

there was no stipulation in the protocol for advantages in safety, and yet the advantages in safety were vast, even exceeding our expectations.

DR. SCHILSKY: Ms. Forman?

MS. FORMAN: There's a lot of emphasis put on convenience for this drug which is a good goal, but traditionally I think patients who are receiving the 5-FU treatment have a prescribed routine for seeing their physician and a certain level of care and testing that takes place. And probably not only is that helpful medically, but it is also a good support system for the patient.

My question is what are you prescribing in this regard for patients who -- assuming this drug is approved, what level of care and follow-up and testing is going to be recommended and how is that going to be done?

DR. CANETTA: Two comments. First of all, I think that if you wanted the philosophy of going towards oral therapy, go towards what we think should be our overall philosophy: patients become more responsible about their own treatment. And in these particular trials,

patients were responsibilized. They were asked to look for diarrhea, were carefully educated and instructed not to play the hero, discontinue UFT at the first signs of diarrhea. They were contacted on a weekly basis by phone by nurses. So, I think that overall there was a more continuous responsibilization of the patient.

In terms of what we plan to do should this drug be approved, obviously as part of the package insert, we have prepared also a patient instruction booklet that will go through all the type of different things that the patient receiving this drug should be looking for.

DR. SCHILSKY: Dr. Lamborn.

DR. LAMBORN: I have a couple of questions just to understand the data. The guideline of the primary analysis was a demonstration that the hazard ratio was above .8, if I understand correctly. Obviously, if we are going to use that as a primary measure, it would be important to know the validity of the hazard ratio in terms of the modeling, and I wondered what had been looked at there.

DR. PIANTADOSI: Steve Piantadosi, consultant.

We were also concerned about this issue and it had been raised early on by the FDA. I have a couple of analyses that reflect on this. The first one is slide J14.

This slide shows on the horizontal axis follow-up time and on the vertical axis the estimate of the actual hazards in the two treatment groups. The motivation for the question is that the model that's used to estimate the hazard ratio is assuming proportionality of those hazards, which in this kind of display would be reflected by two parallel lines.

Now, one can look at this picture and say these lines are not parallel to one another, but we have several comments here.

Number one, these curves are drawn in the presence of near identity of the hazards in the two treatment groups, so that in fact they really are on top of one another. Had they been separated by a large treatment effect, they in fact would have been roughly parallel to one another.

In spite of that, there's a fix-up if you disbelieve that the hazards are proportional over all time.

For example, the agency noted that the survival curves crossed at approximately 24 months, and so we performed an analysis that estimated two different hazard ratios, one prior to 24 months and a second after 24 months, so that we'd be examining one hazard ratio during this period of time and another hazard ratio later. That analysis is shown on the next slide, which is J13.

I am sorry. Before we do that, this is the test, an explicit test of your question, nonproportionality the test rejects showing that the usual procedure for testing demonstrates the hazards are not proportional.

The fix-up or the analyses I referred to are shown on the next slide, which is beginning with J13. Actually let's skip J13 and go straight to J18.

So, in this analysis, we use the same model but we allow for two different hazard ratios, one early before 24 months and one late. You can see what happens. Before 24 months, we have a hazard ratio estimate that approximates that that we see in the entire study. It's over .9 the lower bound, in spite of the fact that this estimate is based on substantially fewer events than the

total, only the early events, is roughly equivalent to the regulatory objective. The late hazard ratio, after 24 months, is actually in favor of the UFT arm and the lower bound is almost demonstrating statistical superiority in the later time period.

The analyses that were presented originally in a sense average these two hazard ratios, which I personally don't think is inappropriate. But nevertheless, this is the answer to your question.

DR. LAMBORN: While you're up there, I'll ask you a second question, which others might also wish to comment on. Often in demonstrating non-inferiority, a one-sided confidence interval is used, and I noticed that in this case the more conservative two-sided confidence interval was specified. I wondered if there was a reason for that.

DR. PIANTADOSI: Not a very good reason, and that may be appropriate in this setting.

I appreciate the regulatory vagaries in trying to define the appropriate hurdle for equivalence. The one-sided bound I think was chosen initially and, if I remember

correctly, was specified in the protocol. The two-sided was used to be conservative primarily, and in addition the adjustment for that confidence bound, because of the interim analysis, is also an attempt to be conservative.

There's a lot of fixation on that lower confidence bound, and quite honestly, I'm not sure that it's a big worry, whether it's .82, .8, or .79. The agency is quite concerned about it, as evidenced by the preamble to their questions. But in fact, there's very little evidence in the data that support values of a hazard ratio at the lower confidence bound, as you know. The data are supporting very strongly a hazard ratio of around .95, and while we should have a look at the precision with which that hazard ratio is estimated, there's just as much support for a beneficial hazard ratio as there is for a harmful hazard ratio. So, I don't know that we need to focus too much on the lower bound.

DR. LAMBORN: I have one remaining question, back to a general one, which is the second study. Initially time to progression was stated as the primary endpoint, which I assume meant that when the study started,

you thought in fact that you would have a beneficial effect versus the regimen that you had selected there. So, I'd like a comment on the fact that that sort of slipped away.

DR. CANETTA: The second study was a confirmatory study and was a smaller study. It was designed with the notion at the time of it being not yet a meta-analysis, but several comparisons of continuous infusion regimens of 5-FU versus bolus regimens of 5-FU. And those trials, after being reported, although they did not show a survival advantage consistently, at least the dose at reported time to progression seemed to imply a time-to-progression advantage.

The other concern was the fact that with the disparity in the retreatment regimen in the first study, we needed to make sure that we had a study that addressed the time to progression issue at the appropriate time without reassessment bias.

DR. LAMBORN: Yes, but my question is one of the questions that has been posed is whether the control regimen in the second study was less than an optimal control, and the fact that you anticipated an improvement

in time to progression would imply that you also felt that this was in some ways a suboptimal regimen. So, I'm trying to understand because you did indicate you expected to have improvement, not equivalence.

DR. CANETTA: No. As I said, that was not the thinking. The thinking was that UFT and leucovorin would provide a more continuous exposure to the active moiety ultimately delivered, 5-FU, more like a continuous infusion, not mimicking a continuous infusion, but providing sort of mini-boluses to the patient. And if UFT/leucovorin behaved like a continuous infusion type of regimen, it could have shown a superiority in time to progression.

But we didn't believe that the 012 control arm was suboptimal. In fact, what has been used reflects what is the actual practice in several clinics around the world. And in fact, the dose intensity that has been administered supports that notion.

DR. SCHILSKY: Maybe let me just restate Dr. Lamborn's question because I still don't think you answered it. The briefing documents indicate that the analysis

plan, the statistical design of the 012 study, was based on a hypothesis that there would be a superior time to progression for the UFT/leucovorin arm. The study, as the data have been presented, indicates that that hypothesis is rejected, that in fact superiority was not achieved. So, I think that's at the heart of your question. In fact, it does lead to some other questions I guess about whether the study was sufficiently powered to accurately give us any other estimates since it was designed as a superiority trial.

DR. CANETTA: Again, the primary endpoint of that trial was, indeed, the time to progression, and that's how the sample size of the trial was calculated. In a regulatory type of environment, survival is the endpoint that is required, and this trial provides supportive evidence for that effect.

DR. SCHILSKY: Dr. Nerenstone.

DR. NERENSTONE: I just have two brief questions.

The first is neurotoxicity in the early evaluation of UFT was dose-limiting and a problem. What

was that neurotoxicity and was it looked for in these larger trials and what was found?

DR. CANETTA: I'm sorry. If I understand correctly your question?

DR. NERENSTONE: Neurotoxicity was discussed as being one of the reasons that UFT development did not continue forward in early --

DR. CANETTA: I'm sorry. Tegafur.

DR. NERENSTONE: Sorry. Tegafur. Was that looked at in these larger trials and what was the result?

DR. CANETTA: In fact, we happen to have the data because Mead Johnson, which is a subsidiary of Bristol-Myers Squibb, supported the IND for tegafur, and these data have been filed with the FDA as part of the IND for tegafur, and we pointed out these results.

Can we see the slide?

DR. BENNER: Under that IND, tegafur was studied in these six trials, some of which had a 2 to 1 randomization with a larger proportion of patients being assigned to treatment with the tegafur. That's why there's an imbalance with 127 patients treated with tegafur.

The patients enrolled compared to the current experience. The age is very similar. These are patients with metastatic colorectal cancer. There was at this time an inclusion of patients with worse performance status than had been seen in our current clinical trials.

7 percent of these patients out of all of the tegafur treated patients had a prior chemotherapy prior to the tegafur. The percentage of liver involvement was lower than in our trials where it was close to 80 percent.

Tegafur was given for 21 days split t.i.d.

Here looking at CNS toxicities. At the time the toxicities were assessed, this was prior to the CTC scale, and all grades were included. You can see that the CNS toxicities included headaches and dizziness predominantly, although some patients were reported to have confusion as well associated with the tegafur.

DR. SCHILSKY: Steven, I'm sorry to interrupt, but in the interest of time, could you just comment on the incidence of neurotoxicity in the 011 and 012 studies. I think that's what we really want to know, the neurotoxicity for the UFT/leucovorin.

DR. BENNER: The incidence was lower. I'm trying to pull up the exact percentage for you. The reason for that is that when you give the tegafur, as it's converted to 5-FU, the 5-FU is rapidly catabolized. So, when you have to give enough tegafur to get therapeutic plasma levels of 5-FU when you use it alone, you have a much higher concentration of tegafur, as you saw from the previous studies, and that is what contributes to the CNS toxicities that are seen with tegafur but not seen, as you can see, here, a lower incidence for the UFT/leucovorin. In comparison, in those trials I showed you, 33 percent of the patients treated with tegafur had a CNS toxicity at each course.

DR. SCHILSKY: That says peripheral nervous system. Do you have data on central nervous system toxicity?

DR. BENNER: You can see here for the two phase III trials pooled together.

DR. NERENSTONE: I guess my only other concern is that because these are good performance status patients and you saw perhaps a higher incidence in poor performance

status patients, if this oral medication is approved, you may actually be treating much worse performance status patients than here, and that might be something that needs to be talked about as a warning in terms of looking for problems in the future.

DR. CANETTA: We actually believe that there is a pharmacological reason why tegafur alone induces this type of toxicity. If you want, we can run through preclinical and clinical PK data demonstrating that it has nothing to do with performance status.

DR. NERENSTONE: No, that's not necessary at this point.

My other question is probably a more philosophical one. Somebody questioned the role of leucovorin, whether it was needed at all. I actually have a different question. The phase II study upon which the UFT dose was based, which was study 5, used a 500 milligrams per meter squared dose, but it used 150 milligrams of leucovorin. At that dose in the phase II study, a 44 percent response rate was seen, and that was the reason it was taken to the phase III trial.

However, in the phase III trial -- and I understand your reasoning -- the dose of leucovorin was halved or even more reduced. In fact, your response rate was 11 percent.

We're certainly used to seeing diminished results when you go from small numbers of phase II to a larger phase III, but a quartering of the response rate seems to be a bit dramatic. Do you have any thoughts about why that happened?

As a clinician, quite honestly, an 11 percent response rate in metastatic colon cancer is not very encouraging.

DR. CANETTA: We share your opinion of the relative value of response rate in this particular setting. Yet, the way we operate, particularly for a phase III trial, we are quite paranoid about reassessing response rates. So, the response rates that you see reflect the fact that we had responses confirmed with subsequent CT-scans and so on.

The reality, when you go back to the issue of the phase II, the phase II trials were done in single and

highly qualified institutions, and the dosage of leucovorin that was given was actually a super-saturating dosage. When we discussed the design of the phase III trial with the agency, we did address the issue of the fact that the dosage of 25 to 30 milligrams 3 times a day would result in total absorption of leucovorin.

Now, going back for one second to the leucovorin issue, obviously when we designed the trial, we wanted to make sure that UFT and leucovorin given orally was at least as good as the best accepted control arm. That is why we chose IV 5-FU and leucovorin as a control arm, not to be accused to be biased against the control arm. And we were aware of these trials that were maturing after the meta-analysis indicating there was a potential advantage for 5-FU and leucovorin over 5-FU alone. So, we simply wanted to make sure that the control arm was the, quote/unquote, most active and certainly the most accepted control regimen.

DR. SCHILSKY: We're running a little behind, so I'm going to ask for questions from Dr. Raghavan and Dr. Kelsen and, Scott, if you have a burning question, we'll

give you the last word. So, Derek?

DR. RAGHAVAN: I'm still confused which is, I guess, a chronic state of mind, but there's one major issue I don't understand.

I'm happy to accept that 11 months versus the 10 months comes out in my mind as about a year, and so I don't want to fight about median survival values.

But I'm very puzzled about a drug that is introduced for convenience, and I think it's pretty obvious that an oral drug is more convenient than a parenteral drug. If a more convenient drug, which has less mucositis and less myelosuppression, et cetera, is available, I don't understand why measured quality of life doesn't improve. The issue of how we measure quality of life has been covered extensively in the external reviews of what we do at this committee, and yet I'm still puzzled as to why there isn't a substantial measured difference in the patient preference of one drug versus the other. Could you talk about that in detail?

DR. CANETTA: I think that we share your puzzlement. Certainly there are two issues that are worth