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P R O C E E D I N G S (8:05 a.m.)

Agenda Item: Call to Order and Opening Remarks - Janice Dutcher, M.D., Chair, ODAC

DR. DUTCHER: This is the 56th Oncology Drug Advisory Committee meeting. My name is Janice Dutcher from Albert Einstein. I'm chairing the committee. I would like to go around the table and introduce the members of the committee. We'll start with Dr. Simon.

Agenda Item: Introduction of Committee

DR. SIMON: Richard Simon, Biometric Research Branch, National Cancer Institute.

DR. D. JOHNSON: I'm David Johnson, a medical oncologist from Vanderbilt.

DR. SWAIN: Sandra Swain, medical oncologist, Washington, D.C.

DR. SANTANA: Victor Santana, St. Jude's Research Hospital, University of Tennessee, Memphis.

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

MR. GIDDES: Ken Giddes, patient representative from Atlanta, Georgia.

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

DR. TEMPLETON-SOMERS: Karen Somers, the executive secretary to the committee, FDA.

MS. BEAMAN: Carolyn Beaman, consumer representative, Houston, Texas.

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

DR. OZOLS: Bob Ozols, medical oncologist from Fox Chase Cancer Center in Philadelphia.

DR. J. JOHNSON: John Johnson, clinical team leader at the FDA.

DR. SCHECHTER: Genny Schechter, medical reviewer at the FDA.

DR. DUTCHER: As you know, the drugs that are being considered for the next two days, some of them are being considered for supplemental applications. A number of our committee members have been involved in work related to these drugs, so we have had a fairly active conflict of interest discussion for the last couple of weeks. So we are going to be reading a conflict of interest statement for every drug at each application. So we are going to start with the first one.

Agenda Item: Conflict of Interest Statement - Karen M. Templeton-Somers, Ph.D., Acting Executive

Secretary, ODAC

DR. TEMPLETON-SOMERS: I'd like to thank the committee for their patience in undergoing the conflict of interest screening. It has been very comprehensive.

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

In accordance with 18USC Section 208 and 505 of the Food, Drugs, and Cosmetic Act full waivers have been granted to: Dr. Victor Santana, Dr. Kim Margolin, Kenneth Giddes, Dr. James Krook, Dr. Janice J.P. Dutcher, and Dr. Robert Ozols. In addition, full waivers under 18USC Section 208 have been granted to Dr. Richard Schilsky and Dr. Sandra Swain. In addition, a limited waiver has been granted to Dr. David Johnson. Under the terms of the limited waiver, Dr. Johnson will be permitted to participate in the committee's discussion of Gemzar, but he will be excluded

from participating in any vote related to this product.

A copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information officer located in Room 12A-30 of the Parklawn Building.

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

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

With respect to all other participants, we ask in

the interest of fairness that they address any current or previous involvement with any firm whose products they may wish to comment upon. Thank you.

DR. DUTCHER: We are now going to begin the open public hearing. One half hour has been allocated. The first speaker will be Catherine Adelson.

Please introduce yourself and state if there is any financial support from the company.

Agenda Item: Open Public Hearing I

MS. ADELSON: My name is Catherine Adelson. Hoffman-LaRoche bought my ticket and paid for my room.

I am a cancer patient at M.D. Anderson Hospital in Houston, Texas. I am here to verbally and visually acclaim the benefits of the drug capecitabine, also known as Xeloda, which has been developed by Hoffman-LaRoche.

I was first diagnosed with breast cancer in March 1987. I had a mastectomy and was symptom-free for two and a half years. In January 1990, a needle guided biopsy confirmed metastases to the bone, and I began what seemed to be a myriad of cancer drugs, which included several intravenous chemotherapy regimes.

In September 1996, my blood showed abnormal liver enzymes of prevens(?). By the end of October an ultrasound

confirmed two lesions on my liver. Beside liver metastases I had disease in a number vertebra, several ribs, the ilium, and the ischium and both femurs. Because of bone pain I was taking ibuprofen and percocet every 4-6 hours, 24 hours a day.

I found that that combination was no longer working well, and had had a prescription MS cotton filled, after briefly trying dilaudid, which made me feel worse. My oncologist at Anderson suggested I join a clinical trial in which they were participating. The drug was capecitabine or Xeloda.

My dosage was 4,600 milligrams a day taken orally for two weeks, and then one week off. By the end of the first cycle I was in less pain, and has quit taking the percocet. By the end of the second cycle I had quit taking the ibuprofen, because the pain had been reduced to minimal aching.

By April 1997, by five months into the treatment an ultrasound of my liver showed that the lesions were gone, and my liver enzymes had returned to normal. I don't think even Hoffman-LaRoche really believed this, because a month later they asked for another ultrasound, and they wanted to see the actual films.

So here I am, 17 months later I am still taking capecitabine. I have had two reductions in dosage amounts because of toxicity, however, the only side effect I have experienced is hand-foot syndrome, which I treat with lac-hydrin and bag balm. The intensity of redness varies depending on where I am in the cycle. By keeping my feet and my hands well lubricated, they do not hurt, and it is side effect which is very easy to live with.

At this time I still experience some achiness, but for the most part I take no pain medication. My physical activities are only minimally restricted.

The most recent ultrasound done in February of this year showed that my liver is still clear, and the blood work supports those findings. A bone scan done at the same time showed no progression, and some improvement in bone density.

I have always supplemented mainstream treatments with weekly prayer groups and a mind-body support group and visualization. These all helped quiet my sometimes anxious spirit. Prayer is my way of offering thanksgiving for this wonderful life I have, and gratitude for the researchers that made this restoration possible.

When I become fearfully depressed, my oncologist

reminds me that none of us knows our quantity of life. Capecitabine has done a remarkable job of improving my quality of life, for whatever quantity I may have.

Thank you for listening to me, and I hope you will approve this very, very fast.

DR. DUTCHER: Thank you very much.

The next speaker is Norma Broin from the Alliance for Lung Cancer Advocacy.

MS. BROIN: Better lung cancer drugs, choice --

DR. DUTCHER: I'm sorry, could you just tell us if you are supported?

MS. BROIN: I'm my next line.

DR. DUTCHER: Okay.

MS. BROIN: Save lives. My name is Norma Broin. I am a non-smoking lung cancer survivor of eight years. I am here to speak on behalf of myself, and on behalf of Peggy McCarthy's organization ALCASE. ALCASE is Alliance for Lung Cancer Advocacy, Support and Education. This is the only lung cancer support organization in the nation that support people with lung cancer and their families.

Their logo is a transparent ribbon. It symbolizes lung cancer's lack of visibility; its invisible lack of financial and research support in society. It is as if the

word "lung cancer" has become a dirty word, a shameful word, a word not to be spoken.

True, a significant number of lung cancers occur in people who smoke. True, 3,000 non-smokers will die from lung cancer each year because of exposure to passive smoke. My lung cancer, adenocarcinoma was diagnosed as having come from passive smoke in my enclosed work environment of airplanes as a flight attendant. Three thousand environmental tobacco smoke deaths would be equivalent to a wide body jet, a DC10 crashing every month of every year, year after year after year.

True, 10 percent of lung cancer deaths each year will be those exposed to radon, asbestos or occupational exposures. Lung cancer is a tragic word. It is not a dirty word. No one deserve to die from lung cancer. The morbidity of lung cancer demands that we hurry and seriously address. Why do so many die? Why do so few live?

Who will speak for lung cancer? I am asking those of you on this Oncologic Drug Advisory Board to by our advocates, to be our voices in the way lung cancer is addressed and acted upon. Years ago I met with a doctor who was the senior compiler and writer of the 1986 Surgeon General's Report, "The Health Consequences of Passive

Smoke." When I met with Dr. Burns, I said, "Dr. Burns, I find it really difficult to believe that I would be one of the first to speak out about passive smoke and lung cancer."

Dr. Burns leaned back in his chair, folded his arms over his chest and said simply, "Norma, people don't live to talk about it." I thought well, we'll see about that.

I left his office at San Diego State University, and from a pay phone there called a fellow flight attendant who also had lung cancer. I said, "Carol, will you speak out about lung cancer with me?" Carol said yes. Carol was dead six months later, leaving behind a 2 year old son. At time my children were 5 and 7.

The grim reality is that lung cancer survival today is not appreciably better than it was when I had lung cancer in 1989. Why? I realize that early detection is a problem, but lack of early detection should not be used as a excuse to say we can't treat or cure cancer.

For this meeting I called my brother-in-law, who is an oncologist-hematologist. He was on the front lines of treating cancers and lung cancers. I asked him, "What do you think the problem is?" He said, "Norma, we need better lung cancer drugs." I will take it a step further than

that. We need not only better lung cancer drugs, we need better late stage lung cancer drugs, since that is when so many lung cancers are discovered. We need a variety of lung cancer drugs for the various types of lung cancers.

I would like to see earlier and better diagnostic testing for lung cancer. I would like to see the lung cancer patients to be educated by their doctors. Cancer patients should not be spectators in their treatment of lung cancer. They should be an active participator with the doctors who care for them.

Knowledge is empowering. With knowledge, people can make the best choices for themselves. They can choose the treatment that will afford them the best quality of life, knowing the pros and cons of each drugs that is put into their body. With choice comes hope. Give the lung cancer patient hope.

I cannot praise the organization ALCASE enough. Support of lung cancer patients is one of the many aspects of this organization. For a lung cancer patient to speak with another lung cancer patient of like cancers is not only therapeutic, it can be life saving. When one says, this is working for me. Maybe you should ask your doctor about it. Or, if you fly there, they are doing this particular

treatment.

Networking and connecting, empowering the lung cancer patient, giving a choice is important. I'll tell you why. This is not a big thing, but it was very important to me. After my lung cancer surgery, I wanted to know others who had survived their lung cancers. I wanted a hero. I wanted a success story. Where I couldn't find any lung cancers, anybody who had any type of lung cancer, who had survived longer than I had, became my hero.

When the media print that I'm a lung cancer survivor, I receive calls from people who have lung cancer, or the calls from the family members wanting to know what worked for me. I do not have an unlisted phone number for that very reason, so that people can contact me, because I know how important it was for me to have a hero, to have a success story, a person who survived lung cancer. I listen. I share what I know, and then I direct them to ALCASE. It just means a lot to know that somebody has beaten their lung cancer.

I realize there is an a economic issue of treating lung cancer or any cancer, but it seems people with lung cancer in many cases are just written off as unsalvageable and sent home to die. No choice. No hope. Sometimes in

the realities of business, we forget the human factor and what being part of humanity is all about. It is about hope, wants, desires, feeling, loving, laughing, compassion. It is about life. It is about living.

Because eight years ago I did not die from lung cancer, I will share a little of what an additional eight years has meant to me in my life. I have lived to see my son, who had a serious speech difficulty, be able to overcome it and become his school's representative in debate. I have been there for him to pin his Boy Scout pins on me. I have been there for his academic and sports accomplishments. I have been there for him.

I lived to see my daughter get her learner's permit, and I now hope to live through the practicing expertise of this part. I have been there for this young girl as metamorphosed into a beautiful young woman. I have been there to see her academic, athletic, and religious accomplishments. I have been there for her.

I have lived to see the first class action suit filed against the tobacco companies that I put together to go trial. I have climbed Mt. Fiji with my family. I have been able to serve in my community and in my church. I have lived to see my husband advance and achieve success in his

military career, and I was there by his side. I was there to see his devotion to family, religion, his country. I was there for him.

My purpose in speaking before you today has been to ask you, the advisory board, to be advocates for those with lung cancer, or those who will have lung cancer. To implore you to spend the money to do the lung cancer research. Spread the word that lung cancer is a tragic word. That it represents a disease that society can no longer ignore.

Give people with lung cancer hope. Give people with lung cancer choice. Give people with lung cancer better lung cancer drugs. Spend the money, do the research for the treatment and the cure. Give people with lung cancer life.

Thank you.

DR. DUTCHER: Thank you very much. We have another statement.

DR. TEMPLETON-SOMERS: This statement was received too late yesterday to be included in the agenda. It is the from the National Alliance of Breast Cancer Organizations, and I would like to read it into the record for you. I have been asked to read this statement by Amy Langer, executive

director of NABCO, the National Alliance of Breast Cancer Organizations, who regrets that she is unable to appear in person before the committee today.

The National Alliance of Breast Cancer Organizations is the leading non-profit resource for education and information about breast cancer, and a network of 375 member organizations. We serve patients, survivors, members, medical professionals, policy-makers, the media, corporations, and the general public through publications and phone, fax, and Web site access to our information services department.

Among those with the most urgent need for our help and direction are women with advanced treatment resistant breast cancer. Despite encouraging advances, medical science still has limited treatment options to offer these women. Experts often disagree on the course of their care, and cure is not available. It has been reported that over 1,000 different systemic therapy regimens for breast cancer are currently in use, but they employ only a handful of active drugs.

These facts come as a confusing and cruel surprise to most women in their families once advanced breast cancer is diagnosed. Breast cancer affects women physically,

psychologically, financially, and socially in harnessing the resources to cope with the full toll of the disease often demands every ounce of strength a woman and her family can muster. A sense of desperation can often threaten the equilibrium a woman and her supporters struggle to maintain, once it becomes clear that she has exhausted all therapeutic options.

At this particularly vulnerable time in a woman's battle with disease, NABCO seeks to reassure her that she has not failed therapy, but rather that therapy and the current achievements of scientific research have failed her. Women need and deserve to be encouraged by their caregivers to keep the battle going, and to know that the active treatment phase of therapy has not concluded prematurely. The good news is that several agents have shown promising results in initial investigation and offer hope, even for the most treatment resistent breast cancers that so far defy aggressive systemic approaches.

Understandably, women with few or no more treatment options are devastated, and they are also angry. This anger and the legacy of frustration and helplessness that families feel after women's death from breast cancer has fueled one of the effective public policy movements for

our time. The letters, visits, and in your face life lessons of hundreds of thousands of survivors and supporters has brought about a dramatic increase in the amount and sources of funding for breast cancer research.

We encourage the committee to keep these survivors and supporters in mind, and in particular, those who are facing third or even fourth line treatment. If there one common plea behind the activism of women living with breast cancer, it is this: give us more treatments to try; let us take our chances with agents that may keep us alive, even if a cure remains elusive.

Women with everything to lose are risk takers, as callers to NABCO consistently demonstrate. Patients, family members, as well as clinicians seek the most up-to-date information from NABCO. Those with unresponsive disease are among the most challenging for us all. We share in and accept the frustration that advances against breast cancer must often be incremental, rather than the giant steps we hope for.

The work of this committee should be influenced by the accelerated pace of patient knowledge and needs, which must always be balanced by adequate and compelling scientific evidence. We hope that increased funding for

breast cancer research will offer a rich pay off, especially in illuminating what causes the disease and how to prevent it, but in the meantime, all we can do is find breast cancer and treat it.

The best treatments in the world cannot yet reliably prevent breast cancer from returning, newly aggressive and powerful beyond our current ability to conquer it. However, we will certainly help physicians manage advanced and metastatic breast cancer by offering new and different agents that prolong women's lives, consistent with good quality of life, with this informed decision determined by each woman herself

, not by aggregate statistics.

If we can make more active agents available to women with advanced breast cancer, we can hold out the hope that these women will be alive to greet the news of a breakthrough, and perhaps one day a cure.

Thank you for your attention.

The statement of disclosure says that NABCO has received unrestricted financial support from the three corporations with agents to be reviewed by the Oncologic Drugs Advisory Committee at this meeting: Eli Lilly and Company, Hoffman-LaRoche, Incorporated; and Bristol-Myers

Squibb Oncology.

Thank you.

DR. DUTCHER: Well, the committee does appreciate the eloquent and courageous statements from patient groups and from individual patients. We appreciate your input, and we certainly will take it into consideration as we talk about these agents, because we all would like new drugs for these diseases.

So with that, I think we will go ahead. Are there any other statements? Then we will proceed with the discussion of gemcitabine, and we'll start with the sponsor's presentation. Dr. Pederson.

Agenda Item: NDA 20-509/S-005 Gemzar (gemcitabine HCI) - Eli Lilly and Company, Sponsor Presentation, Introduction - Anders Pedersen, M.D.

DR. PEDERSEN: My name is Anders Pedersen, and I am the medical director of the Gemzar team at the Lilly Research Laboratories.

Gemzar has been approved for the treatment of locally advanced and metastatic pancreatic carcinoma. Today we are seeking additional approval for gemcitabine as a single agent, and in combinational with cisplatin for the treatment of patients with locally and metastatic non-small

cell lung cancer.

Gemcitabine is a nucleotide with two fluoride molecules substituted into the general position here, and which is named gemcitabine or Gemzar.

I'll briefly go through the mechanism of action. The active metabolite dFdCTP competes with dCTP for incorporation into the DNA, thereby inhibiting the DNA synthesis. The mechanism with which it does that is masked DNA chain termination, because after the dCTP is incorporated into the DNA molecule, an additional nucleotide is allowed to be incorporated into the DNA stream.

This seems to prevent the normal DNA polymerase from repairing that defect that is caused by the incorporation, thereby making it more difficult to change the DNA back to a tumor cell.

In addition, depletion of the nucleotide pools in the cells by inhibiting the ribonucleotide reductase. This causes a general depletion not only of the dCTP with dFdCTP competes for inclusion to the DNA strip, but also generally decreases other nucleotides needed for DNA and RNA synthesis. This is a unique intracellular prolonged half life that we see with this nucleotide is caused by the inhibition of the intracellular deamination of the compound.

After my introduction, Prof. Einhorn will give an overview of chemotherapy in non-small cell lung cancer. Following the overview, Dr. Alan Sandler from Indiana University will present a study of JHEX. This study was agreed with the FDA as a pivotal study with survivor's endpoint for the full mature data set of 522 patients.

In addition, it was agreed that where there are data, interim analysis would be performed when 300 patients were enrolled into the study, with an endpoint of time to phase of disease and response rate as the primary endpoints provided that we could provide the full survival data on the whole population subsequently. Dr. Alan Sandler will then present both the interim analysis on the 522 patients that is now mature.

Following that, Dr. Rafael Rosell from Barcelona, Spain will present two controlled supported, randomized studies, the first one being gemcitabine and cisplatin versus at that time the study was initiated the most widely used combination being cisplatin and etoposide, the other one being gemcitabine as a single agent also against the widely used combination, at that time cisplatin and etoposide. Finally, Prof. Einhorn will summarize the Phase II studies and draw all the conclusions from the

presentations.

In addition, we have with us today consultants. We have Paul Bunn from Colorado University. We have Dr. Claude Denham, who is one of the main investigators of the JHEX study, and Prof. Dewey Conces, who is professor of radiology, and has been one of the independent reviewers assessing the response rates of the pivotal JHEX study.

Dr. Einhorn.

Agenda Item: Sponsor Presentation, Overview of Chemotherapy in NSCLC - Larry Einhorn, M.D.

DR. EINHORN: Good morning.

Lung cancer is a major problem in the United States and much of the world. This introduction slide pales in comparison to the very elegant and eloquent presentation we heard earlier from Norma, the ALCASE representative. She put this on a personal and on a national basis, with the problems that we, as physicians, and she as a cured patient face dealing with this dreadful disease.

In 1998, this year, we will see 171,500 newly diagnosed cases, and sadly, 160,000 death from lung cancer. Not only is this the number one cause of cancer deaths in men and women in this country, but it actually exceeds the

numbers two, three, and four causes of cancer death combined.

Today we will be talking specifically about non-small cell lung cancer, which comprises 75 percent of all cases of lung cancer. For patients who are diagnosed with non-small cell lung cancer, the initial immediate decision is whether their disease is operable and receptable, however, even after surgery the great majority of patients with lung cancer will recur within two years, and become candidates for some form of chemotherapy.

In the past, 15-20 years ago, the primary basis of chemotherapy for non-small cell lung cancer was based upon the two drug combination of cyclophosphamide and adriamycin or doxorubicin. These were three common regimens that were used 15-20 years ago: the CAP regimen, which included cisplatin; the CAMP regimen, which included methotrexate and procarbazine; and the MACC regimen, which included methotrexate and CCNU.

Despite promising single institution studies with reasonable response rates and survival time, these older regimens were not able to be confirmed by American cooperative group studies from the Southeast, Eastern Cooperative Oncology Group, showing very low response rates

and relatively meager median survival times.

During the past 15 years, the basis of almost all chemotherapy regimens has included a platinum compound. In the decade of the 1980s, there was controversy as to whether platinum-based chemotherapy had a salutary effect upon survival for patients with disseminated lung cancer. Several meta-analyses were done because some positive studies were seen, and other studies were negative compared to best supportive care.

This particular meta-analysis published in the Lancet five years ago evaluated seven published studies including 706 patients, where a platinum regimen was compared to no chemotherapy. There was a modest, but statistically significant improvement in survival for disseminated lung cancer associated with platinum-based chemotherapy. Well, despite the findings that platinum chemotherapy was superior to no chemotherapy at all, there remained controversy as to whether one form of platinum therapy was superior to any other form of platinum therapy.

This very nice research study by Dr. Ted Splinter, published in 1990 in the European Journal of Cancer retrospectively reviewed almost 4,000 patients in 27 published studies, platinum regimen A versus platinum

regimen B, with a wide variety of response rates, but sadly virtually no evidence that one platinum-based regimen was superior to another platinum-based regimen, as 26 of these 27 Phase III studies failed to substantiate and prove survival of platinum combination A versus platinum regimen B.

An example of several of these studies have been done by the American Cooperative Group System. This Southwest Oncology Group study randomized 680 patients to five different arms, cisplatin/etoposide; cisplatin/etoposide with metho-GAG(?); cisplatin plus vinblastine; mitomycin-C, vinblastine, cisplatin, the MVP regimen; and an alternating regimen with 5-FU oncovin, or vincristine or mitomycin-C, alternating with the CAP regimen, with relatively low response rates, and a median survival time within a very narrow range of 4.9 to 5.9 months.

The only regimen that had a response rate greater than 24 percent was also associated with the lowest median survival time in this large Phase III study.

The Eastern Cooperative Oncology Group randomized 486 patients to this four armed regimen: the CAP regimen; the MVP regimen; cisplatin plus vindesine; and etoposide or

VP-16 plus cisplatin. Response rates ranged from 17 to 31 percent; survival from 5.3 to 6.2 months, again, a very narrow range of survival. Once again, the regimen that curiously had the highest response rate, was associated with the lowest median survival time.

This ECOG study randomized almost 700 patients to five different regimens: MVP; cisplatin plus velban; MVP alternating with CAMP; single agent carboplatin or single agent CHIP, a platinum analog. The response rates were 6 percent to 20 percent, and with the exception of this outlier of carboplatin of 7.4 months, median survival time again was in the very narrow range.

Carboplatin is a single agent, and another cooperative group, the CALGB did not have anywhere close to this type of median survival time with single agent carboplatin.

Well, in the 1990s there has been a resurgence of interest in chemotherapy in non-small cell lung cancer, not based upon new permutations and combinations of these older agents, as shown on these multiple slides, but based upon newer agents, the taxanes, and tomorrow you will hear the Bristol-Myers Squibb presentation for paclitaxel; ironotecan or CPT-11, a topoisomerase-1 inhibitor; vinorelbine or

navelbine. This drug was recently approved by ODAC and the FDA for treatment of non-small cell lung cancer, both as a single agent, and in combination with cisplatin. And of course this morning's presentation with gemcitabine.

Vinorelbine or navelbine has been studied in Europe, especially in France where it came from, and in the United States as a single agent; 1,146 patients in 15 studies have been reported in the report by Thierry(?) LeChavalier, which was presented at the Dublin World Lung Cancer Congress, and published earlier last year.

The overall response rate as a single agent was 24 percent, however, more recent studies and in the United States, that response rate is closer to 15 percent, with a median survival time of 32 weeks.

Vinorelbine was compared in Phase III study to a regimen that was not known to have any effectiveness in the treatment of non-small cell lung cancer, 5-FU plus leucovorin. A 2:1 randomization was done for patients with favorable performance status and not prior chemotherapy. This Phase III study confirmed the lack of efficacy, at least as measured by response rate, with 5-FU plus leucovorin with a modest 12 percent response rate, with single agent vinorelbine. However, there was a favorable

impact upon survival, with 25 percent one year survival within vinorelbine compared to 16 percent with 5-FU plus leucovorin.

A Phase III study was also done in Europe. This Phase III study compared monotherapy with vinorelbine, versus vinorelbine plus cisplatin, versus a different vinca alkaloid vindesine plus cisplatin, with the same high dose cisplatin on both arms.

This was a multi-center European study, reported by Thierry LeChavalier. Over 600 patients entered this study. As is common in many European studies, almost half of these patients had Stage III rather than Stage IV disease. Favorable performance status, as 80 percent of these patients had performance status 0 or 1.

This Phase III study demonstrated several things. First of all, single agent vinorelbine, with this modest 14 percent response rate was competitive to the more toxic cisplatin plus vindesine regimen as far as response rate, and as far as median survival was concerned. This is not dissimilar from a study you will be hearing later this morning comparing single agent gemcitabine to the combination of cisplatin plus etoposide, which will be presented by Dr. Rosell.

More importantly, this Phase III study demonstrated the superiority of the combination of cisplatin plus vinorelbine compared to cisplatin plus vindesine, with a statistically significant improved response rate, and an improvement in median survival time. This database formed the grounds for approval of vinorelbine for both single agent and in combination with cisplatin.

This Southwest Oncology Group study was completed after the FDA approval for vinorelbine in non-small cell lung cancer; 432 patients randomized to single agent cisplatin at 100 mg/m^2 versus the same cisplatin plus vinorelbine. All patients had favorable performance status, 0-1.

I would like for the committee to try to keep in mind these figures as we listen to the gemcitabine presentations that will follow my talk. The response rate for cisplatin plus vinorelbine was 26 percent compared 12 percent for single agent cisplatin. Eighty-one percent of the patients on the combination had Grade 3-4 granulocytopenia, compared to 5 percent. This is not surprising, as when we combine two drugs, with one of them being myelosuppressive, to single agent cisplatin, a drug that is largely devoid of myelosuppression, this is the

figure that one expects to see.

Progression free survival, two month improvement. Overall survival, two month improvement. One year survival, up 36 percent. Again, if we can keep these figures in mind as we listen later to the gemcitabine presentations. Two month improvement in progression free; two month improvement in overall; and 36 percent, one year survival.

This is what the survival curve for this study demonstrated. The curve on top was cisplatin plus vinorelbine. The curve on the bottom was single agent cisplatin.

Well, with that as a brief introduction to chemotherapy in non-small cell lung cancer, I would like to now introduce Dr. Alan Sandler, who will be discussing the Phase III study of single agent cisplatin versus cisplatin plus gemcitabine, study JHEX. Alan.

Agenda Item: Sponsor Presentation, Study JHEX - Alan Sandler, M.D.

DR. SANDLER: Thank you, Larry.

As Dr. Einhorn mentioned, the study I will present is a pivotal trial called JHEX, comparing single agent cisplatin to the combination of cisplatin plus gemcitabine in patients with advanced metastatic non-small cell lung

cancer. This was randomized, multi-national, multi-center trial that was conducted in 5 countries at 55 sites by 70 investigators.

From August 1995 to February 1997, 522 eligible patients were entered on study. For the purposes of the interim analysis the accrual was from August 1995 through August 1996, a total of 309 eligible patients.

This study was based on Phase II trial conducted by the Hoosier Oncology Group involving 28 eligible patients with advanced non-small cell lung cancer that revealed a response rate of 31 percent and a median survival of 8.4 months.

The schema for the study is depicted here. Patients were stratified by disease stage as defined by status IIIA, IIIB, or Stage IV, and by performance status using the Karnofsky scale and grouping patients in Karnofsky performance state 70 and 80 versus 90 and 100.

Patients were randomized then to receive one of two arms, a control arm of cisplatin 100 mg/m^2 given 1 day every 4 weeks, or the experimental arm of the same dose of cisplatin, with addition of gemcitabine in 1 gm/m^2 given on days 1, 8, and 15, again, cycles repeated every 4 weeks. Nonprogressing patients were allowed to receive a maximum of

6 cycles therapy.

The endpoints for the complete study were survival. In a prospective statistical design that was designed to detect a 33 percent difference in median survival with a power of 80 percent or greater, requiring a total of 520 patients.

Secondary endpoints for the overall study included objective tumor response, and various time-to-event efficacy measures such as: time to progressive disease; time to treatment failure; time to objective tumor response; duration of response for responding patients. Also relative toxicities between the two arms, and changes in quality of life.

As was noted by Dr. Pedersen, the majority of my discussion will be on the interim analysis, whose primary objectives, as previously agreed upon by the FDA and Eli Lilly were objective tumor response and time to progressive disease. Again, a prospective statistical design was attempted to define a two months difference in time to progressive disease that was also felt to be clinically relevant. It was powered to have at least 80 percent, and it was requiring actually 300 -- that's a typo.

The inclusion criteria for this study is as

follows: histologic or cytologic confirmation of non-small cell lung cancer, again, patients must have been staged as IIIA, IIIB, or Stage I; patients must have received no prior chemotherapy; and prior radiation therapy was allowed only if not involving indicator lesion or lesions; Karnofsky Performance Data Scale was used 70-100; and again, patients must have adequate bone marrow reserve as manifested by a hemoglobin 9, a platelet count of 100,000, and a total white count 3,500.

Summary of baseline disease characteristics, again for the interim analysis involving 309 patients as listed in the next two slides. The median age overall was 63. Two-thirds of the patients were male, and the usual histologic diagnoses for non-small cell lung cancer are depicted here. There appears to be a slight increase in the number of patients with adenocarcinoma in the cisplatin alone arm, at 49 percent versus 30 percent, but all these disease characteristics were not statistically significant between the two arms.

Further baseline disease characteristics, again for the interim analysis. Two-thirds of the patients had metastatic disease, one-fourth of the patients had Stage IIIB disease, and less than 10 percent of patients in either

arm had Stage IIIA disease.

Performance statuses listed here. Again, bear in mind the stratification was grouping 70 and 80 versus 90 to 100. When this was performed, there was no statistical difference again, between the two arms.

Efficacy results for the interim analysis of 309 patients reviewed a tumor response of 32 percent for the combination of gemcitabine and cisplatin, versus only 10 percent for the control arm of cisplatin alone. This was highly statistically significant, with a P value of less than 0.0001.

It should be noted that all responses were reviewed by an independent panel that included two radiologists, all of whom were blinded to the treatment arm.

I would like to take a moment to show three slides that illustrate one responding patient that was in question between the FDA's interpretation of response and ours. This is a patient, a middle-aged gentlemen with squamous cell carcinoma with a tumor mass that is obvious here. It is spending out flora. This is a pre-treatment CT scan.

For CT scan performed after two cycles of therapy illustrate the virtual resolution of the mass, with essentially unmeasurable disease remaining behind.

Confirmation scan is listed here. Again, this patient was considered a partial remission by Eli Lilly, however, by the FDA there were no distinct measurements that could be given here, and it was felt to be non-valuable.

This is the Caplan-Meyer(?) Curve showing time to progressive disease, again for the interim analysis. Median time to progressive disease with the combination arm was 5.8 months, versus the control arm of cisplatin at 3.7 months. This is a difference of 2.8 months, and the Caplan-Meyer Curve is depicted here, and obviously separated between the two.

I will comment on the efficacy results from the final analysis, commenting only on overall survival, 522 patients, median survival in favor of the gemcitabine/cisplatin arm at 9.1 months, versus the median survival of the cisplatin alone arm at 7.6 months, a difference of 1.5 months. That was highly statistically significantly different. One year survival probability of 39 percent versus 28 percent.

It should also be commented upon that similarities between the two treatment arms as seen in the interim analysis, such patient characteristics, toxicities, and response rates were consistent as well in the overall

analysis.

This is the Caplan-Meyer curve again for all 522 patients entered on study illustrating the overall survival differences between the two treatment arms. Gemcitabine and cisplatin in the yellow here, and the cisplatin only arm in orange, here.

A question was raised by the FDA statistical reviewer concerning potential differences in survival outcomes between patients treated in North America versus those patients treated in Europe based upon this retrospective Cox proportional hazard model for survival. Three factors that were utilized were treatment, region (Europe versus North America), and then treatment by region interaction.

As you can see, the only real statistical difference, a significant prognostic factor was for treatment, and there was clearly no statistical difference by region. The P value for treatment by region interaction was only 0.0880.

To further evaluate this question the sponsor performed a similar retrospective Cox proportional hazard model for survival, including the three factors that were previously mentioned, in addition to other known prognostic

factors for metastatic non-small cell lung cancer which included: disease stage; age; performance status; and gender.

As you can see here, once again treatment becomes the statistically significant prognostic factor. There is no statistical difference seen for region or treatment by region, and the usual prognostic factors seen for metastatic non-small cell, such as disease stage and performance status, again becomes statistically significant.

This point is further illustrated by this Caplan-Meyer curve which shows the overall survival for patients treated on the gemcitabine and cisplatin arm in yellow, and then a slide here in red looking at the gemcitabine and cisplatin arm for patients only treated on North America, which is virtually superimposable on that of the gemcitabine/cisplatin overall curve. Should in fact these statistic be driven by the European nations, one would have expected it would have been inferior to that of the overall curve.

Next I will be discussing toxicity, here, hematologic toxicity, again centering on the interim analysis of 309 patients. Not unexpectedly, the combination arm of gemcitabine and cisplatin had statistically more

significant Grade 3 and Grade 4 hematologic events when compared to the non-myelosuppressive single agent cisplatin.

An important point, however, is that despite the increase in percent of patients experiencing Grade 3 and Grade 4 neutropenia, there was only 4 percent of patients experiencing febrile neutropenic episodes on the combination arm, versus only 1 percent on the control arm of cisplatin. This was not statistically significant.

More patients did require aggregate blood cell transfusions at 34 percent versus 10 percent, however, the majority of these aggregate blood cell transfusions occurred later in the course of therapy, and given the larger number of responders on the combination arm, the median number of cycles received for patients on the combination arm was 4 versus 2 on the cisplatin alone arm.

Although there was an increase in the number of patients requiring platelet transfusions on the combination arm, there were no serious hemorrhagic events seen in either arm. Also importantly, there were no toxic deaths on this study in either arm.

Further toxicity evaluation, looking at renal and hepatic functioning as manifested be elevations in creatinine or transaminase at Grade 3 and Grade 4; there are

no statistical differences between the two arms, and exceptionally low as well.

Nonlaboratory toxicities -- nausea, vomiting, alopecia, neuro hearing, and neuro sensory -- there are no statistical differences between the two arms.

This slide looks at other nonlaboratory toxicities involving fever, infection, dyspnea, and hemorrhage. Again, there are no statistical differences between the two arms. I would like to comment on the incidence of Grade 3 and Grade 4 dyspnea in patients on this study; 10 percent for the combination arm of gemcitabine and cisplatin, versus 6 percent on the cisplatin alone arm.

Reviewing the individual patient data with notes that in only one patient on either arm could the dyspnea be attributed to drug treatment. Other patients experiencing dyspnea were either dyspneic at the time of entrance on the study, because of their underlying lung cancer, or other intercurrent diseases developed prior to or during therapy.

So then in conclusion in terms of the interim analysis of JHEX comparing gemcitabine and cisplatin versus cisplatin alone, the combination of gemcitabine and cisplatin has a statistically significantly greater response rate than single agent cisplatin, at 32 percent versus 10

percent, with a P value of less than 0.0001.

The time to progressive disease is also substantially longer for the combination of gemcitabine and cisplatin when compared to patients treated with cisplatin alone, with median of 5.8 months versus 3.7 months, a difference of 2.1 months, highly statistically significant by Wilcoxon and log rank analysis.

Bone marrow suppression was more pronounced with gemcitabine and cisplatin than cisplatin. There were no serious adverse events as a result.

Nonhematologic toxicities occur at approximately the same frequency in both treatment arms, and they were rather mild.

Lastly, the conclusion for the overall analysis for study JHEX, survival is significantly longer for patients treated with the combination of gemcitabine and cisplatin when compared to patients treated with cisplatin alone. A median survival of 1.9 months versus 7.6 months, significant by both Wilcoxon and log rank analysis.

The one year survival for patients treated with the combination arm as compared to the cisplatin alone arm is also greater at 39 percent versus 28 percent respectively.

Thank you for your time. Dr. Rosell is next, and will discuss the trials JHEX and JHBR.

Agenda Item: Sponsor Presentation, Studies JHBR and JHEZ - Rafael Rosell M.D., Ph.D.

DR. ROSELL: Thank you. Good morning, ladies and gentlemen. I am very happy to contribute the studies independently. The first study is a randomized trial comparing the combination of gemcitabine plus cisplatin versus cisplatin and etoposide in the treatment of locally advanced and metastatic non-small cell lung cancer. This study was carried out in Spain in 14 different institutions, and include 135 patients that were included between July 1995 and July 1996.

In this trial patients were studied according to gender, performance status, and disease stage and randomized to gemcitabine at the dose 1,250 mg/m^2 permitted on day 1 and 8 every 3 weeks, plus cisplatin at the dose of 100 mg/m^2 on day 1. Cycles were every three weeks, and was compared with cisplatin at the same dose of 100 mg/m^2 on day 1, plus etoposide, 100 mg/m^2 on day 1, 2, and 3, and it was cycle repeated every 3 weeks.

The reason to repeat cycles every three weeks was at that time it was commonly used, this regimen and this

schedule. Patients who obtained response were allowed to continue for three months for a maximum of six cycles.

The primary objective of the study was to assess the objective tumor response of this combination, and for this reason the center size was calculated to 62 patients per arm, to become aware that 45 percent response was obtained in the experiment arm, and it was 20 percent in the standard arm.

Secondary points were to look for the time to progressive disease, overall survival, to compare the toxicities, and finally, to make an assessment on quality of life issues.

The inclusion criteria are summarized on this table. The patients were to have histologic or cytologic diagnosis of Stage IIIB or IV non-small cell lung cancer. No prior chemotherapy was allowed. Prior radiation was permitted if it was not only the site of measurable disease. Performance status as measured by Karnofsky scale was 60 or greater, and finally adequate bone marrow reserve.

One hundred thirty-five patients were involved in this study, 69 on gemcitabine/cisplatin and 66 on the cisplatin/etoposide arm. The male/female ratio less the proportion of cases that are diagnosed in Spain, and the

histological diagnosis was squamous cell carcinoma.

Half of the patients at the time of diagnosis had Stage IIIB, and half had Stage IV. Most of the patients had good performance status as defined by 80 or greater. Only 15 percent of patients had performance status of 70.

When we looked at the response rate, you can see that on gemcitabine/cisplatin arm no complete response was observed, with 41 percent, which was almost double the response obtained in the cisplatin/etoposide of 22 percent, with a P value significant at the level of 0.02.

Also, time to progression of disease was 6.9 months for the gemcitabine/cisplatin combination, over 4.3 months for the cisplatin/etoposide regimen, with the log rank and Wilcoxon tables significant.

A longer trend to median survival was also observed, on the gemcitabine and cisplatin arm, 8.7 months, in comparison with 7.2 months for cisplatin and etoposide.

Here we display the survival cuts according to the Caplan-Meyer model in which on the yellow line we can see the longer time to progression of disease on the gemcitabine/cisplatin arm, with a P value of 0.01 on the log rank, and the Wilcoxon of 0.007.

Also a longer time to median survival was also

observed, also the yellow line on the gemcitabine/cisplatin combination, in comparison with the cisplatin and etoposide arm.

When we look at the side effects, specifically hematologic toxicity, a higher frequency of neutropenia was decided in the cisplatin and etoposide arm, in comparison with gemcitabine and cisplatin arm, and this difference is highly significant with a P value of 0.009.

Conversely, more thrombocytopenia was found on the gemcitabine and cisplatin arm, where the P value was 0.04, however, when we looked at the requirements of patients, you can see more patients on the cisplatin and etoposide were subject to febrile neutropenia, 8 patients, and that required hospitalization for a total period of 71 days. In the gemcitabine/cisplatin arm, only 5 patients, 7 percent, required hospitalization for a total of 18 days.

More patients on the cisplatin and etoposide arm required platelet transfusions, and the requirements for red blood cells were similar in both arms.

Nonlaboratory toxicities are listed in this table. In summary, nausea and vomiting in our study was most frequently on gemcitabine/cisplatin arm, but the difference was not significant. The only significant different was

detected on alopecia, that was higher on the cisplatin and etoposide arm.

We can conclude from this study that the combination of gemcitabine and cisplatin does appear to be a statistically significantly advantage in the response rate, as compared with the classical cisplatin and etoposide combination, with 41 percent versus 22 percent response, with a P value of 0.02.

Secondly, the time to progression to disease was significantly longer in the gemcitabine/cisplatin arm as compared to the cisplatin/etoposide, with a median of 6.9 versus 4.3 months, which with Wilcoxon and log rank are statistically significant.

Finally, the toxicity profile of the combination of gemcitabine/cisplatin was no different than was found with the etoposide/cisplatin combination.

Now I am going to present the second study. This is a European study that focused on comparing the activity of gemcitabine as a single agent versus cisplatin/etoposide in the treatment of locally advanced or metastatic non-small cell lung cancer. The mission was to compare with cisplatin/etoposide was to confirm the activity of gemcitabine as a single agent in Phase II studies of

simulation, and avoid selection bias.

This was a European study that was conducted at a multinational level and involved 33 institutions, included 147 patients in the accrual period, which was relatively short of July 1995 to January 1996.

Patients were again stratified according to the disease stage, locally advanced versus metastatic, and performance status, and randomized to receive either gemcitabine as a single agent at the dose of 1,000 mg/m^2 on day 1, 8, and 15 every 28 days, or the combination of cisplatin at the dose of 100 mg/m^2 permitted on day 1, plus etoposide, 100 mg/m^2 permitted on day 1, 2, and 3 every four cycles. This is a different schedule in comparison with the previous study. The cycles were repeated every 28 days, and a maximum number of cycles was allowed to be 6 to those patients with stable disease.

The primary objective was to compare the objective tumor response, and other secondary issues were to analyze various time-to-event efficacy measures such as the duration of response for responding patients, time to progressive disease, survival, to compare toxicities, and finally to make an assessment in quality of life issues.

The summary of inclusion criteria is similar as

the previous study that I have shown.

One hundred forty-seven patients were included; 72 on the gemcitabine arm, 75 on the combination of cisplatin/etoposide. Most of the patients in this European study were male, 78 percent of the overall patients included, and the primary histologic diagnosis was adenocarcinoma at 47 percent, followed by squamous cell carcinoma.

Three-quarters of the patients at the time of diagnosis had Stage IV disease; less than 20 percent had Stage IIIB; and less than 10 percent had Stage IIIA.

The vast majority of patients had good performance status as the schedule of 0 and 1, and only 13 percent of a performance status of 2. A slightly higher frequency of patients with a performance status of 2 was observed on the gemcitabine arm.

The response rate was similar in both arms; 80 percent of patients on the gemcitabine in single agent obtained a response. In total, 12 patients had PR. In the cisplatin/etoposide arm, 15 percent performance response was observed; 11 patients achieved PR. The difference was not significant.

Let me just show you one example of response.

This is a 61 year old male with adenocarcinoma, but the time of entering in the study has a pneumonia in the upper left lobe, with several lesions in both lungs. After he received the second cycle of chemotherapy the pneumonia is almost resolved, and the lesions were barely visible. For that reason, we allotted this patient to investigators in the peer review as a PR level, however, FDA's assessment was the patient was not allowable as the residual lesion was no longer measurable.

This is one month later. You can see the dramatic effect of the treatment, as no residual lesions are apparently visible.

Time to progression of disease was not different in both arms, 3 months on the gemcitabine arm; 3.2 cisplatin/etoposide arm. No differences were observed on median survival, 6.6 months on the gemcitabine arm; 7.6 months on the cisplatin plus the etoposide combination.

You can see here the overlapping survival curves displayed for the gemcitabine in single agent, with the cisplatin/etoposide arm.

When we focus on the toxicity, according to the protocol on the gemcitabine in single agent arm blood tests were required to performed every week, on day 1, 8, and 15,

and you can see that the very low profile of neutropenia was detected, in contrast with the cisplatin/etoposide arm, in the protocol only once per month were required to repeat the blood count. For that reason, this is not representative of the blood count anemias that can be detected.

This is reflected in the cisplatin/etoposide arm as 5 patients, 7 percent had neutropenic sepsis that required hospitalization for a total of 51 days. No patients on the gemcitabine in singular required hospitalization, none had neutropenic sepsis. Blood platelet transfusions were required in as a low a proportion of patients as in cisplatin and etoposide arm.

This table reflects again the hematologic toxicity according to the investigators' assessment, that more frequently, blood tests for patient care. You can see that the gemcitabine neutropenia and thrombocytopenia is the same as was analyzed, while on the cisplatin/etoposide arm reflects more accurately the clinically relative of 36 percent of the neutropenia on cisplatin/etoposide arm.

According to the investigators' assessment, the difference in neutropenia and thrombocytopenia was statistically significant in comparison with gemcitabine.

Nonlaboratory toxicities are listed here,

basically almost three times more frequently nausea and vomiting Grade 3 and 4 was observed on the cisplatin/etoposide arm, and nausea and vomiting was in the gemcitabine single agent. The only difference that is statistically significant besides nausea and vomiting was alopecia, 61 percent on cisplatin/etoposide arm.

On this table are listed other reasons that patients required hospitalization for reasons related to the drug administration, again almost double the number of events on the cisplatin/etoposide arm in contrast with the gemcitabine as a single agent.

When we looked for additional ancillary measures that these patients required as a consequence of the treatment, you can see that in the cisplatin/etoposide arm, specifically antiemetics were mandatory in 100 percent of the patients, and most of these on the cisplatin/etoposide arm also required dexamethasone and other drugs.

Finally, we can conclude from this European study that in chemo-naive patients with advanced non-small cell lung cancer gemcitabine as a single agent is at least as effective in terms of response rate, time to progression disease, and overall survival as the combination of cisplatin plus etoposide.

Gemcitabine was revealed to be less toxic than the combination of cisplatin and etoposide, and required less supportive care as measured by hospitalizations for neutropenia, requiring less blood transfusions.

Now Prof. Einhorn will summarize the conclusions of the studies.

Agenda Item: Sponsor Presentation, Summary and Conclusions - Larry Einhorn, M.D.

DR. EINHORN: Thank you.

Gemcitabine has been one of the most widely studied single agents in the treatment of non-small cell lung cancer. Studies done in Europe, in Canada, in South Africa by very experienced lung cancer physicians such as Hina Hanson(?), Francis Shepard, and Raymond Abrat(?), as well as studies done in Japan and in the United States demonstrate a remarkable reproducible response rate, with a range of 20-25 percent in these Phase II, nonrandomized studies.

Furthermore, median survival time of 10.2 months, and one year survival of 40 percent with single agent gemcitabine was observed in these nonrandomized studies.

As far as toxicity, in three of these studies with single agent gemcitabine, hematological toxicity is

relatively mild. Grade IV granulocytopenia, anemia, or thrombocytopenia is almost anecdotal with observation. Modest to moderate Grade 3 granulocytopenia is seen. There is almost a lack of thrombocytopenia with Grade 3 or Grade 4 toxicity.

As far as clinically meaningful endpoints of granucytopenic fever, infection, or hemorrhage, again, a very low incidence of serious Grade 3 or Grade 4 toxicity with single agent gemcitabine in these nonrandomized studies.

Furthermore, non-hematological toxicity of nausea, vomiting, peripheral neuropathy, and azotemia, with the exception of this one outlier from this particular study here, again is remarkably low in its incidence.

The combination of gemcitabine plus cisplatin was been performed in these five nonrandomized Phase II studies, totaling 222 patients, with an overall response rate of 40 percent, median survival time of 11.1 months. Again, these are nonrandomized studies, with a one year survival of 44 percent.

Dr. Rosell just presented the results of study JHEZ, comparing single agent gemcitabine versus a regimen that is known to be active and widely used both in Europe

and in the United States at that time, cisplatin plus etoposide. Showing comparable response rates, survival, and one year survival, with single agent gemcitabine compared to the two drug combination of cisplatin plus etoposide.

And as you have heard, the survival curve was non-significant. At no point in the survival curve was there any evidence of superiority of the cisplatin/etoposide arm compared to the single agent gemcitabine arm in this particular study.

There was, however, significant reduction in toxicity, comparing single agent gemcitabine to the active, widely used regimen of cisplatin plus etoposide, with a reduction in granulocytopenia from 8 percent to 45 percent with the combination, which includes 36 percent Grade 4 granulocytopenia, compared to 1 percent Grade 4 granulocytopenia. Thrombocytopenia, 1 percent versus 20 percent, including 10 percent Grade 4 thrombocytopenia.

Perhaps of more importance to patients who receive this therapy, the two side effects that both patients the most with any cancer, with any chemotherapy regimen are nausea and vomiting, and alopecia. The incidence was statistically and clinically less with single agent gemcitabine, 11 percent versus 30 percent, despite not

needing routine use of 5-HT_3 antagonists for antiemetics, as was done in the cisplatin plus etoposide arm. Single agent gemcitabine is devoid of alopecia, compared to the 62 percent incidence with an etoposide plus cisplatin regimen.

Dr. Rosell also presented the results of study JHBR, comparing cisplatin plus gemcitabine to cisplatin plus etoposide. The response rate was almost twice as high favoring the gemcitabine arm, 22 percent versus 41 percent, with a statistically significant improvement in time to progression of 2.6 months, 4.3 months, compared to 6.9 months.

This study was not powered to show a difference in survival with the sample size in this Phase III study, however, the trend was clearly there, suggesting an early survival advantage for gemcitabine/cisplatin compared to etoposide plus cisplatin in this Phase III study.

Dr. Sandler presented the interim and final results of study JHEX, the study comparing single agent cisplatin to the combination of cisplatin plus gemcitabine. We saw over a tripling of the objective response rate, 10 percent compared to 32 percent with a P value of 0.0001, a 2.7 month improvement in the interim analysis in median duration of remission, a 2.1 improvement in time to

progressive disease, all with a P value here of P equals 0.0009 by log rank.

And of course this is the survival curve for the analysis of all 522 patients. I would point out several things on this survival curve. First of all, the control arm of single agent cisplatin has a very respectable median survival time of 7.6 months, and a very respectable one year survival of 28 percent.

But more importantly, this study and the Southwest Oncology Group study of vinorelbine/cisplatin versus cisplatin demonstrates conclusively for the first time that we no longer need meta-analysis to demonstrate superiority of new drugs combined with platinum, compared to platinum alone or older types of regimens in the management of non-small cell lung cancer.

In conclusion, single agent gemcitabine has been one of the most widely studied drugs worldwide in non-small cell lung cancer. Toxicities such as myelosuppression, nausea, vomiting, alopecia, mucositis, and organ toxicity are minimal. This makes this drug as a single agent very attractive for elderly or unfit patients, or patients who are not felt to be candidates for platinum combination chemotherapy.

The response rates worldwide are remarkably reproducible with a narrow range of 20-25 percent. Single agent gemcitabine in the study presented by Dr. Rosell was as effective as the active regimen of cisplatin plus etoposide as far as response rate and survival, and was associated with a very significant reduction in Grade 3-4 granulocytopenia, 8 percent versus 45 percent, and that included Grade 4 granulocytopenia of 1 percent with gemcitabine and 36 percent with cisplatin plus etoposide.

Thrombocytopenia, 1 percent versus 20 percent, including 10 percent Grade 4; nausea and vomiting, 11 percent versus 30 percent; and alopecia, 0 versus 62 percent.

I would conclude on my comments of single agent gemcitabine that I know of no single agent in non-small cell lung cancer that has a higher response rate, a better median survival time, or an improved one year survival than does gemcitabine. Furthermore, I am not aware of any active single agents in non-small cell lung cancer that have less toxicity.

The combination of gemcitabine plus cisplatin was evaluated in the randomized study of gemcitabine plus cisplatin versus cisplatin plus etoposide, again, as

presented by Dr. Rosell. There was almost a doubling of the objective response rate, 22 percent versus 41 percent, with 2.6 month improvement in time to progression, all statistically and clinically significant, favoring the gemcitabine platinum over the older etoposide plus cisplatin regimen.

Finally, the randomized study that Dr. Sandler presented of JHEX comparing gemcitabine plus cisplatin to cisplatin as a single agent, the interim analysis of 309 patients revealed over a tripling of the objective response rate, 32 percent versus 10 percent, and a 2.1 month improvement in time to progressive disease of 5.8 versus 3.7 months.

The survival analysis for all 522 patients demonstrated a clear survival advantage with P value of 0.004 by log rank, and 0.012 by Wilcoxon. Furthermore, as Dr. Sandler mentioned, the final analysis of all 522 patients revealed the same improvement in response rate and time to progressive disease as well.

Well, thank you very much for your attention.

Agenda Item: Questions from the Committee

DR. DUTCHER: Are there questions from the committee for the sponsor?

DR. SCHILSKY: I wanted to ask Dr. Einhorn a question for a minute. Larry, I'm just curious. I wonder if you could give us your view again about the relationship between response rate and survival in non-small cell lung cancer?

DR. EINHORN: Yes, this wind has kind of blown us away, but the question was my opinion about the difference in response rate and survival in non-small cell lung cancer. I will give you my personal opinion, which is not necessarily shared by all lung cancer investigators.

I think response rate is very important as a potential marker for new drug activity, either monotherapy or combination chemotherapy regimens. It is also probably important in reducing sizes of tumor obviously, and perhaps symptoms that a patient has. However, it is probably of and by itself not a surrogate marker for survival, unless it is associated with a high complete response rate.

Again, my prejudicial personal viewpoint is not limited to non-small cell lung cancer. I think that is true with any solid tumor that we deal with; that response rates are important for determining drug activity, but not necessarily a surrogate marker for survival of and by itself.

DR. DUTCHER: Could some of you comment on the additional myelosuppression with the combination of Gemzar and cisplatin. There was quite a difference between that and single agent. Do you want to talk a little bit about the synergy?

DR. SANDLER: There was as noted, again increased evidence of myelosuppression. There was increased thrombocytopenia and more anemia that was seen, clinically not significant. It has been shown in vitro data that there appears to be synergy between these two agents, hopefully against tumors, but most likely also perhaps against normal tissue as well.

I think it is typical in terms of combining agents in chemotherapy that you expect more myelosuppression with combination therapy than with single agent therapy, and particularly one like cisplatin, which is known to be relatively mild.

DR. BUNN: Can I make a comment? I know the one of the questions for the committee is does the increase of efficacy outweigh the increase in toxicity? Clearly, with respect of myelosuppression, cisplatin combined with gemcitabine is more myelosuppressive than cisplatin alone. I think everything has to be taken in context.

The myelosuppression -- this committee grappled with that same issue several years ago with vinorelbine. In the comparison of vinorelbine and cisplatin, and cisplatin alone, vinorelbine with cisplatin was way more myelosuppressive than this.

With respect to patients, besides not liking vomiting and losing their hair, they don't like to die, and a very important issue here is no patients died from toxicity. When you hear any other presentations of large cooperative groups, almost always there are patients dying from toxicity with this disease, because they have a lot of co-morbid diseases to begin with. I think it is very instructive, the number of toxic deaths in any of these studies.

DR. SCHILSKY: Alan, I just wanted to ask one follow-up question about the myelosuppression. Did you look to see if there was any relationship between extensive myelosuppression and whether the patients had previously received radiotherapy or not? You didn't tell us anything about what percentage of patients in the study had gotten radiation, and I'm curious to know if perhaps those are the patients who have the more severe myelosuppression.

DR. SANDLER: Yes, and I believe we actually have

a couple of slides that will illustrate that point. In general though, the number of patients that did receive radiation therapy were rather small. I believe it was less than 15-20 percent, therefore the numbers are also small in terms of making comments between the two. I think there were enough patients without radiotherapy; those patients do have some myelosuppression with the combination whether they have or have not received radiotherapy.

I think the major thrust of the results is that there really were not untoward effects. There were no hemorrhages that were seen; there were minimal episodes of neutropenic fever, and as Dr. Bunn mentioned, there were no toxic deaths.

Now this is the slide that illustrates again, the interim analysis with the 9 patients, 15 percent on the combination arm, 16 percent of patients on the single agent arm, only 47 patients. It's just small numbers.

DR. SCHILSKY: Do you know anything about whether those patients have worse myelosuppression?

DR. SANDLER: I'm not certain that we actually have a slide on that.

DR. MARGOLIN: Just to go back for a moment, and I'm sure we'll talk about it a little bit later, on the

myelosuppression specifically, the thrombocytopenia. It looked like in the JHEX Phase III study there was significantly increased thrombocytopenia at levels that were severe enough to require platelet transfusions versus platinum alone.

Whereas at almost identical dose intensities, at least with the Gemzar, and actually if anything reverse dose intensities of the platinum, which is given less often on JHEX study, that there was a lot less thrombocytopenia requiring transfusion in the JHBR study from Spain. So I was curious about how that might be explained, other than perhaps by patient selection.

Then the other part of that was really the concern that in the population of patients that would be treated here, these are community drugs. These are not going to be drugs that are going to be routinely restricted to sophisticated university medical centers, where platelet transfusions are available quickly. In many communities, HMOs, et cetera, platelet transfusions are rather difficult to come by on a routine basis. So I would just like to hear the company's comments on that, or perhaps Dr. Rosell.

DR. PEDERSEN: Could you restate the question so I can understand it?

DR. MARGOLIN: The apparent difference in thrombocytopenia requiring transfusion between JHBR and JHEX in the gemcitabine plus platinum arms, where the Gemzar was about the same dose intensity, and the platinum dose intensity was actually a little lower in JHEX than in JHBR.

DR. PEDERSEN: I think we can have a specific comment from Dr. Rosell about that study, but in general the two different treatment practices obviously are different in different countries. So your inclination to use transfusion may be different in terms of taking the consequence of the count and the follow-up. That was something was very difficult for us to put a figure on it, since how do you handle that?

DR. ROSELL: This is a very interesting question. The study was a multicenter study. That means that it involved the participation of different hospitals. These hospitals are part of the same homogeneous group. In Spain we have a lung cancer group that is called the Spanish Lung Cancer Group. It includes hospitals, university hospitals, public hospitals, and at the same the oncology service. This way I feel that there was no bias for not having adequate health care in terms of blood transfusions.

Also, four patients, two in each arm, became

clinically hemorrhagic that was attributed to hemoptysis. Two patients on the gemcitabine/cisplatin arm had no thrombocytopenia, and two cases on the cisplatin plus etoposide, one had thrombocytopenia, Grade 1, and the other thrombocytopenia, Grade 4.

DR. EINHORN: Somewhat of a generic question on myelosuppression. When we look at Grade 3 and Grade 4 myelosuppression, it is basically a number on a laboratory slip. What is more important are the biological events. Having said that, I think it's good to also remember for example in the JHEX study of single agent cisplatin versus cisplatin plus gemcitabine, that the patients who randomize on the gemcitabine arm were getting their points on a laboratory slip determined once a week, compared to once a month on the cisplatin arm.

Also, at least as far as anemia, cisplatin causes cumulative anemia. Because the gemcitabine arm was better, there was a meeting of four courses or four months of treatment versus two months of treatment.

Now the question you raise about the community level, I think one of the things that is different about JHEX compared to studies that are done through American cooperative groups is that this was basically entirely a

community-based study done by our Hoosier Oncology Group, which has 80 percent of the patients put on at the community, and Claude Denham is here, who can address the TOPA, and I would assume that is basically 100 percent community from TOPA.

So at least for North America, at least for the United States, which put on the majority of the patients, this was indeed a community-based, not cancer center-based study.

DR. MARGOLIN: By the same token, however, I think that the people in TOPA are proud to be considered a very sophisticated level of community oncology.

DR. DENHAM: Actually, a very large percent of these patients were treated in the Longview, Tyler, West Texas, Odessa, Rio Grande Valley -- really definitely community oncology settings. Actually, I think we do tend to provide platelet transfusions as outpatients. Patients were supported when their plate count dropped below a certain level. Very few bleeding problems occurred.

DR. SWAIN: I had a question in looking at the survival data in the JHEX study and the total group, not just the interim analysis. Do you have data or information on what kind of therapy patients got after their initial

treatment? Let's say did they get vinorelbine or taxanes, and was there an imbalance in region in the U.S. and Europe?

DR. PEDERSEN: We do have that information, yes. Generally, I can tell you that if you take the two treatment arms, that you would probably expect also when you have a single agent treatment in one treatment arm, or a combination treatment in the other treatment arm, that there would be a higher trend toward giving subsequent treatment on the single agent treatment arm, and we have seen that here.

We do have lists of all the types of treatment they have had, which is a very mixed bag of common drugs, but not used with any particular tendencies, that are all going on through a particular regimen after that. We certainly can provide that.

DR. SWAIN: I guess I was interested in the navelbine, to see if there is a difference in the two treatment arms for that, and also the taxanes.

DR. PEDERSEN: Specifically, they received navelbine as a single treatment or a taxane as a single arm treatment?

DR. SWAIN: Right.

DR. PEDERSEN: We haven't lumped them together.

This is the list of all patients. Note that this is not just the interim analysis patients, but all patients; the number of different kinds of drug therapies they received post-JHEX study. There is a slight tendency to more vinorelbine treatment in the cisplatin only treatment arm, but other than that, it is very well balanced. Some patients in the cisplatin arm actually have received gemcitabine post-study.

MR. GIBBES: In your studies why wasn't carboplatin used in some of the studies instead of cisplatin?

DR. PEDERSEN: At the time that these studies were initiated cisplatin was the most widely used agent for non-small cell lung cancer. It was the only one that had shown that there was a survival advantage to use that agent as a basis for chemotherapy. That was the reason for that.

DR. MARGOLIN: This is at the risk of opening I guess a Pandora's box, because there is sort of a glaring absence of any mention of the quality of life data. I suppose it will be discussed later by the FDA reviewer, but I think the reason to bring it up here is because what we are going to be voting on is sort of patient choice and a doctor choice between regimens that may be a little more

toxic, and provide a modest survival benefit or some other positive outcome benefit. The decision will have to be whether it is worth it.

So I guess the question is, what happened to all quality of life analyses that were referred in each of these studies?

DR. PEDERSEN: Certainly Dr. Einhorn, you made some general statements about that.

DR. EINHORN: Kim, I think certainly in a study like JHEX where there is a survival advantage, I think the survival advantage speaks for itself. In the other studies, quality of life is clearly important to doctors, regulators, and especially to patients.

I have been involved with attempting to do quality of life studies for over 15 years in lung cancer, and it's a challenge. There is a wonderful article which was published in the January issue of the European Journal of Cancer by one of the leaders in the field, Dr. Hopwood. She stated in the article that trying to do quality of life questionnaires in clinical trials is much more of a formidable task than was realized, and there is a problem with collecting all the data and missing data sets, both initially, and especially longitudinally with the study.

I think a lot of this has to do with many factors -- patients being too ill, or just receiving bad news and not given the questionnaires to fill out; the physicians not taking them responsibly and giving them the questionnaires; not having training sessions for qualified people who are administering the questionnaires; and also instructing the patients on how to fill them out.

So it is a laudatory goal to try to get quality of life information, but it is difficult to do that. Now despite that, and this particular study base, the JHEZ study that looked at single agent gemcitabine versus cisplatin plus etoposide, they used what is felt to be the best prospectively validated quality of life instrument, which is an EORTC core questionnaire of 30 different questions, which is not specific for lung cancer, as well as lung cancer module, LC13, that asks questions about dyspnea, hemoptysis, cough, and some treatment related components.

When you are looking at two regimens that have 18 percent and 15 percent response rates, you are probably not going to globally impact upon lung cancer-related quality of life. Certainly I would argue, however, that for patients to have the module of less nausea and vomiting, and less alopecia, that that does impact favorably upon the patient's

quality of life, despite the fact that the global scores of looking at the 30 core questionnaires and 13 LC13 did not show a difference in quality of life in that particular study.

Again, I think it's a matter of capturing all the data and looking at specific components, as opposed to the global entity. At least that is my take on the quality of life instrument. I think we still have a long way to go in assessing quality of life properly as we need to in lung cancer studies and in other solid tumors as well.

DR. BUNN: Just another quick comment. The only study that has been able to do this was the physicians of the United Kingdom that have studied mitomycin-C, etoposide, and cisplatin, the most commonly used regimen before all these new drugs in Europe, certainly a regimen that has considerably more nausea and vomiting and myelosuppression than anything we've heard about today.

In that study it did both Stage III and Stage IV patients. There was a highly statistically significant advantage in terms of quality of life in terms of who got chemotherapy and less supportive care. Of course those questionnaires were filled out by the patients, but the physicians as you know in Europe are very pessimistic about

using chemotherapy for lung cancer.

If you look at the data in this study, it is very similar to what happened with vinorelbine and platinum versus platinum, and that is a huge drop out of patients, but what you can tell is everything looks the same. Even in areas where you can expect a difference, there are differences for nausea and vomiting, but no differences in overall quality, as Larry mentioned.

So unfortunately, it's just another example of where people tried hard to look at quality of life, but were unable to show anything, because the patients dropped out.

DR. D. JOHNSON: I have a couple of questions, some of which relates to my conflicts by virtue of the fact that I have a lot of experience with this particular product, and know some data that were not presented today.

With reference to quality of life, the one issue that might be helpful would be that in the United Kingdom, Dr. Nick Thatcher has done studies with single agent gemcitabine, and has looked at changes in symptoms related to the tumor itself, and the benefits that have been seen with this product, and compared it to single modality treatments like radiation therapy, where at least in advanced disease there is no survival advantage, but a

reputative symptom improvement.

I don't know if you have any of those data you want to share as supportive data.

DR. PEDERSEN: I can briefly summarize. As you state, there was a study where he did analyze the patients which were last stage disease patients that in one treatment arm received radiotherapy, or with their supportive care most, and gemcitabine as a single agent, and looking at quality, could he detect a quality of life difference in favor of gemcitabine in this study.

The reason that we have not included that further in this discussion is also summarized by the FDA reviewers, is that we did not find the design of the study to be well controlled and adequate and comparable to our purposes. But you are right, that is some of the data that they have.

DR. D. JOHNSON: So that's hearsay then, because I wanted to pursue briefly a point made by Dr. Einhorn in his summarization that this would be useful in the elderly or unfit. I think what he meant by that -- and I would never presume to project what Dr. Einhorn thinks about this -- but I'm thinking he's thinking about single agent gemcitabine rather than the combination of gemcitabine and cisplatin. Is that close to being correct?

DR. EINHORN: Not only close, but right on.

DR. D. JOHNSON: Good, because I wanted to make the point that in the sponsor's presentation and in their summary, they make a specific point about the fact that there were no responders seen in patients who had PS-2 with this particular combination. I do think that there are plenty of data to indicate that PS-2 patients do poorly with combination therapy. This may in fact be not a good regimen to administer to that group of patients.

I wonder -- I may have missed it in the presentation -- what level of the significant toxicities that concern the committee, such as thrombocytopenia and renal toxicity was actually observed in the PS-2 as opposed to the PS-0 and -1 patients? Do we have that data? Do you have any breakout of that data?

DR. PEDERSEN: Are you talking about the combination chemotherapy?

DR. D. JOHNSON: Correct, and actually I would be interested in the single agent data as well. I realize there are only a small number of patients with poor performance status, but nevertheless it would instructive to see those data.

DR. PEDERSEN: I think we do have a table that we

have it broken down, that breaks it down into the performance types of patients. This is survival. I think there should be a toxicity. This shows it broken down into two categorizations.

DR. SANDLER: While we are waiting, I might be able to add something to that. Two comments; the way that the data was initially divided was performance status 90 and 100 versus 70 and 80. Certainly, Dr. Johnson, 80 is actually performance status 1. So the two data sets that would look at 70 and 80 versus 90 and 100.

But we also broke it down for patients with KPS of 70, to look at patients who fit the performance standard 2 criteria. There should be data on a slide on that.

DR. D. JOHNSON: I think what's particularly important while you are searching for the slide, it's important to note that the median age for this disease is into the middle to high 60s. On trials it is often as low as 60 or 62, but in reality in the United States the median age of this disease is probably 66-67. So when you are talking about elderly and "medically unfit," these data are very important.

DR. SANDLER: So as I mentioned, this is again the way the original stratification was. It was 70 and 80

versus 90 and 100. The 70 and 80 lumped some KPS 1s with KPS 2s, but there doesn't appear to be any statistical difference between the two treatment arms, although there is a slightly higher amount of thrombocytopenia in the better performance status patients.

I do think there is actually another slide, 70 versus 80, then 100. So you have anemia, a 29 percent Grades 3 and 4, versus 24 percent. Looking at Grade 3 for granulocytopenia, 60 versus 57 percent. As this gets fuzzier and fuzzier, thrombocytopenia, 43 percent versus 53 percent; no dramatic difference, and again, if anything a little bit more thrombocytopenia with the better performance status patients.

DR. D. JOHNSON: But as you point out, probably reflects the fact that they are the ones who continue on with the treatment.

So other concern I have is that with -- speaking now from my own experience with the combination of gemcitabine and cisplatin -- my impression is that it's a renally toxic regimen, even in experienced hands. The data do not reflect that here, but I don't recall seeing any specific mention of renal toxicity from the JHBR trial for example, which I don't know if I missed it, or if those data

can be presented?

Before you answer that question, I would like to know how was renal function assessed? Was it merely a monthly creatinine, or were patients getting creatinines on a weekly basis when they were getting gemcitabine as well?

DR. ROSELL: In JHBR study there was no severe renal toxicity, although one patient in our hospital on the gemcitabine/cisplatin arm, after receiving the second cycle of chemotherapy, had severe neutropenia and thrombocytopenia, pneumonia and renal failure. This was the only toxic death that was observed.

From the assessment of renal function, this was the baseline level. Then on day 15 was repeated, the clearance of creatinine and was analyzed for full renal function.

Let me just make a personal comment. In our country we have a large experience with the use of gemcitabine as single agent in elderly patients. It is well tolerated, and is a satisfactory treatment for these patients with very advanced disease and poor performance status. Only we are using commonly gemcitabine as a second line chemotherapy, because for us unfortunately we have no scientific data to support my comments.

DR. D. JOHNSON: But you did show us data of 10 patients who got single agent cisplatin that subsequently got gemcitabine in the JHEX trial, but you didn't tell us whether those patients responded to that gemcitabine or not. You know I'm sure, so what did happen to them?

DR. PEDERSEN: It's a small sample size.

DR. D. JOHNSON: I realize it's a small sample size, but if all 10 responded, I'd be impressed. I'm assuming that wasn't the case. Also, it would be interesting to note whether they responded to the navelbine.

DR. DUTCHER: One more question.

DR. KROOK: One of the questions that we are going to have to address is in the JHEX study, and it has also been brought up here that at least on the American side, a lot of these was done by people like myself in the community centers. The question is, in the European, which is 192 patients, were these university centers or community centers?

My second question, which relates is we were also told early on that in studies done in Europe in lung cancer there are more IIIA. Are there more IIIA patients in the European group out of that group? Can we relate any of this to the difference we are going to have to discuss in

survival?

DR. PEDERSEN: First of all, the treatment centers in Europe were predominantly university centers. In most of the countries where these studies occurred, all treatment does occur in the university centers. So that is not a choice.

DR. KROOK: I truly believe it's the same. I'm asking the question, because it came up here. So we have universities mainly, CCOPs in this country, and universities there.

DR. OZOLS: Just a question about how confident you are about the doses that were used. How important is the dose intensity of these drugs in combination?

DR. PEDERSEN: We do find that both the dosages that have been used in the two combination studies 1,000 and 450 mg, our effective is shown here. We do not have any reason to believe that one particular dose is better than the other. We have no comparison data that supports that. The uses of them, a three week versus four week regimen, if you calculate that over a three monthly period with different week rests, you actually have it closer to a theoretical similar dose intensity.

I think the actual equivalent would have been 150

or something like that in the three week duration to be exactly the same doses over the three month period as the other one. So in terms of dosage, I think with that in mind we're talking about less than a 10 percent difference. I don't think that we would be able to detect any difference in that.

DR. KROOK: Do you think you need a dose of cisplatin at 100 in combination?

DR. PEDERSEN: I cannot tell you that. We haven't studied that. I don't know.

DR. TEMPLE: The major focus here is obviously on the combination product. I want to ask you a question about the amount of therapy. Basically, I don't understand, again, what the theory is as to how one is supposed to prove it works. There hasn't been any presentation on the effectiveness of the combination compared to the platinum.

In an equivalence trial one has to know that one is comparing something to a regimen that has a defined effect. One has to decide whether one has some assurance that the effect that there is of the control has not been lost. You do that with confidence intervals, and you make guesses about what the effects are.

I don't see any of that. This is all been

described by Tom Quinten(?) for example and others. I don't see anything like that here. The only you see is that survival is a little worse. What is the theory as to how one should conclude that monotherapy is effective?

DR. EINHORN: That is a fair question. I think when we look at the history of chemotherapy in this disease, and look at the decade of the 1980s, and the meta-analysis, and I showed you one of four different meta-analyses, there is a survival advantage in meta-analysis of platinum combination chemotherapy compared to best supportive care, and the most common regimen worldwide is the cisplatin plus etoposide regimen.

One can argue is that an active regimen? It is not a wonderful regimen, but it is an active regimen in survival compared to best supportive care with platinum-based regimens in general.

Now as far as single agent gemcitabine, the study of JHEZ with a number of patients on it, I do not see anything as a clinician, not as a statistician, to show me any confidence level that at any point in the survival curve is single agent gemcitabine inferior to what I feel is an active regimen of cisplatin plus etoposide. It had a slightly higher response rate. The median survival time was

better for cisplatin plus etoposide, but as you well know, median survival time is a single point on the survival curve. Again, that survival curve was absolutely superimposable.

Finally, when we look at the JHEX, where I think there is incontrovertible evidence that adding gemcitabine to cisplatin shows a clear survival advantage compared to cisplatin alone, I know of no example in any disease in oncology where an inactive drug is added to another drug, and shows a survival advantage. I argue that we are adding an active drug to cisplatin, gemcitabine namely, to show a survival advantage.

DR. BUNN: I agree that's a difficult question. One of the issues here, as you know there was a vote with vinorelbine to approve it as a single agent partially based on two things. One was to compare some of the 5-FU and leucovorin. I don't think anyone in this room would want that study repeated with gemcitabine since 5-FU and leucovorin is so inferior.

So if you are not going to compare a single agent to something like 5-FU and navelbine or 5-FU and leucovorin to get that support right there, what are you going to compare it to? What it was compared to was the most

commonly used regimen in Europe and in the United States, namely etoposide and cisplatin.

If you look at the single agent data in that study, or any of the other ones, it is identical to the vinorelbine data with respect to the percentage of people alive at any time going, with respect to response rate, and any other parameter.

So it is a difficult question. As we make advances in treatments, it becomes more and more difficult to figure out how to totally evaluate a single agent. Here I think you have to say that in terms of response, survival is equivalent to etoposide and cisplatin, even though you can't rule out a minor difference.

There was also another study that wasn't presented here, down in Taiwan of identical design comparing single agent gemcitabine to etoposide and cisplatin with identical results.

DR. TEMPLE: One answer to some of that is make the study large enough to have the potential to show a difference if there was one. This is a very small study. The confidence intervals overlap I'm sure with the possibility of no response at all.

DR. PEDERSEN: Actually, the confidence interval

is 10 to 29 on that one.

DR. SIMON: I didn't ask that question, because I think the data that was presented is not an adequate therapeutic equivalent study. It does not support the conclusion that there is not a deterioration of survival when gemcitabine is given as a single agent.

However, given the fact that the benefit in survival from the combination of cisplatin and etoposide is so small, I think it would probably be practically impossible to design an adequate therapeutic equivalents trial. I don't think you could conclude that there is not a deterioration in survival when it is given as a single agent.

DR. SWAIN: I wanted to get back to the incontrovertible survival data in the JHEX study, and ask a question about that. In the FDA review the survival analysis is done by stage. I wanted for you all to show that data -- I'm sure you have it -- and give you a chance to discuss that. Specifically, maybe Dr. Bunn could make a comment on it.

DR. PEDERSEN: You would like to the survival curve for JHEX?

DR. SWAIN: Right, for all patients, since that

was one of your stratification factors. More of the patients were Stage IV.

DR. SANDLER: This is again the final analysis of all 522 patients by disease stage broken down. We'll look at gemcitabine plus cisplatin for Stage III, 86 patients here in yellow. You compare your arm of cisplatin alone in Stage III in blue. That certainly is a statistically significant difference between the two arms.

If you then look at Stage IV patients alone, you have gemcitabine plus cisplatin in what I now know is orange here, and then the cisplatin alone for metastatic disease, which is in the green. There are differences between the line, although the numbers are smaller, these numbers are comparable to the numbers that were in the interim analysis. Although they don't reach statistical significance, there was a trend suggesting again that the combination is superior than cisplatin alone in Stage IV, but with smaller numbers of patients.

DR. EINHORN: There is 44 percent Stage III on the Thierry LeChavalier study with vinorelbine, but it is only 14 percent IIIA. Even in Europe most IIIAs are not treated with chemotherapy so most of these Stage III patients are IIIB.

DR. SANDLER: In our study it was only 7 percent of patients were IIIA in JHEX.

This is a slide of all patients, looking at stage. Combined Stage III here, around 31 percent Stage III in North America, as compared to 38 percent in the combination arm in Europe, and 27 percent here. So it would appear to be comparable.

DR. BUNN: I'm not sure totally what your question is. If you look at every large study, you get the same results here. If you talk to Dave Johnson next to you, whom I once asked at an ASTO(?) meeting the same question. If you look at the ECOG study, if you look at IIIB patients, they do better than Stage IV, and there is a wider separation. That's the same in the Southwest Oncology Group.

As you know, there is a meta-analysis to show in Stage III patients that chemotherapy plus radiation is better than radiation alone. There is no such meta-analysis or proof that radiation plus chemotherapy is better than chemotherapy alone.

There are two small randomized studies that suggest that combined modality might be better than chemotherapy alone, but there is certainly no proof of that.

In the U.S. there is much more of a tendency to treat IIIB with combined modality rather than in Europe on the basis of those two small randomized studies, but I think again, the danger totally consistent with every other large study.

DR. SWAIN: I guess I was more interested in the Stage IV patients, and the lack of benefit in that large group.

DR. BUNN: A subset of analysis -- if you were going to do a study with just Stage IV patients, you would probably have a larger N, but to show the survival differences. That would be true with the ECOG or large studies as well, because differences are a bit greater in IIIB. Probably you might need a meta-analysis.

I think if you look at vinorelbine, in the discussion that was held at this same meeting with that, again, subset analysis with that in vinorelbine and platinum versus platinum, there weren't statistical differences when you did the subset analysis for just Stage IV. That's a very common finding.

DR. SANDLER: Actually, if you like, there is a slide that shows the numbers, the median survival at Stage IV between the two treatment arms. The difference between the two arms is roughly the same in terms of the overall

median survival as is seen with the overall study.

Again, here is gemcitabine and cisplatin, Stage IV patients only, 8.3 months; cisplatin alone, Stage IV patients only 6.8 months. A total of approximately 360 patients. The difference between the two arms is 1.5 months, virtually identical for the overall difference of the study of 9.1 versus 7.5 months, of course with the numbers being slightly lower, because patients who live, do not live as long as their Stage III counterparts.

DR. DUTCHER: Thank you very much. We're going to take a 15 minute break.

[Brief recess.]

DR. DUTCHER: Dr. Schechter.

Agenda Item: FDA Presentation - Genevieve Schechter, M.D., FDA Reviewer, Gang Chen, Ph.D., Statistical Reviewer

DR. SCHECHTER: Dr. Dutcher, members of the committee and guests, today we are here to gemcitabine for the treatment of non-small cell lung cancer. Gemzar is indicated as a single agent or in combination with cisplatin for the first-line treatment of patients with locally advanced (Stage IIA or IIIB) or metastatic (Stage IV) non-small cell lung cancer.

This is the FDA team. I would like to say thanks to the team for all their help.

The basis of this application is three Phase II single arms trials, three randomized trials, and 25 additional Phase I/II/III studies of gemcitabine, or in combination with other chemotherapeutic agents and/or radiation in non-small cell lung cancer.

The Phase II data will only be presented here briefly. What was submitted were the study summaries. No source data was submitted. There was a review of the published literature. Our FDA efficacy results are based on an intent-to-treat analysis when possible, but the FDA, as we said, did not have access to the raw data.

We know that these studies were conducted in Europe, Canada, and South Africa. According to the published literature, all three studies has Stage III and Stage IV disease. Using an intent-to-treat analysis we were able to come up with response rates between 19.5 to 20.5 percent.

Although the studies were conducts at different dose levels (from 800 to 1,250 mg/m^2) there was little difference observed between the response rates and the survival. Poorer survival in some studies may have had more

to do with the performance status and other factors than the dose. The discrepancies between the sponsor's study reports, the published literature, and ODAC briefing document need to be clarified.

There are three Phase III trials, as you are aware. The first one was JHEZ. This study had a dosing schedule of 1,000 mg/m^2 weekly for three out of the four weeks, versus etoposide 100 mg/m^2 daily days 1-3, every four weeks with cisplatin 100 mg/m^2 on day 1. This study was conducted in Europe and the Middle East between July 1995 and January 1996.

The primary objective of this study when written was to determine the difference in response rate between arms. Secondary objectives were: to evaluate the quality of life; improvements in the disease-related symptoms; they wanted to characterize time to event information; and characterize toxicity.

These studies were randomized and stratified in Stage III versus IV, performance status, and center.

Protocol issues that we have for this study were that these studies were not submitted to the agency prior to submission of the NDA. There was no definition in the study of treatment failure; time to treatment failure; or time to

progression. The sample size of 147 was designed to detect a difference in response rate based on a response rate of 45 percent for gemcitabine versus a response of 21 percent for the comparator.

We had no information in this particular trial on follow-up therapies of any type. There was also a lack of information on methods of tumor assessment during follow-up. The duration of response was based on the WHO definition, which is basically from the time of randomization until the time of progression of the responder.

Demographics -- this was well matched and homogeneous in all regards. About 19-25 percent of the patients were women. The median age was young, 58-59, with a 53 percent adenocarcinomas in the gemcitabine arm, and 41 percent in the etoposide/cisplatin arm. The reason I mention this is there some published literature to indicate that gemcitabine works better in adenocarcinomas than in squamous carcinomas.

One hundred percent of the patients in the study were Caucasian. The performance status was excellent, 80-100 percent of the patients being performance status 1 or 0. Ten percent of the patients on each arm had chest radiotherapy prior to study, and 23 and 26 percent

respectively were Stage III disease.

The disposition of the patients on the study -- 14 of the patients were alive at last follow-up on the gemcitabine arm, versus 12 on the etoposide/cisplatin arm, and 7 on the gemcitabine and 6 on the etoposide/cisplatin arm were without progression. As expected, the majority of the patients died from lung cancer. In this particular trial we had more patients on the etoposide/cisplatin who died from other causes.

Interesting things about the study was that only 15.3 percent of the patients on the gemcitabine arm were able to complete the entire six cycles of therapy. Seventeen percent of the patients on the etoposide/cisplatin arm completed six cycles of therapy. Nine point seven percent of patients on the gemcitabine arm, and 9.3 percent of the patients on the etoposide/cisplatin arm were discontinued because of adverse events. So we have an adverse event rate of about 10 percent.

We looked at responses. Now I know we are very harsh in our responses when we look at this data, and we apologize. It is all in the eyes of the beholder, you know. We have about a 9 percent response for each arm, which has a P value of 1.00. There cannot be a P value of greater than

1.00.

The median duration was longer on the gemcitabine arm as compared to the etoposide/cisplatin arm, but there was no significant difference.

The time to progress and the time to treatment failure on both arms are about 0.7 months apart. The median survival is numerically inferior. Again, there is no significant difference between treatment arms.

As we noted, there is no difference in response or time to event parameters. Less than 20 percent of the patients completed six cycles. There was less than one month's difference between the time to progression and the time to treatment failure in the study. The median survival on the gemcitabine arm as we noted was 6 months versus 7.3 months.

JHBR was a Phase III trial with 135 patients. This was conducted in 12 centers in Spain. There were two treatment arms. The dose of gemcitabine is higher here. It is 1,250 mg/m^2 day 1 and day 8. The cisplatin is again 100 mg/m^2 on day 1. This was compared to the etoposide/cisplatin regimen that was used in the previous study, except that we have a 21 day cycle here.

The primary objective of this protocol in this

design was compare response rates. Secondary objectives were to compare toxicity; to evaluate changes in the quality of life; compare overall response; study cost effectiveness of treatments; and to determine the median survival. The sample size of 135 was based on a difference in response rates, which again, the gemcitabine response rate was assumed to be 45 percent, versus the comparator response rate of 20 percent.

Stratification was to be gender; performance status; disease stage; investigational center, with the WHO definition of response. The treatment plan called for six cycles, although one enthusiastic investigator gave one patient seven cycles of gemcitabine.

Information on post-study radiotherapy was provided. There was no information on other therapies as post-treatment, surgery or chemotherapy. The method of tumor follow-up post-study was not again defined.

We want to compliment Dr. Rosell on the excellent conduct of his study. Our auditor was very impressed with the fact that all the patients on this trial were admitted to the surgical service. When they were found to be inoperable in Stage III, therefore they were transferred to the medicine service and given the choice of being on this

protocol or nor.

The auditor did note in doing this that it was extremely difficult to assess tumor size using the protocol definitions for response or for progression.

The JHBR patient disposition, again slightly more patients are live on the gemcitabine/cisplatin arm, as compared to the etoposide/platinum arm. There are two patients with their updated statistics as of January 1998, who are alive without progression.

Again, the majority of the patients have died from disease, and patients died from other causes, which again, is slightly higher on the etoposide/cisplatin arm, but similar.

Forty-six percent of the gemcitabine/platinum patients, and 28 percent of the etoposide/cisplatin patients were able to complete the six cycles of therapy.

The demographics of the study. This was a study of white males of middle age. There were slightly more patients with good performance status on the gemcitabine/cisplatin arm, about equal Stage III and Stag IV. The adenocarcinomas were well balanced on this study, and there were only four patients on this study who had prior chest radiotherapy.

Again we see a significant response rate in favor of the gemcitabine/cisplatin arm. The median duration of response, however, between the two treatment arms was not significant.

There was a significant difference in time to progression of 1.5 months in favor of the gemcitabine/cisplatin arm. There was a difference in treatment failure that was significant. What is interesting to note here is that there is a greater difference in the time to progression and time to treatment failure on the gemcitabine/cisplatin arm. There is no difference in the median survival, although numerically it is slightly better for the gemcitabine/cisplatin arm.

So in summary we note significant differences between the arms in response rate, time to progression, and treatment failure. There is no difference in the duration of response or in survival -- significant difference.

The median survival, as we know, is 8.7 months versus 7.0 months in a study where 50 percent of the population is Stage IIIB and 50 percent is Stage IV, and about half of the patients have a performance status of 80 or less.

We had twice as many patients on the study who

discontinued treatment on the gemcitabine/cisplatin arm for adverse events, as on the etoposide/cisplatin arm. We have eight patients who chose to discontinue therapy with gemcitabine/cisplatin, while only two patients chose to do so on the etoposide/cisplatin arm.

The pivotal trial for this review was JHEX. This Phase III trial was conducted between August 1995 and February 1997. The dosing schedule for this gemcitabine arm was 1,000 mg/m^2 weekly for three out of four weeks, with cisplatin 100 mg/m^2 on day 1, versus --

[Dr. Schechter is interrupted by a comment off mike.]

Well, that's interesting. We have just changed the pivotal trial. Anyway etoposide 100 mg/m^2 -- I'm sorry, it's just the cisplatin 100 mg/m^2 on day 1 of every four weeks. Let's home nothing else has been changed.

The primary objective of this trial as originally written was to compare survival between the treatment arms, with secondary objectives to compare the tumor response; quality of life; time to progression; time to treatment failure; duration of response; and time to response, and to look at the plasma concentrations of gemcitabine and its derivative dFdU.

Central randomization for this trial. The stratification was to be based on three things: stage (III versus IV); Karnofsky's performance status (90-100 versus 70-80); and by center (there were 48 centers in North America and 15 in Europe.

The sample size was 522. It was supposed to be 520; 522 patients were actually enrolled. This was based on a 33 percent difference in survival rate at one year between the treatment arms, according to the protocol as originally written. The timing of the analyses for all time to event endpoints was not defined in the original protocol.

An additional unplanned interim analysis using time to progression as a primary endpoint was added to this study design. This was based on 309 patients who were enrolled prior to August 1996, but completed six months or more of treatment. The protocol amendment describing the unplanned analysis was appended, and the revised protocol was submitted in July 1997.

With regard to the study design, the post-study chemotherapy and radiotherapy treatment information was provided for the first 309 patients on whom I have information. Follow-up methods for assessment of progression were not defined. Differences in the

definitions for progression and duration of response is noted, using the Sauve(?) definition of progression here, which is an addition of 10 centimeters or less or a 50 percent reduction in overall tumor size -- I'm sorry, for progression -- and 50 percent increase of 10 cm^2 or more. The duration of response was measured from the date of response until the date of progression.

The FDA review is based primarily on the 309 patients. The data on the other patients will be submitted. There was no quality of life data for either Finland or Germany on this study. Quality of life data was collected in the United States and in Britain.

We had 155 patients on the gemcitabine arm, and 154 on the platinum arm. The patients were well balanced, homogeneous in all respects. We note that the median age on this trial is slightly older than the other trials by about four years. We have representation from minority races on this study.

Interestingly, there are five patients in the interim analysis group for whom I have no performance status. I don't know how they were stratified.

With regard to histology, 17.4 percent of the patients on the gemcitabine/cisplatin arm in the interim

group did not have histology reported versus 13.6 percent on the cisplatin arm.

In this study we looked at pre-study radiotherapy, and we found that 9 percent on the gemcitabine/cisplatin arm, and 11 percent on the cisplatin had radiotherapy prior to -- this would be radiation therapy to the chest prior to entering on the trial. In the gemcitabine arm there was one patient who had radiation in 1992. There were two patients in this arm with the radiation, one in 1980 and in 1988.

The disposition on this trial was based on the entire 522 patient population. There are more patients alive on the gemcitabine/cisplatin arm. The majority of the deaths again are due to disease. An equal number of patients in each arm die from other causes.

It is interesting to note here that for those platinum patients who survive, there is a similar survival without progression.

The response rate is significantly better, 23.2 percent versus 6.5 percent. The median duration of response is about four months greater, and is also significantly better on the gemcitabine/cisplatin arm. The median time to progression is 2 months greater in the gemcitabine/cisplatin arm. It is again, significant.

Problems that were encountered in reviewing this was that there were patients on this study who were receiving treatment, what I consider therapeutic radiation to the chest, lung, and mediastinum while on the study. We assigned the progression date the day they began radiation therapy. It is outlined in the review.

The post-study follow-up again is a problem. We don't have any defined methods of tumor assessment on the study, so patients were seen every three months, but how they were assessed is unknown.

Treatment failure, there is one month difference between the two arms in treatment failure, and it is significant in favor of the gemcitabine/cisplatin.

We looked at these results, and we see that there are an equal number of deaths on both arms. That twice as many patients had disease progression, and that was the reason for failing treatment on the cisplatin arm. There were 35 discontinuations for adverse events on the gemcitabine/cisplatin arm as compared to 23 on the cisplatin only arm. There were 18 patients who chose to discontinue therapy on the gemcitabine/cisplatin arm, compared to 11 on the cisplatin arm.

Looking at survival for the interim analysis

group, we have a median survival in the gemcitabine/cisplatin group of 8.7 months, versus 7.5 months with the cisplatin group. There is no significant difference between the arms in terms of survival based on the interim analysis of 309 patients.

For the entire group the median survival by our calculations was 9 months versus 7.5 months for the cisplatin arm. This is in favor of gemcitabine, with a P value of 0.004; with a 95 percent confidence interval at 8.2 to 11 months, versus 6.5 to 8.4.

It would seem appropriate to do an exploratory subset analysis to look at survival by stage. There are 36 patients who were Stage IIIA. The survival for those patients on the gemcitabine/cisplatin arm was 14.5 months, versus 7.2 months for the cisplatin only arm. In the Stage IIIB patients the survival is 13.6 months, with a survival of 8.9 months. There were 129 patients in this group, and there is a statistically significant difference in survival in this exploratory subset analysis.

With regard to the Stage IV patients the median survival in the gemcitabine/cisplatin arm is 8.3 months, and 6.7 months in the cisplatin arm. In this subset of 350 patients we could not find any difference in the survival.

In doing this review, we learned that there seemed to be a difference in survival by region. In North America the median survival was 8.6 months for the gemcitabine/cisplatin arm, while in Europe the median survival was 7.9 months. There is no difference between these two.

When we look in Europe, we discovered that we have a dichotomy. We have 9.4 month survival advantage on the gemcitabine/cisplatin arm, and a 6.3 month survival advantage on the cisplatin arm. There seems to be a difference of about 1.6 months here, while there is only less than a month's difference here.

We tried to look at this by country to see why this was coming. We're always curious. We noted that in Finland we had 26 patients enrolled, but we had 13 months survival on the gemcitabine/cisplatin arm, versus 8.7 months median on the cisplatin arm. In Germany the survival of 109 patients, 10.8 months with the gemcitabine/cisplatin, and 5.2 months for the cisplatin arm, a five months difference. In Britain we note a 1.5 months difference. We note that there is no significance here. This is kind of similar to the U.S. in terms of survival. This P value is highly significant for survival again, for gemcitabine/cisplatin in

Germany.

We wanted to consider reasons why we could have this kind of effect. One of the questions would be a difference in randomization. We looked through the randomization, but is always homogenous. There is no dishomogeneity here.

There is a slight tendency to have more patients with earlier stage disease and better performance status in Europe, more Stage IV patients on the cisplatin arm; just a quirk of fate.

Duration of follow-up, the study in Europe started nine months later than the study in the United States, so the follow-up is about one year less in Europe than it is in the United States.

We thought about an increased number of adverse events, particularly since the survival was so poor in Germany in the final arm. We looked at. In the information that we had, we found no difference in the adverse events, and I think Laurie really has looked at the whole study and found no difference in adverse events.

Laurie has also looked at dosage difference. At this point I'm going to stop, and I'm going to let our statistician present a little bit more information about

this region effect.

DR. CHEN: Thank you.

So I will take a few minutes to present a statistical review on gemcitabine for non-small cell lung cancer. This presentation is outlined as follows. First, I will summarize the study JHEX. Then a statistical issue regarding treatment by region actually will be addressed. Due to the treatment by routine action, survival benefit in each region will be evaluated. Discussions for possible reasons will follow, and discussions will be raised.

Study JHEX was an open label randomized, multicenter Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with advanced non-small cell lung cancer. The randomization was stratified by center, performance standard, and disease stage. The primary endpoint of the study was survival.

A total of 522 patients were enrolled in the study, among them, 192 patients were treated in Europe, and 303 patients were treated in North America.

The study detected an overall significant difference of 1.5 months in median survival between the two treatment arms, favoring the gemcitabine combination. Data available for review at this time are all patients for

survival endpoints, interim patients for dose information, prognostical factors, and toxicity.

Quality of life was factored in North America and Britain. For some reason, quality of life factors were not collected in Germany and Finland. So my initial concern was that the trial might have been conducted differently in Europe and in North America. This prompted an examination of the treatment of region to action. Treatment by region action is an important issue in a trial which is emphasized in ICH guidelines.

This analysis detected an apparent treatment by region. The P value of the test was 0.088. Due to this interaction, the treatment factor was evaluated for region respectively. This slide shows that a significant difference of 3.1 months in median survival was observed in Europe favoring the gemcitabine combination while only a 0.7 months difference in median survival was observed in North America.

This raises a question, why was the treatment in fact different between North America and Europe? To explore possible answers we performed some subset analysis. I would like to emphasize that the analysis only explores this phase(?), and no conclusions will be made.

First, I would like to share with you part of ICH guidelines regarding issues on treatment by region action. The ICH guideline states that if a treatment by center action is bumped(?) this should be interpreted with care, and vigorous attempts should be made to find an explanation in terms of other features of trial management or subject characteristics.

In the absence of an explanation, marked quantitative interactions imply that alternative estimates of treatment effect may be required, giving different weights to the centers in order to substantiate the robustness of the estimates of treatment effect.

Based on interim data we explored the relationship between dose and survival. We found that those patients treated in Europe had a significantly higher mean gemcitabine dose than those patients treated in North America. It appears from this data that a high dose is associated with longer survival.

This raises the following two questions: (1) why was there a difference in mean gemcitabine dose administered for treatment between North America and Europe?; (2) is there an association between dose and survival? However, a further analysis shows a contrary result. Based on the

interim data we selected tentatively a gemcitabine dose level of 900 mg/m^2 as the cut off point to group patients into either lower or high dose group.

This slide suggests that patients treated with low gemcitabine dose had a longer median survival. The difference in median survival between the low and the high dose group is even bigger than that between the two treatment arms. To address this apparent discrepancy in dose effect relationship we need the dose information for all patients.

Similarly, if we choose a gemcitabine dose level of 800 mg/m^2, the results are the same.

We also examined the recruitment before and after interim analysis. We noticed that a significant changing in the rate was observed. Before the interim analysis cut off date August 31, 1996, about 240 patients were enrolled in North America, and 70 patients were enrolled in Europe, while after August 31, 1996, the majority of patients were enrolled in Europe.

The question is, why was there a change in the rate of recruitment between North America and Europe after the interim analysis?

The interim population consists of 70 European

patients and 239 North American patients. Based on the interim data, a trend to offer survival benefit had been demonstrated in Europe, but not in North America. That consistent result was presented in the second pivotal study.

Questions raised are summarized in this slide. Why was the treatment effect different in North America and Europe? Why was there a significant difference in region in gemcitabine dose administered for treatment between North America and Europe? Is there an association between dose and survival? We need the dose information for all patients. Why was there a change in the rate of recruitment between North America and Europe after the interim analysis?

I would like to acknowledge the efforts extended by Dr. Schechter, Dr. Johnson, Dr. Koutsoukos, and Dr. Chi in the studying of the issues here.

Thank you.

DR. SCHECHTER: I did want to back up a minute. I think we did have an answer. The study in Europe was started nine months later than the one in the United States. The one for this problem was a patient pool problem, if I understand correctly. So they problems accruing in the United States, so they opened a center in Europe. Randomization was done centrally.

Lilly was kind enough to respond to these issues, and I think that there was no difference in median dose intensity between the United States and Europe when all patients were examined. We did get answers about the adverse events.

The piece of information that is lacking here is that there is a tendency in some centers for those patients who have earlier stage disease, who have shrinkage of their tumor, to have surgery and resection and/or radiation in a neo-edging(?) kind of setting. This could possibly explain this different. I don't know, because no information on that type of therapy was submitted, and I don't have information on the last 211 patients.

We'll then go on now and talk about toxicity. The safety profile. For the safety profile, we looked basically at the three comparative trials to try and get a good picture of the type of toxicities. This discussion will include: the dosing intensity; death; study discontinuations due to drug related adverse events; and selected toxicity information.

Median dose intensity. In JHBR the median dose intensity was 92.8 percent of expected. In JHEX it was worse. It was 80.9 percent of expected. The gemcitabine

dose per cycle was 2,300-2,400 mg/m^2 for these studies.

Some of the toxicity that is reported has to be considered in light of the dosing schedule. For some schedules where you are giving a drug for a week, the toxicity is unavoidable, whereas if you are doing the treatment once a week, you can adjust or alter that dose based on the toxicity that you see when the patient returns for their day 8 and day 15 injection.

With regard to dose reduction, omissions, and delays, in JHEZ about 45.8 percent of the patients on gemcitabine alone had dose reduction, omission, or delay; 26 on the etoposide/cisplatin arm, or 34.7 percent.

On JHBR, 81.2 percent of the patients on the gemcitabine/cisplatin arm had some kind of dose reduction or delay, some dose adjustment, and 68 percent of the patients on the etoposide/cisplatin arm had a dose adjustment.

On JHEX we had 88.4 percent of the patients who had to have a gemcitabine adjustment, and 31.6 percent of the patients on the cisplatin arm have a dose adjustment; far more patients having gemcitabine dose adjustments at the second and third treatment.

There is only one patient on this trial who had a platinum alone adjusted.

There are only 7 patients who were able to complete up to four cycles of therapy without some kind of dose alteration in the gemcitabine arm of the gemcitabine. Cisplatin, 23.4 percent of the patients had some kind of an inter-dose reduction, omission, or delay. Now for the gemcitabine it was a hematologic, usually lymphopenia and thrombocytopenia. On this arm, as we would expect, the majority were for renal related abnormalities, although thrombocytopenia did occur in one instance actually.

Treatment related hospitalizations. JHEZ had 42 hospitalizations of which I felt 10 were treatment related. There were an additional 15 that were questionable. On the etoposide/phosphate arm there were 39 hospitalizations of which 22 were related I thought.

On JHBR we had 26 hospitalizations on the gemcitabine/cisplatin arm. The cisplatin arm had 13 out of 33, relatively balanced.

When we get to JHEX, we had 109 hospitalizations based on the information in the access database. There were some patients who were hospitalized twice during the cycle. So while you had 96 reported hospitalizations, sometimes it was two. Information about the reason for hospitalization was not included in this database, and was gathered from the

appropriate tables in the NDA.

This is 63 out of 109, and the cisplatin arm was 30 out of 83. Now of these 63 there were 23 that were for nausea and vomiting, and there were an additional 7 that for related things. These are broken down.

Now let's just talk about some selected toxicities. We have a comparison of a 35.4 percent CTC -- I'm sorry. We used in this study, the common toxicity criteria grading. In the other two studies it was the WHO toxicity grading, and there is a little bit of a difference between them.

We have a 35.4 percent Grade 3/4 hemoglobin toxicity compared to a 4.9 percent incidence. This was, I believe, a hemoglobin of less than 7.5 gm/cm; 34.2 percent of the patients had red blood cell transfusions, averaging four units per patients, compared to 9.7 percent on the final arm. In all fairness, this is about 4.2, and this is about 3.1 units per patient.

We didn't see any increase as the cycles increased. I think that is brought out in the new deal. So I said 201 units versus 51. I find this kind of interesting, because on JHBR there were only 20 units of red cells transfused. I don't know whether that was in 20

patients, and was 1 unit per patient or whether it was less.

Platelet toxicity, 51.7 percent of the patients on the gemcitabine/cisplatin arm had Grade 3/4 platelet toxicity; 3.5 percent on the cisplatin arm.

Two hundred and thirty-three plus platelet transfusions were administered in 34 patients. There is in review, something about 10-30 units or I think 10-30 bags, because a unit of platelet is usually 10 bags. Sometimes this was recorded in bags and sometimes in units. No one uses one unit. It is usually 6-10 units together. So you are not sure exactly how many platelet transfusions were administered. There were none on the cisplatin arm.

Neurotoxicity -- neutrophil toxicity. We had 58 percent of the patients on the gemcitabine arm, versus 4.9 percent on the cisplatin arm. Hospitalizations for febrile neutropenia were double, although this is a small incidence. The incidence of Grade 3/4 infections is 3.3 percent versus 0.7 percent, again, not many, but there is an increase.

We had no information provided on the use of hematopoietic growth factors in this study. I think for patients that toxicity, these could be used.

Disturbing is the neurotoxicity. We had Grade 3 neuromotor toxicity reported in 15.9 percent of the patients

on the gemcitabine/cisplatin arm, and only 4.2 percent of the patients on the cisplatin arm, so that's three times more, and not explained.

Grade 3/4 neurocortical toxicity was reported in 4.6 percent of the patients on the gemcitabine/cisplatin arm, but 0.7 percent on the other arm. The other toxicity wasn't too much worse on the combination arm.

Renal toxicity. Now with regard to the treatment related signs and symptoms, renal toxicity was reported as abnormal renal function, renal failure, so it was kind of difficult to get a really good handle. Either we're talking about the Grade 3 creatinine elevations. They were reported in 5.4 percent of the patients on the gemcitabine arm, compared to 2.1 percent in the cisplatin arm. This is the interim group. Remember, I don't have the data for the whole group.

Grade 3/4 hypomagnesemia was reported in 9.4 percent of the gemcitabine/cisplatin patients, versus 2.4 percent of the cisplatin patients, three times more. There was one patient who had Grade 4 hypomagnesemia who had a cardiac dysrhythmia from this.

The Grade 3 hypocalcemia was reported in three patients on the gemcitabine arm, and one patient on the

cisplatin arm. So there seems to be some kind of potentiation of the neurotoxicity.

I am not going to discuss the other toxicity, but I do have information available for those toxicities. I do have a comparison. I did look across studies, and I do have some overheads if anyone is curious about it.

In summary, we have a statistically significant survival advantage of 1.5 months for the gemcitabine/cisplatin arm, compared to the cisplatin monotherapy. This survival advantage was observed primarily in Europe, and in earlier stage disease.

About 80-90 percent of the patients treated on the gemcitabine/cisplatin combination required gemcitabine dose adjustments for toxicity.

No significant improvement in any quality of life parameter measurements were documented in three randomized trials. We have information for the majority of patients on all three studies.

Gemcitabine as monotherapy in a randomized trial had a low response rate of about 7 percent, and it had a median survival time that was numerically inferior to the control arm. No time to event endpoints were statistically significant. The toxicity profile was acceptable in this

study.

In the Phase II trials I didn't mention this. When looking through the published literature on survival, that ranged from 7.0 to 9.2 months, with the one trial based on the 76 patients out of the 84 considered evaluable. For the other 8 patients who did not complete two cycles of treatment, that response rate was 7 months. The median survival was 7 months. So we have somewhat of a difference as we noted. There were discrepancies in the Phase II data.

Thank you very much for your attention.

Agenda Item: Questions from the Committee

DR. DUTCHER: Thank you. Are there questions from the committee for FDA?

DR. D. JOHNSON: Genny, what is not clear to me from the presentation from the sponsor -- and you may or may not have access to the information -- is these differences that you have shown us in toxicity, at least in part might be explainable on differences in numbers of cycles of therapy that individuals might receive.

For example, if one gets only one cycle of cisplatin in single agent cisplatin, one is not going to develop neurotoxicity, but if one is getting on average six

cycles of Gemzar and cisplatin, then one would develop neurotoxicity potentially. I don't know whether that type of analysis was or could be done. Do we have that data?

DR. SCHECHTER: I don't have the data readily available. I could probably do an analysis, but it would probably take a considerable length of time to correlate the data well. I thought you question was very interesting.

I did look at red cells and platelets, looking through the cycles to see if there was cumulative. For the other ones I couldn't easily do this.

DR. D. JOHNSON: For that data that you did look at, were there cumulative toxicities, and is that the explanation for the differences?

DR. SCHECHTER: For the red cells I didn't think so. For the platelets I sort of thought so. See, I didn't look at the Grade 2 either. I only presented the severest toxicity. The review got conducted in a finite period of time.

DR. SIMON: I wanted to ask Dr. Chen, the comments you made about dose, wouldn't those potentially be biased if you used total dose, and if the patients on the gemcitabine arm stayed on trial longer, and lived longer, wouldn't they tend to have a higher dose, for example in Europe than here?

So observing that there was a relationship between dose and survival doesn't say which is causing which.

DR. CHEN: What we used actually was the gemcitabine dose administered for treatment. We used total dose. Then we did not do that kind of analysis.

DR. SIMON: You mean dose per course? Is that what you are saying?

DR. CHEN: Per treatment. Actually, there were treatment cycles, and actually our figure, I assure you, is a mean dose for treatment. It is the total dose divided by the treatments.

DR. SCHECHTER: Computerized information was submitted for each cycle, and then it was totaled, and that's what you used, right, Gang?

DR. CHEN: Right. Also, I would like to add that these analyses is surely we what we call a mixed analysis, because we don't know what should we choose exactly, the total dose of mean gemcitabine dose, or dose intensity as the parameter to analyze the relationship between dose and survival. Now I think we need to explore further after we get all the dose information for all the patients.

MR. GIBBES: In the various sponsor studies and looking at the JHEX study, patients who received gemcitabine

plus cisplatin seemed to have more adverse effects than the patients who just received cisplatin. Is there any reason to think that these drugs increase each other's side effects more than by themselves?

DR. SCHECHTER: I think that the toxicity is more than additive, possibly synergistic in some areas in neurotoxicity. That's my impression. The company has confirmed that there is synergy. You know, it's interesting, because I understand there is a big ECOG study going on. Are any of you involved? Does anybody have any information about that study?

DR. D. JOHNSON: That's another one of my conflicts. ECOG has a 1,200 patient study underway that has four arms, that is evaluating four separate currently used regimens, including gemcitabine and cisplatin. That trial has close to 700 patients now. At the initial interim analysis done for toxicity purposes, principally because for the first time in more than a decade we had elected to include performance status 2 patients in the study, previously having excluded those individuals because of concerns of toxicity, but because of our impression as clinicians that these regimens were somewhat less toxic, we included them.

In the initial analysis of 100 patients per arm, approximately 15-20 percent of whom were PS-2, the overall toxicity assessment showed no difference in those four arms. I should tell you that the other arms are cisplatin and taxol, which is our alleged standard arm; carboplatin and taxol; and cisplatin and taxoter(?). The dose of cisplatin for all the arms is identical except for the gemcitabine arm, which has 100 mg/m^2, precisely the dosages that were presented here today.

The overall analysis shows no difference in toxicities. If one look at PS-0 and PS-1 patients, there is no differences, however, if one looks at PS-2 patients, there are marked differences in toxicities. I don't know that I'm really at liberty to divulge the differences, but it is considerable, and renal toxicity is one of those toxicities.

So I think perhaps the more intuitive individuals will figure out what that is, but suffice it to say that it is also the basis of some my questioning.

DR. SCHILSKY: I wonder if you could just clarify something about the interpretation of the JHEZ study. That was the gemcitabine alone versus cisplatin and etoposide. You characterized that study as being a randomized Phase II

study.

DR. SCHECHTER: Well, I copy titles.

DR. SCHILSKY: The question I'm trying to get to is whether it is valid to compare the two arms of that study for any efficacy parameter. I'm trying to decide. In my own mind the usual definition of a randomized Phase II trial is a trial which does not usually have sufficient statistical power to draw any comparisons with respect to efficacy parameters.

So if that is the case with this study, then I think really what we have is a Phase II study of single agent gemcitabine, which is not particularly impressive with respect to the outcomes. And we have a Phase II study of cisplatin/etoposide which is equally unimpressive with respect to the outcomes in the particular patient population that is studied.

So if you agree with that, then I'm not sure that we actually have any comparative data with respect to single agent gemcitabine.

DR. SCHECHTER: That's probably a correct way to interpret that. It was based on response rate, and it was to look at toxicity profiles.

DR. D. JOHNSON: I have another question to ask

you, Genny, that you may or may not have the data. You broke out the patients in the JHEX trial based on stage. The only group in which you were able to demonstrate in a subset analysis, a statistically significant difference in survival was the Stage IIIB patients.

Of all the patients that one would include in a study like this, they are probably the most heterogeneous group, and where one could expect potentially to see a disparity of allocation of patients, which in fact could account for the differences, as much as the difference that you showed.

Do we know if anything about these Stage III patients? Again, I heard nothing in the presentation. I don't know if you got in the raw data -- specifically, what I want to know is how many of these patients were IIIB on the basis malignant plural effusions, and were those patients equally distributed in the two arms? That is an important issue. Those patients function like Stage IV; IIIB patients who do not have plural effusion function more like IIIA.

DR. SCHECHTER: There was no information provided as to how the patient was staged prior to enrollment in the study. There were protocol criteria, but no information

that was sent to me about that information. I have no idea. I did notice -- I was pointing out with that radiation therapy there are two patients who are Stage IIIB had radiation in 1980 and 1988, and one in 1992. So that is a problem. I don't have that information.

DR. DUTCHER: Does anyone from the sponsor have that information?

DR. SANDLER: We do have some information in terms of plural effusion. There were small numbers in both arms of around I believe six patients or so in either arm that IIIB plural effusion.

DR. D. JOHNSON: Recognizing the numbers are small, but presumably they were reasonably well balanced in the two arms. You couldn't account for this survival difference based on the huge disparity?

DR. SANDLER: At least not with respect to plural effusion -- the patients with IIIB with plural effusions.

DR. SCHECHTER: Is this data from the whole study or from the interim group?

DR. SANDLER: That would be the whole study.

DR. MARGOLIN: I'm sorry to keep focusing on this platelet transfusion issue, but I still am curious about one thing. When you gave the data for the higher incidence of

requirement for platelet transfusion in the combination group in JHEX versus platinum alone, and the caveat that the raw number you were given, that you are not sure if that represents units or episodes. I think it would be very crucial to have that answer.

In addition to that, to know whether the platelet transfusion requirement was somewhat front loaded in that the dose adjustments required by the protocol pretty much took care of the problem, or it was an ongoing, sort of continuous problem that didn't get resolved by dose adjustments in responders?

Now we have a very modest median survival difference of six weeks. Once somebody is basically recognized as requiring platelet transfusion, they are also in the doctor's office every two or three days, and on those days that they get a transfusion, they are sitting there for several hours, heavily premedicated, chills, et cetera. I just think we really need to know the impact of this problem in that group. It's rhetorical. I realize you don't have an answer.

DR. SCHECHTER: I went to look at the transfusions, and that's how I discovered a discrepancy. I do see there are more at greater time periods. But the

patient's dose was being adjusted at the same time.

DR. D. JOHNSON: I actually have one last question that is probably better addressed to the sponsor, but it does impact on what Kim is asking. That is that some investigators have made a lot out of the sequencing of this doublet of cisplatin and gemcitabine. The data were all lumped together, perhaps very appropriately, the Phase II data.

But in the literature some investigators, specifically the Indiana investigators have used a day 1 sequencing of cisplatin and gemcitabine. Other investigators in Italy have used their cisplatin on day 2 based on some preclinical work. The South African investigators have used day 15 administration of cisplatin.

There are seemingly differences in the toxicity profiles specifically related to the incidence of thrombocytopenia. Now that may be real, or it may be manufactured or imagined. I have my bias about that. I wonder if the sponsors want to comment about that before for us, since that appears to be an issue for many people; certainly Dr. Margolin.

DR. PEDERSEN: You are correct that there are some studies that have used exactly those schedules that you

referred to. In the studies that have been conducted, there have been raised questions of whether by giving the gemcitabine and cisplatin early on, like either on day 1 or day 2, you get more of a neutropenia episode versus more leukopenia episode with the cisplatin on day 15.

Obviously, it is very difficult to make straight comparisons between studies. We don't have a final conclusion of that, which of the two is the optimal way of doing it, where you get the best toxicity profile. But you are correct, the question has been raised in the earlier demonstrations versus the later demonstrations and the cycle of the cisplatin is great.

DR. SANDLER: I would like to try and make a comment regarding transfusions and packed red blood cells and platelets in the JHEX trial. It did appear, at least as I reviewed the data, that for packed red blood cells at least, there appeared to be more transfusions, events defined as patients receiving transfusion in cycles 4-6 versus 1-3. We have a slide that shows that.

Platelet transfusions, at least as represented by patients receiving transfusions -- I'm not sure of the exact number -- appeared to be similar throughout.

In terms of active blood cell transfusions, this

is cycles 4, 5, and 6. These are 1-4. Cycles 1 and 2 had number of transfusions here. It appears that 19, 23, 29, in cycles 3.

Now what this takes into account is again, the number of transfusions. Bear in mind again, patients that are less patients at risk, so the patients achieving transfusions is actually going up. Because there are less patients who are actually at risk, less patients are receiving cycles 4, 5, and 6.

DR. SCHECHTER: It goes from 5.2 to 24.6, the maximum in cycle 5, and it drops down in cycle 6 to 18.2 percent of the patients.

DR. D. JOHNSON: Can you go back one slide? I'm not sure I understand your numbers there. Your number at the top, N equal is the number of patients. What is the 1-1-2-0 there? What is that?

DR. SANDLER: That's the number of patients experiencing that.

DR. D. JOHNSON: Oh, the common toxicity criteria.

DR. SANDLER: Percent, sorry.

DR. D. JOHNSON: So that's 1 percent, 1 percent, 2 percent, 0 percent, is that what you're saying?

DR. SANDLER: Right.

DR. D. JOHNSON: So the numbers down below were the number of patients or the percent of patients?

DR. SANDLER: Those are the number of transfusions themselves.

DR. D. JOHNSON: So in cycle 1, 11 patients received red blood cells versus 8, is that what you are saying?

DR. SCHILSKY: That says that there were 11 transfusions give. It doesn't say how many patients got the transfusion.

DR. D. JOHNSON: One patient may have gotten 11 transfusions or 8 patients may have gotten 1 transfusions?

DR. SCHECHTER: It's eight patients in cycle 1.

DR. D. JOHNSON: That's what I'm trying to figure out. If it's one patient that gets 11 transfusions, it doesn't matter too much to me. But if it is 11 patients getting 30 transfusions each, that matters a lot.

DR. SANDLER: I'm told this is numbers of transfusions, not numbers of patients.

DR. SCHECHTER: Eleven units?

DR. SANDLER: Eleven transfusions. It may have been 2 or it may have been 3. So it probably represents 3-5 patients. I can't tell you.

DR. D. JOHNSON: So now you are telling me in cycle 6, 26 episodes of transfusions versus 3 in cycle 3?

DR. SANDLER: Right, and again, less patients at risk.

DR. D. JOHNSON: It would appear to be 25 percent versus about 5 percent.

DR. J. JOHNSON: I think it is interesting to reflect that the patients on the gemcitabine may have gotten more courses, and therefore they got more transfusions, but whatever it was, that was a cost of achieving the six week additional survival in this group of patients. So I'm not sure how much emphasis we should place on the fact that it happened because they got more courses. It happened.

DR. D. JOHNSON: It may be that transfusions cause you to live longer.

DR. EINHORN: I'd like to comment. I keep hearing this six week median survival time. It's the wrong thing to focus on. I'm in danger with people like Dr. Simon here, of looking foolish. Median survival time is a single point in a survival curve, and it facilitates supporting an abstract where you can't put in the survival curve.

You don't want to concentrate on median survival. You want to look at the whole curve. This is not a study

that shows a six week difference in median survival. This is a study that at all points in the survival curve, shows a statistically, and I feel clinically significant difference.

The same thing with JHEZ. Dr. Schechter mentioned that there was a 1.5 month difference in survival favoring etoposide and cisplatin versus gemcitabine. That happens to be the one point on the entire survival curve were there was the widest separation. Those survival curves are absolutely superimposable. That one single point, they diverted minimally. The rest of the survival curve, they are the same.

At the tail of the survival curve, which is far more important than the middle part of the survival curve, the gemcitabine arm was on top of the etoposide/cisplatin arm, but there was no difference in the survival curves on JHEZ. Median survival time is somewhat of an arbitrary, artificial designation, rather than looking at the entire survival curve itself, which is the important thing.

MS. BEAMAN: I do feel that there is a reason to place a little emphasis here. I keep hearing the term "increased survival" being used rather loosely, and where we should look at the curve, and all of this. I think that it may be better to call it extended time; extended time by one

month, extended time by three months.

Then on the other hand, what is time when the quality of life isn't clarified? Is it with or without quality of life? Are they getting the transfusions to stay here one month or two months longer? That's very confusing that you would want to focus on one particular -- you want to get away from one particular point. The entire curve, yes, I quite agree, is important, but length of time in total misery.

I heard you mention nausea and alopecia. Those are not the two most frightening things to a cancer patient. I beg to differ with you there. Being here, and having some degree of quality of life during that time is also extremely important and at the top of the list.

Just a comment.

DR. EINHORN: I think that was nicely stated, and I agree. I just want to correct one thing. I said the most important side effects of chemotherapy, not of the disease, but of chemotherapy to a patient that bothers the patients most, and this is reported in the literature, during chemotherapy is nausea and vomiting and alopecia or loss of hair.

The questions that you raised were very pivotal.

The only answer that I can give to that is that there was no evidence that there was any detriment to quality of life with the superior survival on the JHEX compared to single agent cisplatin.

Yes, it's true that there are more transfusions required on this study. Yes, it's true that on the CDC slip there is more lowering of white blood count and hemoglobin. Yes, it's true that there is more transfusion. No, it's not true that there is any evidence that there was worst quality of life for compensate for the increased survival.

MS. BEAMAN: Is there evidence that there wasn't?

DR. EINHORN: On JHEX a different type of quality of life assessment was looked at, and I don't believe that that data was presented or given. Anders, do you want to comment on that at all?

DR. PEDERSEN: The quality of life analysis on the JHEX study was not completed for the review by the FDA to look at. There has been no indication whatsoever that there is any difference in the quality of life between the two treatment arms. There are no indications that prolonged survival is obtained at the expense of quality of life by getting the treatment, as you are asking the question.

MS. BEAMAN: I realize that you are the expert

that is showing me the data.

DR. SCHECHTER: Carolyn, I did a look at survival, and I did a survivor's cycle analysis for the interim. When I did that I found that there are 25 patients who got gemcitabine/cisplatin in less than three cycles who are survivors. There were two patients on that arm who got no treatment that are reported to be survivors. So I find this whole question -- I'm not sure. I'm very disturbed. We did not find any difference in our analysis of quality of life data.

DR. LIEPA: Keep in mind that the FDA has not had the opportunity to review this data. This is a preliminary analysis of the quality of life information from the JHEX study. This is simply looking E scores. The fact is the summary of the domains of quality of life, and takes into account also the lung symptom subscale. So it's a total.

As you can see when you look at the mean scores, there is no difference throughout treatment of quality of life. There is no apparent decrease, no apparent difference between the two treatment arms.

DR. SANTANA: What is the end for each of the cycles? How many of the patients are responding for each of the cycles? Has that been adjusted?

DR. LIEPA: We have not taken into account the loss of patients over time. So you can see that it does rapidly decrease, and that is based on the number of patients, number of observations. So it does reflect the decrease.

DR. CHEN: This was based on the quality of life data in North America only, or based on which part of your data?

DR. LIEPA: This was based on all patients. We did not have the patients in Germany and Finland participate, and in the amendment when we added those sites, there were not translations available at that time. So that was the only reason those patients were not included; simply because we did not have a validated instrument to utilize in patient population.

DR. CHEN: So basically, your analysis was based on the patients treated in North America and England, right, the quality of life?

DR. LIEPA: This is based on North America and the U.K.

DR. KROOK: I think I'm probably giving away my age a bit here, but the way we used to look at some quality of life was the change in the performance status, several

studies that I at least recall where the status performance status at least improves.

Can we show in the responders perhaps some not long detailed thing, but the judgment of the physician or whoever that the performance status -- I realize in the Karnofsky if we go from 70 to 90, that there is an improvement. We used to look at that as quality of life. Was there any effort to do that, a change in the performance score? I realize we had it down to -- correct me -- 60 or 70 in the randomization.

DR. PEDERSEN: We have not analyzed that.

DR. DUTCHER: Are we ready to look at the questions?

DR. D. JOHNSON: Jan, I actually have a question that I'd like to pose to the FDA regarding some procedural issues before we start to address the questions, and it's really to the Bobs. That has to do with the -- I recognize that this is a drug that has already received FDA approval for one indication. Perhaps the requirements here are somewhat different, but I think at -- and I haven't spoken to any members of the committee -- but I was actually surprised that we were given interim to review, when in fact the full data set are available.

That is very confusing to me, because what we have heard today in large part is an interim analysis, which did not have survival as its endpoint. Candidly, a lot of the discussion that has gone on today from my perspective is interesting, but if there is a true survival advantage, and there is no overt evidence of deterioration of quality of life and no excessive toxicity, I'm inclined to approve such a drug, whether it is this drug or some other.

All I know is that I hear that the full data show that there is a survival advantage, so I'm really confused about my role. I am surprised, because if it is okay for us to take the interim, and then hear that there are other data that show survival, then I can go forward with answering these questions pretty easily, frankly.

I'm interested in the policy. Does it differ when we are looking at a supplemental application? Dr. Temple mentioned this a little bit earlier, and I'm not sure I really understood your question, although I think you were thinking what I'm thinking about this.

DR. DE LAP: Well, I do feel that we're a bit out on a limb when we accept applications that represent interim data on a study for which full data are going to be available at some point in the not too distant future.

Obviously, there is a trade off between getting applications in and processed and acted on as quickly as possible versus waiting for all of the mature data to be available.

I think in this setting we do have the updated results of the survival on all the patients, and I think that that is very important. So I think that we are satisfied that there may be a body of evidence that is sufficient here for advisory consideration, because again, for the most important endpoint we do feel that the full data are there. For the other endpoints, in terms of making an assessment of relative toxicity, things of that nature, we have quite a bit of the data, although we don't have all of it.

I think that's the one area where maybe the policy might be a little bit different for a supplement versus an original application, because with a supplement we do have a primary experience regarding the safety of the product. It may not be as critical to supplement that with additional safety data from further studies.

Does that help?

DR. D. JOHNSON: Yes, it does.

DR. TEMPLE: Remember, we don't decide when a company feels its database is adequate to support approval

of a new claim. So we have an application to review. If we thought the data were just on their face, inadequate to support it, we could refuse to file it and so on, or we could turn it down without bringing it to you.

But as long as it is reasonably credible, we would like your advice. Your advice could be don't approve it until you get the rest of the data. That's perfectly reasonable advice for a committee to give. As Bob says, we now have the survival data on the largest and most critical study.

What I was griping about before was the monotherapy claim, which as you said, I couldn't quite understand the theory of what would make that persuasive.

DR. D. JOHNSON: But in fact, I could, if I had confidence in the survival data, I believe I can make appropriate extractions from existing data, which is what I think I hear we're doing in some other ways, to make an argument. And that's why I was asking the question, because we are going to come to that, and there will, I suspect, be a lot of discussion about it.

DR. TEMPLE: You are completely free and encouraged to say whatever you think about the state of the data. We bring it to you, because we had an application

that we had no grounds for rejecting out of hand and saying it's not fileable. So you are our source of advice.

Agenda Item: Committee Discussion and Vote

DR. DUTCHER: All right, we have a fairly lengthy exposition of the questions. I will just read the proposed indication: as a single agent or in combination with cisplatin for the first-line treatment of patients with locally advanced (Stage IIIA or IIIB) or metastatic (Stage IV) non-small cell lung cancer.

You have the table of the analysis and of the toxicities.

Questions:

1. In the study JHEX, analysis of the 309 patients for whom full data has been submitted to the FDA shows no statistically significant difference in survival between the Gemzar/cisplatin and the cisplatin treatment groups.

In this study, an updated survival analysis on 522 patients shows the Gemzar/cisplatin treatment to a better MST by 1.5 months, with a P value of 0.004. Complete data was not submitted on the 213 additional patients for other efficacy parameters, dosing and toxicity. Thus, the FDA

analysis of this study is not complete.

In the updated survival analysis of study JHEX, there is an unexplained disparity between Europe and North America. In Europe (192 total study patients) the Gemzar/cisplatin regimen MST is 3.1 months better, with a P value of 0.0025) and in North America (330 total study patients) the Gemzar/cisplatin regimen MST is 0.7 months better (P value of 0.157).

Should this disparity impact on our interpretation of the study survival results? If so, how?

Should we vote? All those who believe this disparity should impact our interpretation raise your hand. All those that vote that it should not? Abstained? Okay, so that was unanimous to assume that was random at this time.

[Whereupon, Question 1 was answered affirmatively.]

2. In the study JHEX, does the better efficacy on the Gemzar/cisplatin treatment arm (especially the 1.5 month longer MST) outweigh the increased toxicity of this regimen?

Would anybody like to discuss this issue? Dr. Simon?

DR. SIMON: I guess I would like to make a comment about something that sort of is related to this, but not directly this. I would have liked to have seen -- I'm not sure that there really is even this survival difference. I would have liked to have seen a confirmatory study demonstrating that there is a statistically significant survival difference.

Some diseases in some setting, it's impossible to do that. For advanced lung cancer, I think it's quite feasible to do that. Basically, I enter sort of an analysis like this saying a priori I view the likelihood that say the combination compared to cisplatin is associated with even a two month survival improvement of median maybe.

My a priori, I believe the odds are 10:1 against that. Then a study is done that comes up with a P value of 0.04. When I crank in at the end of that, my assessment as to whether there is a two month or more survival improvement, it changes from 10:1 against, to 2-3:1 in favor.

So now I'm willing to entertain that this looks like there is something of value here, but it would take a confirmatory study to demonstrate to me that that is real.

DR. MARGOLIN: My comments will be slightly more

clinical than Dr. Simon's elegant statistical comments.

I think that we're trying to make a pretty big decision based on some study designs that have recognized flaws -- that's one comment -- or insufficiencies I guess.

The other is my concern that again, I try to think about what is going to happen in the real world if we approve this drug. Because of the toxicity in the combination regimen, more adjustments and more corners are going to be to cut in the hands of the doctors who actually deliver these to patients. Since the benefit is so borderline, to recognize that it's statistically significant, but its clinical significance is probably very modest, we may just lose that by the things that people will do to deal with the toxicity.

DR. DUTCHER: Well, in terms of that, I guess the question I have is do we even know what dose here with all these dose adjustments?

DR. D. JOHNSON: Let me make some comments from a clinical point of view as well, and back up a little bit to the meta-analyses that have been alluded to. First of all, the best supportive care in patients who have advanced disease, the median survival for these patients is about four months.

If one uses cisplatin-based chemotherapy, using drugs available to us prior to 1990, the median survival is approximately six months. So there is maybe an eight week improvement in median survival. I totally agree with what Dr. Einhorn says regarding the survival curves. It's really one point one wishes to look at, but

I think it's useful to look at some benchmark figures.

So you go from about four to six months. At one year with supportive care, 10 percent of patients will be alive; with cisplatin therapy 20 percent of patients will be alive at one year. You get roughly a doubling of the survival rate. That is not alive and cured, that is just alive.

With this particular product what we see is a further six week improvement in median survival. So now you are talking about 12 weeks total over supportive care if one makes an extrapolation. I realize this is not a statistical test.

Also, we are seeing a survival rate of around 40 percent at one year -- not 10 percent, not 20 percent, but 40 percent. Even if you lump in some of the patients such as the Stage IIIs, which I would personally believe partly

accounts for this shifting of the curve, I think nevertheless it seems to me that you are seeing an improvement in survival.

Beyond that, it is incremental, to be sure, modest to be certain. But if we had made these modest, incremental improvements in the war between the states, I would be the president today.

DR. OZOLS: I agree with Dave -- I agree with him about the war -- I agree that I think this is a clinically beneficial incremental improvement in a very difficult disease. The one year survival again, is 39 percent versus 28 percent, and the survival curve is about as good as you are going to see in this disease. I think it is as good as anything we have seen in a comparative trial that this committee has looked at or is in the literature.

The toxicity, I think a large part of that is again, clearly the doses may not be right. This is something that needs to be figured out. In your trial, gemcitabine was the only drug that was combined with cisplatin at 100. So maybe we don't need 100. Maybe some of that interaction between the drugs causes a success of thrombocytopenia and so forth.

Taken on a whole, I think at a minimum the

physician and the patient should have their choice about this, to look at the toxicity, to look at the benefit. I think it is real. It is statistically significant. I wouldn't support another 500 patient trial just to confirm this. I think we should take the data on the whole, and I think it is a clinically important advance.

DR. KROOK: I guess I would like to comment on the fact that the toxicity -- Bob and Dave have talked about the survival -- but I don't see worse toxicity in this than perhaps the disease, plus whatever we want to give does. I don't see that the toxicity is that much worse. So I guess I look at it that way, as this is a regimen that is relatively tolerable. We are in a disease that unfortunately has a lot of toxicity in itself; just look at the death rate and all the things that go with this disease.

DR. SANTANA: I'm the only pediatrician in the group, so I don't treat patients with lung cancer, so I have an unbiased opinion with a lot of the issues that are being discussed. I think Dr. Ozols in my opinion, hit it on target. Given that there may be a suggestion that there may be some efficacy, I think we need to give the physicians and the patients the choice. As long as we are clear with what the potential adverse events are and effects, and the

patient and the physician have the choice if they want this therapy or not.

DR. DUTCHER: I would also like to comment that we have focused on the hematologic toxicity, but in fact these studies were not done with a platinum analog that we're all now used to using that does cause significant hematologic toxicity in addition in this disease. I think the paradigm for treating this disease has changed a little bit in terms of being able to deal with the supportive care better.

DR. SCHILSKY: I guess I'll just add my two cents. I tend to agree with most of the comments that have been made. I think the difficulty for me, as someone who doesn't treat a lot of lung cancer patients is how to evaluate this particular combination in the context of the universe of therapies available for lung cancer patients.

It seems to me to be pretty clear that gemcitabine/cisplatin is superior to cisplatin alone. Cisplatin by itself is probably not commonly used as a therapy for patients with non-small cell lung cancer. So I guess the challenge to the oncology community is when the patient walks in the door with the diagnosis of non-small cell lung cancer, and you have your initial opportunity to make a treatment recommendation on the best possible therapy

for that patient --

DR. DUTCHER: You put them on the ECOG study.

DR. SCHILSKY: Well, sure, but since unfortunately not every patient goes on the clinical trial, there are practical decisions that have to be made. The issue that I think will be a challenge to all of us is do you treat that patient initially with cisplatin and gemcitabine? Do you treat them with cisplatin and vinorelbine? Do you use a regimen that includes a taxane? Of course we don't really have data to guide us in making those decisions.

We will have, I'm sure, marketing to guide us in making those decisions. I suppose that on balance, ultimately physicians and patients should have the opportunity to make those choices among a variety of regimens that appear to have activity. It is difficult to grapple with where you position these various regimens relative to one another in the universe of available therapies.

DR. OZOLS: I think the ECOG study will give us some guidance in that. Again, there are always going to be patients who don't fit in those type of criteria, where for some, gemcitabine for whatever reason, is going to be a preferable alternative than cisplatin combinations.

I think again, having that availability of an active drug that has demonstrated in this trial, I think will be useful in the overall armamentarium. It's a difficult disease, where often we are treating on the basis of toxicity, performance status, and all sorts of considerations go in.

DR. SIMON: I can see how it gives a medical oncologist a broader decision, but I can't really see how it gives any benefit to the patient.

DR. D. JOHNSON: It is probably worth making one other -- and this is sort of intuitively obvious to physicians and patients who are involved in the care of patients. There are randomized studies though that have used supportive care. When we talk about toxicity of treatment we ignore toxicity of disease.

It's not like lung cancer goes away. In fact, in the one study which look at this really carefully from Canada, it turned out that the best supportive care patients had infinitely more toxicity than people who got what many of us consider to be so-called ineffective therapy. I didn't even touch on cost analyses, which showed that that group also cost more money to take care of.

So I do think that we have to put into context

what these toxicities really represent, and understand that untreated non-small cell lung cancer, like a lot of cancers, is not a benign process, and these patients do very poorly.

So I think when we focus in on the treatment-related toxicities, they are very different, as they are in this trial, but if you look at the disease-related toxicities, they may also be very different in favor of the treated arm. That's the only point I'm trying to make.

DR. TEMPLE: I have no comment at all on whether the benefit is worth it or anything like that, but I did want to make an observation about the kind of data that we have to deal with here, because it contrasts so sharply with what you often have to deal with in this committee.

These aren't Phase II studies with no control group where you get to see a response rate, and guess endless and infinitely about what the real benefit is, which is never supported by clinical data showing that symptoms go away, or hardly ever. It is also not a trial in which people have tried to show equivalence to some regimen whose activity in that particular setting is not knowable.

What you actually have are modest differences, but you have differences between treatments in well designed trials, two of three of which were designed to try to show

those differences, which from the narrow point of view of trying to understand what actually happened, as opposed to what might have happened, is unusual, and I guess from our point of view refreshing.

We urge a lot of attempts to show differences, and often just see equivalents under circumstances where that is hard to interpret. So from just talking about the kind of database available, not what you should conclude from it, this is certainly relatively speaking, unusual. Rich might like to see another trial doing that, and that would be a pleasure, but usually there is no trial showing a difference. It is relatively unusual, so I just wanted to observe that.

DR. DUTCHER: Okay, so Question 2, for those who do think that the study shows better efficacy on the Gemzar/cisplatin treatment arm, which outweighs the increased toxicity of this regimen, please raise your hand? Nine. Those who do not? Those who abstain?

[Whereupon, Question 2 was answered affirmatively.]

3. Is Gemzar approvable for the use in combination with cisplatin for the palliative treatment of Stage III and Stage IV non-small cell lung cancer?

Comments? Want to just go to a vote? Okay, is Gemzar approvable in combination with cisplatin? All those who feel yes, please raise your hand. Nine, yeses, and one abstention -- a no. Nine yes, one no.

[Whereupon, Question 3 was answered affirmatively.]

4. Is the study JHEZ a well controlled clinical trial demonstrating that Gemzar as a single agent is safe and effective for the palliative treatment of non-small cell lung cancer?

Comments? Dr. Johnson?

DR. D. JOHNSON: Having said everything I have said earlier, this is the thing that I find problematic. I actually think that this is what Dr. Temple was addressing earlier. This trial was not designed for that purpose. It is clearly not designed for that purpose. It stated so in the objectives. So I don't know how one can conclude that it's a well controlled trial demonstrating that this agent is safe and effective, since that wasn't the purpose of the trial in the first place.

It is a small, randomized Phase II in my view, not a Phase III, that looked at response as the primary

endpoint. I completely agree again with Dr. Einhorn's comments vis-a-vis response. It is a useful thing for assessing whether or not one wishes to pursue a drug in a particular disease, but in terms of an efficacy endpoint, especially in advanced non-small cell lung cancer, it has time and again, as he showed on his slides, proved to be an inadequate surrogate for demonstrating the ultimate impact of a drug on survival.

So I personally find this as a difficult one. If they want to recraft the question so that I can infer information from this, then I would be willing to answer the question in a different way. But as Dr. Simon pointed out, if you are trying to show that this thing is equivalent to platinum/etoposide, this study simply does not do that.

DR. DUTCHER: Let me give you another question. Does the --

DR. D. JOHNSON: Aggregate indicate -- I think that's a different question, and I think I would answer that in a different way.

DR. OZOLS: That is Number 5.

DR. D. JOHNSON: That's right.

DR. DUTCHER: Do you want to vote on 4?

DR. D. JOHNSON: Well, I can't vote, so I don't

care whether you vote or not.

DR. TEMPLE: We would ask you to identify the basis for a favorable conclusion, if you reach one, I mean the evidentiary basis.

DR. DUTCHER: Let's vote on 4. Is this trial a well controlled clinical trial demonstrating that Gemzar as a single agent is safe and effective for the palliative treatment of non-small cell lung cancer?

All those who say yes, please raise your hand. One. All those who say no? Nine.

[Whereupon, Question 4 was answered negatively.]

So looking at the aggregate of the Phase II data available for Gemzar:

5. Is Gemzar approvable for use as a single agent for the palliative treatment of non-small cell lung cancer?

Comments?

DR. SWAIN: I hate to disagree with Dr. Johnson, but I will. I think that using his same argument, if you are just using Phase II data which has as the endpoint, response rate data, that is not going not to be very useful in determining efficacy. So that the best you could do would be to give an accelerated approval for single agent gemcitabine, which there are other agents available, so that

wouldn't make sense to do that. So I would have to answer that no.

DR. OZOLS: Again, I agree with some of what you are saying, but if you take a look at the pivotal study, you've got cisplatin which was marginally improved, but definitely improved by the addition of gemcitabine. So you are clearly adding an active drug and making it better. I can see certainly scenarios where patients -- cisplatin may not be indicated, and patients are not going to get cisplatin, and gemcitabine may be the appropriate choice in that type of a situation.

Again, I think it comes down to availability and choice. It is an active agent in non-small cell lung cancer. We are not testing it in these randomized trials if we didn't think it was an active ingredient.

DR. SIMON: I agree that it's an active agent. Is there any evidence of patient benefit?

DR. SCHILSKY: I guess that's the key question in my mind. I think all the data are fairly conclusive that the drug has activity as a single agent. I think by virtue of the vote we just took, it's pretty clear that we agree that the drug adds something to cisplatin chemotherapy, but whether by itself the drug actually produces meaningful

clinical benefit for patients, I don't think we've seen data to suggest that is the case.

I think in my mind the question is unknown. I wouldn't suggest at this point that it doesn't, but I don't think we have sufficient evidence to make a judgment either way.

DR. DUTCHER: We have to remember that as Dr. Temple said, most of the time we don't have all of that information when we are faced with looking at a drug. What we have for this now, for the single agent data, is what we usually have for accelerated approval.

DR. D. JOHNSON: Again, the data, in my view, the aggregate data give me more confidence in the activity, and I do think the randomized trial comparing the combination to cisplatin alone lends further evidence to the activity of the drug.

There are also data that were not presented today that are published, however, in full in the peer reviewed literature that look at single agent gemcitabine compared to platinum and etoposide. There is a German study and a Taiwanese study. They were again random Phase IIs. They were really what we heard from this trial. Those data are totally consistent with what we have seen.

That is, the pattern is no benefit compared to a cisplatin/etoposide, which for two decades was the standard therapy in ECOG for metastatic disease, and which has proven to be better than supportive care alone. So to show that a single agent is equivalent in many ways -- I recognize they are not formal, randomized data, but in a mini meta-analysis one could come up with an argument for doing that.

I, as a clinician, can accept that the two are there. Now I respect the opinions of my colleagues. I have made the same arguments numerous times in other forums about this. I personally would be willing, if I were voting, to vote in the affirmative for this one.

DR. DUTCHER: Other comments? All right, let's vote. Is Gemzar approvable for use as a single agent? Can you separate the two indications, accelerated or not accelerated, or do you want to even get into that?

DR. TEMPLE: Well, you don't really have a very good basis for accelerated. That has to be a situation where there is no alternative therapy. There is, you can use the therapy comparative. So unless somebody thinks of some reason why it has some major advantage or something, it doesn't really solve that problem. I think with all the combination therapies that were already studies there are

other ways to treat the condition. So it does not on its face, seem suitable for accelerated approval.

DR. DUTCHER: Is Gemzar approvable for use as a single agent for the palliative treatment of non-small cell lung cancer? All those who think yes, please raise your hand. Six. All those who vote no? Four. For the reasons discussed.

All right, thank you. We're going to take a break for lunch. We'll be back at 1:30 p.m.

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

A F T E R N O O N S E S S I O N (1:30 p.m.)

DR. DUTCHER: We are going to be discussing capecitabine this afternoon. We have a few new people at table, so those of you who weren't here this morning, and for the new people, I think we will just go around one more time.

[Introductions were made.]

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

In accordance with 18USC Section 208 and 505 of the Food, Drugs, and Cosmetic Act full waivers have been granted to Dr. Victor Santana, Dr. Kim Margolin, Sandra Zook-Fischler, Dr. Janice J.P. Dutcher, Dr. Sandra Swain, Dr. David Johnson, and Dr. George Sledge.

In addition, Dr. Robert Ozols has been granted a

full waiver under 18 U.S.C. 208.

A copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information officer, located in Room 12A-30 of the Parklawn Building.

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

In the event that the discussions involve any other products or firms already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in

the interest of fairness that they address any current or previous involvement with any firm whose products they wish to comment upon.

I thank you for your patience in the conflict of interest statements. Thank you.

DR. DUTCHER: We'll begin then with the sponsor's presentation. Dr. Griffin.

Agenda Item: NDA 20-896 Xeloda (capecitabine) Tablets - Hoffman-LaRoche Inc., Sponsor Presentation - Cindy Dinella, M.D.

DR. DINELLA: Good afternoon. My name is Cindy Dinella, and I'm from the regulatory affairs department at Hoffman-LaRoche. We are pleased to be here today to discuss Xeloda, which goes by the generic name of capecitabine for the treatment of patients with metastatic breast cancer after failure of paclitaxel and an anthracycline-containing regimen.

Capecitabine has been subjected to a worldwide clinical development program for various tumor types. Specifically, in the United States we filed an IND in May 1994. We had an end of Phase I meeting in December 1995, to discuss the breast cancer program. Here we obtained agreement to conduct one large, non-randomized clinical

trial. We agreed on a patient population, the endpoints, and the need to replicate these results across countries.

After the study was completed, we had a pre-NDA meeting with the FDA. Here we discussed the preliminary results of the trial, and obtained an agreement to file based on this one trial. We still needed to confirm the response rate in the most refractory patient population, and we needed to submit a plan for a Phase IV study if approved under the accelerated approval mechanism.

In October 1997 we filed the original NDA. In December we submitted a Phase III protocol, which we would consider as our Phase IV commitment. In February we submitted a four month safety update, and we're here today.

The basis for approval on the single study is the following. The patient population that will be discussed today has no standard alternative therapy. It is a large, multicenter study with clinically significant response rates. This response rate has been replicated across centers and across subpopulations.

The response rate and time to progression have been confirmed by a blinded independent panel. There are multiple endpoints in this trial that show a consistent therapeutic benefit. We have predictable and manageable

toxicity, which is quite important, since this will be an outpatient chemotherapy.

To put these results into context of what is currently being used today will be our first speaker, Dr. Joyce O'Shaughnessy. Dr. O'Shaughnessy is a practicing oncologist and clinical researcher in the area of breast cancer. After Dr. O'Shaughnessy's talk will be Dr. Tom Griffin. Dr. Griffin is the LaRoche capecitabine development program oncologist. He is going to discuss the preclinical rationale for the compound, the efficacy and safety data for the pivotal trial, as well as the safety data from our total safety database, and put this into an overall clinical benefit that supports approval.

For your information, we do have other experts upon request available here today. I would just like to point out two additional investigators, Dr. Joanne Blum, and Dr. Patricia LoRusso.

If you don't have any questions for me at this time, I would like to turn it over to Dr. O'Shaughnessy.

DR. O'SHAUGHNESSY: Good afternoon, colleagues, ladies and gentlemen. I am pleased to be able to provide you today with an overview of some of the principles of treatment for patients with refractory advanced metastatic

breast cancer.

As you are well aware, metastatic breast cancer is a major health problem, and one that will claim the lives of about 46,000 women this year in the United States alone. Metastatic breast cancer is essentially incurable, with a median survival of about two years after documentation of metastases.

Metastatic breast cancer is a very heterogeneous disease, and it has been well documented that a woman's chances of survival is dependent on disease-free interval, estrogen receptor status, her sites of disease, and her tumor burden. It has been estimated that about one-third of metastatic breast cancer patients will live long enough, and will have a high enough performance status to be able to receive second and third line chemotherapy.

Treating metastatic breast cancer patients with chemotherapy is believed to modestly improve survival. The goal of treatment is disease palliation, and generally not cure. Disease response to chemotherapy is likely to be associated with a reduction in tumor-related symptoms in the subset of women who are symptomatic. Anthracyclines and taxanes are the most active agents, and are generally used as the first and second line chemotherapy agents and

regimens depending on a woman's prior adjuvant therapy.

With regard to salvage chemotherapy treatment options for patients who have been previously treated with an anthracycline and taxane, it is important first to note that there is no standard definition in the literature describing metastatic breast cancer patients that are refractory or resistent to both anthracyclines and taxanes.

For this reason, I will offer today a clinical definition for the purposes of my talk, which I think reflects standard medical practice. I will refer to third line treatment as chemotherapy given to patients who have been previously treated with an anthracycline and a taxane, and who are not expected to benefit from additional treatment with the same.

Most patients receiving third line chemotherapy do have significant disease-related symptoms due to advanced boney, lung, liver, or local regional metastases, since single agent chemotherapy is generally administered in the third line setting, because there is no convincing evidence that combination chemotherapy is more effective with regard to overall survival or quality of life.

Turning then to a specific discussion of third line chemotherapy for metastatic breast cancer, it is

important to point out that although patients are currently being treated with a variety of single agents or combinations in this setting, there is no generally agreed upon standard third line chemotherapy for metastatic breast cancer patients who have been previously treated with an anthracycline and a taxane.

In addition, a careful review of the literature reveals that at the present time there are few data regarding the anti-tumor activity of some of the commonly used third line agent regimens specifically in the patient population that has been pretreated with doxorubicin and a taxane.

I think it is also important to keep in mind that interpretation of tumor response rate data in the salvage chemotherapy literature is complicated by: the inclusion of a heterogeneous patient population, with variable amounts of prior therapy; the fact that the studies are, to a large extent, single institution studies; by the variable response criteria that have been used over the past 10-15 years; and because response rates are variably reported as intent-to-treat versus in more selected subpopulations of the study patients; and also because of probably publication bias against studies that end up showing more anti-tumor

activity.

For all these various reasons, and the difficulties inherent in interpreting the response rate data in the salvage chemotherapy literature, which is also quite extensive, I have chosen not to review these data in detail. Rather on this slide I have listed some of the agents and regimens commonly being administered as third line treatment to patients who have been pre-treated with an anthracycline and a taxane.

The single agents shown on the top are more often administered in this setting I think largely due to toxicity considerations. Again, a key point I think is that although these agents and regimens are in use as third line treatment, there are relatively few data that define the response rates of these agents, specifically in patients who have already received an anthracycline and a taxane.

I have summarized what data do exist on the following slide. An important point to keep in mind when evaluating these data is that in these studies the definitions for pre-treatment with or resistance to the anthracyclines and paclitaxel were incompletely described in some cases, and were variably described between studies.

There have not been any randomized trials in this

specific patient population. The data shown here are from single institution Phase II trials. With docetaxel 3 of 26 patients did respond after becoming paclitaxel resistent.

The lack of response in the vinorelbine study I think is the fact that the vinorelbine was given every two to three weeks in this study rather than the standard weekly.

The high response rate shown here in this study is due likely to the fact that this was a does intensive study, with patients receiving 30-35 mg/m^2 of the vinorelbine, which required the continuous administration of G-CSF during this study.

In 96 hour paclitaxel there were 7 out of 26 responders. In this patient population, one-third of the patients had received prior anthracycline.

Lastly, this last study was just published only in abstract form, a 12 percent response rate for continuous infusion; 5-FU was seen in patients, and the extent of prior anthracycline and paclitaxel is not completely described in this abstract, but the title of the study shows that it was aimed directly at patients who had received both prior anthracyclines and paclitaxel.

My interpretation of these studies is that these

currently available data do not clearly point to an existing therapy that is of proven clinical utility in this patient population.

In the last few minutes, I would like to share with you what I believe is an emerging paradigm among oncologists for the treatment of metastatic breast cancer patients, and that is one of a chronic disease model where the goal of treatment is to maximize the duration and quality of patients' lives by controlling disease, maintaining performance status, minimizing toxicity and inconvenience.

Within the context of this chronic disease model the goals for third line chemotherapy are to: reduce tumor-related symptoms; maximize progression-free and overall survival; maintain performance status; minimize toxicity; and enhance convenience and control for patients.

Some potential advantages oral cytotoxic agents may have within a chronic disease model include the ability to titrate the daily dose as necessary to minimize toxicity, provided the agent in question has a short half life. Minimizing toxicity in this way may help maintain patients' performance status. Oral chemotherapy may enhance patient control of therapy; may provide a holiday from IV access;

and may allow patients to spend less time in the oncology clinic.

A recent study has quantitated what I think our clinical intuition would predict, and that is that metastatic breast cancer patients do prefer oral chemotherapy for the reasons of convenience, no IV access, and time outside of clinic. Importantly, however, patients were not willing to sacrifice efficacy for their preference.

In summary, the major points I would like to conclude with are that administering third line chemotherapy to metastatic breast cancer patients can provide palliation of tumor-related symptoms, and is accepted medical practice. There is no generally agreed upon standard chemotherapy for patients with metastatic breast cancer who have been previously treated with an anthracycline and a taxane. In addition, there are relatively few published data which assess the anti-tumor activity of the agents that are currently in use in this patient population.

In my opinion, the currently available data do not clearly identify an existing therapy that has proven clinical utility in patients who have been pre-treated with an anthracycline and a taxane. For this reason, new agents with defined effectiveness are needed.

The goals of third line treatment of metastatic breast cancer patients are to diminish tumor-related symptoms, while minimizing toxicity, and maintaining patients' overall quality of life.

Thank you very much for your attention.

Dr. Tom Griffin will now present.

DR. GRIFFIN: Thank you, Joyce.

Members of the advisory committee, representatives of the FDA, ladies and gentlemen, good afternoon. My name is Tom Griffin.

In 1957, Hoffman-LaRoche, working with Dr. Charles Heilberger(?) of the University of Wisconsin described a rationally designed structural analog of uracil which was successful in disrupting from the pathways in tumor cells. This compound, 5-fluorouracil, subsequently became one of the most widely used drugs in cancer chemotherapy for the past 40 years.

The drug I will present today, capecitabine, is also a private, aggressional drug design, and we believe a worthy successor to 5FU. Capecitabine has several major advantages over currently available chemotherapeutic agents. These include its tumor selectivity in that it is activated by enzymes which are found preferentially in tumor tissue.

It is also an excellent oral drug, and is the prototype for a series

of promising new agents in oncology develop with oral activity. Last, but most important, it has demonstrated significant anti-tumor activity in an extremely difficult clinical situation, namely patients with heavily pre-treated drug resistent metastatic breast cancer.

As Dr. Dinella mentioned, today I will review the preclinical rationale for capecitabine, and some clinical pharmacology studies that show the efficacy and safety of this drug in our pivotal trial in breast cancer, and also further safety data from a pool population of 570 patients; introduce our studies of the impact of capecitabine treatment on tumor-associated symptoms; the clinical benefit response; and conclude summarizing the overall risk/benefit assessment of capecitabine treatment in patients with paclitaxel refractory breast cancer.

The preclinical results which will be presented include a description of the bioenzymatic activation pathway of capecitabine, its anti-tumor activity in nude mouse xenograft models, and experimental evidence of its tumor-selective activation.

Capecitabine a novel fluoropyrimidine carbonate

which has been rationally designed to undergo tumor-selective activation to produce the cytotoxic agent 5-fluorouracil, which then, after conversion to various fraudulent nucleotides, induces tumor cell cytotoxicity.

The first step in this metabolic pathway is hydrolysis of the carbonate group by the hepatic enzyme carboxylesterase to produce the non-cytotoxic intermediate 5-fluoro-5'-deoxycytidine, 5'-DFCR. This then undergoes deamination on the pyrimidine ring by cytidine deaminase to produce a second non-cytotoxic intermediate, 5-fluoro-5'-deoxyuridine or 5'-DFUR.

The enzyme cytidine deaminase is found at high levels in liver and in solid tumors. Finally, the unique five pronged dioxie sugar is removed by the enzyme thymidine phosphorylase to produce 5-fluorouracil. Thymidine phosphorylase is found at high concentrations in a variety of solid tumors, and at much lower levels in most normal tissues.

The preporankyal(?) expression of thymidine phosphorylase by human breast cancer is shown here. This is a ductal carcinoma, which is been stained by immunohistochemistry with either a specific antibody, against thymidine phosphorylase, or an isotope match in the

relevant control.

With the specific antibody, I think you can see the dense cytoplasmic and nuclear staining obtained, and very little staining of surrounding normal breast.

Recently, thymidine phosphorylase has been shown to be identical in amino acid sequence and activities to the breast cancer associated agiogenet(?) factor, platelet derived endothelial cell growth factor. The high expression of thymidine phosphorylase in human breast cancer may be related to a biologically important role in angiogenesis.

An important characteristic of capecitabine is its high degree of anti-tumor activity in preclinical models. For example, capecitabine is much more active than other fluoropyrimidines in nude mouse human tumor xenograft models.

Shown here is the percentage growth inhibition produced by treatment with equal toxic doses of capecitabine or 5FU in nude mice bearing five different human breast cancer xenografts. As you can see, 5FU is the essentially inactive in all five xenografts, while capecitabine induces significant growth inhibition in three xenografts, and actually produces tumor regression in a fourth.

This high degree of activity in preclinical models

appears to be related to tumor-selective generation of 5FU. These studies used the xenograft CXF 280, and what is shown is a comparison of tumor and plasma, C-MAX and AUC-t after capecitabine administration and 5FU administration at MTD doses.

The demonstration of tumor selectivity is compelling in this model. The ratio of AUC obtained in tumor with CAPE of FU compared to the AUC obtained with FU itself is 22. Moreover, the ratio of tumor to plasma with FU administration is barely above 1, where with capecitabine administration it is over 200. Finally, the anti-tumor effect, FU barely inhibits tumor growth in this model, while capecitabine induces tumor regression.

I will now move to clinical studies. For clinical pharmacology studies I will show the pharmacokinetics of capecitabine after oral administration, evidence of its excellent oral absorption, and some preliminary studies demonstrating tumor selectivity in patients.

This slide shows the plasma concentration expressed in micro grams per ml of capecitabine and its metabolites after oral administration. The important findings can be readily seen. The parent molecule is rapidly absorbed in the GI tract and reaches its maximal

level in the plasma within one hour of oral administration.

The two non-cytotoxic intermediates, 5'-DFCR and 5'-DFUR are rapidly generated in the plasma, and circulate at high levels throughout the six hours. In sharp contrast, very little 5FU was seen in the plasma. The C-MAX seen with capecitabine administration is between 80 and 800 fold lower than the C-MAX obtained with routine bolus administration of the 5FU.

In terms of the consistency of gastrointestinal absorption, greater than 70 percent of an orally administered dose on average is absorbed into the systemic circulation, with limited variability among patients.

Finally, I want to show you some evidence of tumor-selective generation of 5FU indications. This figure compares 5FU ratios between primary tumor and normal tissue, normal tissue and plasma, and primary tumor and plasma obtained in colorectal cancer patients after capecitabine administration. This is compared to historical literature data obtained with 5-fluorouracil administration.

I think tumor-selectivity is clearly shown capecitabine. The ratio between tumor to normal tissue is 3.2:1. The ratio between tumor to plasma is over 20-fold:1. In contrast, 5FU shows no selectivity with the very similar

ratios, all around 1.

Here is depicted the major component of the clinical development program of capecitabine. Studies which have been completed are shown in blue; studies which have completed accrual are shown in green; and ongoing studies are in orange.

After standard Phase I trials performed both in Europe and the United States development programs started in either breast cancer or colorectal cancer were instituted for capecitabine. The breast cancer program has both a single agent component, shown here, and a combination chemotherapy component, shown down here.

In terms of the single agent component, 162 patient study was performed in paclitaxel refractory breast cancer patients. In addition, a Phase II trial in patients older than 55 with CMF as a reference arm has been completed, and a study in patient second line after anthracyclines and paclitaxel as a reference arm has also been completed.

Subsequent to this study, a follow-up study which now treated any taxane failure, not just paclitaxel of 75 patients has also been accrued. In terms of combination trials in breast cancer, Phase Is have been in performed in

combination both with paclitaxel and docetaxel. This has led to our recently initiated Phase III trial which compares single agent docetaxel to the combination of capecitabine and docetaxel.

In colorectal cancer a large, randomized Phase II was performed, and we recently have completed accrual of 1,200 patients to Phase III trials with 5FU to leucovorin(?) as a comparative. The topic we will discuss today though is our pivotal trial shown here, in 162 patients with paclitaxel refractory breast cancer.

The protocol objectives of this trial are summarized here. The primary objective is to demonstrate an overall objective response rate of approximately 20 percent, with secondary objectives being determination of duration of response, time to progressive disease, duration of survival, safety of the drug, and impact of the drug in tumor-associated symptoms of clinical benefit response.

The demographic characteristics of the patients entered on the trial are shown here; 163 patients entered the trial, 162 actively received drug. They were treated at 25 cancer centers and community hospitals in the United States and Canada. The average age was 56. The average Karnofsky performance status was 86.

The median time from primary diagnosis of breast cancer to first recurrence was 2.5 years, with 40 percent of the patients being the bad prognostic group of recurrence within two years. Sixty-two patients were premenopausal, 100 were postmenopausal; 135 patients had measurable disease, and it was this population that was used to determine the objective response rate.

A further 27 patients had evaluable disease, predominantly bone metastasis or florin skin lesions. These patients were included in survival, and clinical benefit response analysis were not used to determine the objective response rate.

The patients had widely disseminated breast cancer at study entry. Patients had a median number of organs or tissues involved with breast cancer of 3, with a range of 1-11. The lung and pleura, liver, and bone were frequently involved, usually with multiple metastases. In addition, 38 additional patients had soft tissue disease.

Two-thirds of patients had received prior tamoxifen before entering the study. A further two-thirds had received various second and third line hormonal agents. These patients have been heavily exposed conventional and investigational chemotherapy prior to entry into the study.

All patients had received paclitaxel; over 90 percent of the patients had received either an anthracycline or an anthracenedione; 100 percent received one or another alkylating agent -- cyclophosphamide and thiotepa; 80 percent of them received prior fluorouracil.

Forty-six percent of the patients were third line chemotherapy patients, 46 percent of the patients were fourth line chemotherapy patients. These patients also had received a variety of investigational drugs including antisense(?), palitimide(?) and others.

This demonstrates time to disease progression after last paclitaxel dose of the study population. As you can see, 80 percent of the study population progressed within four weeks of their last paclitaxel dose; 90 percent within eight weeks; 93 percent within 12 weeks, indicating a high degree of refractoriness with paclitaxel.

The dose and schedule used in this trial are shown here. The dose of capecitabine was 2,500 mg/m^2. This was given in two equally divided doses, therefore 1,250 mg/m^2 bid. It was given for 14 days on, then the 7 day drug holiday. This dose had been determined by a standard Phase I dose escalation trial, with nine patients treated at the Phase II. Dose adjustment, based both on Grade 2 and Grade

3 toxicity was instituted and employed in all patients.

The dose modification schema is shown here. As I mentioned, the second occurrence of a Grade 2 toxicity would lead to a dose reduction. The first occurrence would lead to a brief treatment interruption.

Patients were monitored for dose interruption or dose reduction on a daily basis, based on clinical symptoms. The goal was to adjust the individual dose of the patient to allow a chronic outpatient treatment of their breast cancer.

Despite this aggressive dose adjustment schema, we still delivered very high levels of drug over time. This is from the pivotal trial. This is the median dose administered and the mean dose administered compared to plan. You can see out to 30 weeks we're still getting in 80-90 percent of the planned dose.

The response rate in this population in measurable disease patients was 20 percent; 27 of the 135 patients. What is shown here graphically is the percentage of tumor regression in these patients. As you can see, the majority of the patients have more than 80 percent tumor regression, with 9 patients having complete regression of all signal lesions. So these are clinically significant tumor regressions.

Responses were seen in all metastatic sites, and the largest number of responses was seen in liver metastases; 12 of the 27 responses occurred in liver.

The responses with capecitabine can occur quite late in the treatment course, and I think this is unusual for most of the drugs we use for breast cancer. I show that here. This patient had extensive involvement of her liver with breast cancer at the baseline. She showed a very slow gradual improvement with capecitabine, and really never reached a level of regression that would justify a PR category until she was on the drug for eight months.

I show this here. Again, you can see this very slow, gradual regression of the tumor over time. The patient remains on drug at 18 months, and again, continues to slowly regress her tumor. We have seen this in approximately one-third of our responders. It's very late and very gradual response.

The duration of response is shown here by WHO criteria. It was 241 days. We also analyzed various subgroups to make no subpopulation was driving our response rates, and you can see there is great internal consistence there of a response rate across subgroups. In terms of ITT population there was a 20 percent response rate in ITT. The

standard was a little bit higher, about 23 percent.

Patients who had received prior 5FU had a 16 percent response rate; third line patients, about 18 percent; fourth line, 20 percent; patients who had failed bone marrow transplant; patients who had not failed bone marrow transplants; patients with high accruing centers; low accruing centers; greater than 60 years of age; less than 60 years of age; and the evaluable patients even all had very similar response rates of 20 percent. So the response rate seems to be robust and reproducible across populations.

All entered on the study had shown therapeutic refractoriness to paclitaxel. All of the tumor responders had shown therapeutic failure on paclitaxel and anthracycline, however, to try to determine a more rigorous definition of resistance in our patients. We adapted response categories which were published in 1996 by the European School of Oncology Task Force on Drug Resistance to Breast Cancer so that people could analyze their data in a very transparent manner.

The response categories are shown here. We defined three resistance categories. The first was disease relapse within six months of completing adjuvant therapy. The second resistance category, the R2 was objective

response to therapy, followed by disease progression while still on therapy. We defined while still on therapy as progression within six weeks of the last dose of therapy. R3 was the overall response being disease progression, again using six weeks as the cut off.

The report offered a definition of resistance -- stable disease while on therapy for a minimum of four cycles, and assigned that to a failure category, an F3. An F2 category was objective response to therapy, followed by disease progression between 6 weeks and 12 months of the last dose of drug. F1 was relapse within 6 to 12 months of completing adjuvant therapy.

We assigned patients to various F categories and R categories for paclitaxel and anthracycline. Doing this, and looking at the most refractory patients in this population -- and again, I've listed here patients who are resistant to paclitaxel and resistant to anthracycline, resistant to paclitaxel, failure on anthracycline by these definitions, vice versa, failure, resistance or double failure.

You can see the overall response rate in these 90 highly refractory patients was still 25 percent. In fact, the worst population, the double resistance, clearly

resisted the paclitaxel and anthracycline chemotherapy by very rigorous definitions, still showed a response rate in the 20s. So I think we have demonstrated that this drug does have activity in highly drug-resistant patients.

We also confirmed the investigators' assessment of response by a blinded independent review. The objective of this blinded review was to obtain radiographs from all patients with radiographically defined disease. We provided these to our outside consultants, who are essentially the radiology department at Massachusetts General, and we asked them to determine the response rate and the time to progression in these patients, and we provided them with no clinical information, no investigator assessments, and we allowed no interactions back to the investigators. So this was an entirely blinded review of the radiographic data.

What was provided was the anatomic location of the indicator lesions. The x-rays were obtained and redigitized and stored electronically, and then the tumor size was determined through state-of-the-art magnification, contrast adjustment, and computer measurement.

This slide shows the concordance between the independent review and the investigator review. In the 100 patients with measurable disease, with radiographically

defined disease the overall response rate in the population was 20 percent by the independent review, 18 percent by the investigators. The median regression in responding patients was very similar. The median regression in patients with stable disease was very similar.

Here is shown time to progression obtained in a blinded fashion between the investigators and the IRC. You can see the difference, 92 days to 95 days. It was very small. So I think this is clear confirmation of the investigators' assessment of response.

The survival time of the entire treated population is shown here. The survival on median was 384 days.

So to summarize the efficacy we saw, we think we saw a clinically meaningful response rate in these heavily pretreated patients, with an excellent duration of response, and a long survival of greater than a year on median.

For the safety results, what price was paid to obtain these efficacy results, I will show you the number of patients treated with capecitabine, the major adverse events seen in the pivotal trial, and then detailed safety information on the pooled populations.

At this time, 1,275 patients have been treated worldwide with capecitabine, Phase I, II, or III trials with

follow-up and ongoing trials.

In the pivotal trial the most frequent Grade 3 and Grade 4 adverse events were diarrhea, Grade 3, 11 percent, and Grade 4, 3 percent. Hand-foot syndrome, which we developed a protocol-specific grading system for, 10 percent Grade 3, and stomatitis, 7 percent, Grade 3.

There were very few Grade 4 adverse events related to drug, 4 percent. Seven percent withdrew due to treatment-related events. Ten percent of patients were hospitalized due to treatment-related events. Almost all of these were due to the need for rehydration after diarrhea-induced dehydration.

To develop a pooled safety population we combined six studies, three in breast cancer, all Phase II studies, the pivotal trial, the trial of patients who were older than 55, and the anthracycline failure trial with three trials for colorectal cancer, the completed Phase II, and the ongoing Phase IIIs.

To confirm that this pooling was appropriate, we looked at major safety endpoints in the clinical trials, in the pivotal trial, and also in this 570 pool population. What I have shown here is deaths. You can see none in the pivotal trial. We have had seven worldwide in 570 patient

pool. Serious adverse events were very similar incidents. Hospitalizations are similar. Withdrawals due to adverse events, withdrawals due to laboratory abnormalities, and Grade 4 adverse events, there is no great difference between these.

I mentioned we had a protocol-specific definition of hand-foot syndrome. This involved both a clinical domain. The Grade 1 essentially was numbness or swelling or erythema without symptom. The Grade 3 would involve some loss of integrity of the skin, either ulceration, blistering, or desquamation. We also had a functional domain. Whatever the worst domain was took priority in terms of the grade of the disease.

Using this, along with the NCIC common toxicity grading system I want to show you the incidence of major side effects with the severity of Grade 3 or Grade 4 in our pivotal trial, in the pool breast cancer population, in the pool rectal cancer population, and in the entire six study pool of 570 patients.

I think you can see the only toxicity which occurs in more than 10 percent of patients in any of these studies is diarrhea and hand-foot syndrome. The other toxicity is vomiting, nausea, stomatitis, or neutropenia occurred in

anywhere from 2-5 percent of patients.

What is shown here is all related adverse events in the 570 patient population, all grades, Grade 1-4. I think you can see three tiers. Here is the first tier, with the most common adverse events. These occur in 40-50 percent of the patients at any grade. These include diarrhea, hand-foot syndrome, and nausea.

The second tier is shown here. These occur in 15-25 percent of patients at any grade, and they include vomiting, fatigue, stomatitis, and abdominal pain. All the other adverse events occur in less than 10 percent of the patients. These adverse events are usually Grade 1 or Grade 2 when they occur. When they occur with severity of Grade 3 or greater, they tend to be very brief in duration, with a median duration of less than a week, with the exception of hand-foot syndrome.

As mentioned, we attempted to tailor the individual patient dose to tolerance. I think we have been successful in doing that, and decreasing the incidence of adverse events in patients once they reach a chronic dosing schedule. I show here the incidence of adverse events by three week cycles. This is an added total sum of Grade 3s and Grade 4s. The Grade 3s are in yellow; the Grade 4s are

in blue.

You can see the first cycle is when we have our highest incidence of adverse events. By cycle 4 it has gone under 10 percent in toto, and the Grade 4 adverse events have essentially disappeared. When you get out to the more chronic dosing, cycle 8 and 9, the incidence of adverse events is very low.

In our safety population though, there are two findings which I need to show you. One is we did find excessive toxicity in the 14 patients in this 570 patient safety pool who were greater than 80 years of age. The overall incidence of Grade 3 and Grade 4 toxicity was 64 percent.

Now these toxicities were the standard capecitabine toxicities of diarrhea, vomiting, hand-foot syndrome. They were relatively brief in duration. Three of the five patients who reached a response category responded, but still this does seem to be excess toxicity in this small number of patients. We intend to explore this further.

Another safety finding has been the incidence of Grade 3 and Grade 4 abnormalities in total serum bilirubin. We have seen that in 9.3 percent of patients in the pivotal trial, and up to 17 percent of patients in the pool

population. This is due to the fact that it occurs at a much higher frequency in patients with colorectal cancer than in breast cancer.

When we looked at the 96 patients who have shown this abnormality, the great majority had liver metastases or dour(?) tract disease as an explanation for elevated bilirubin. Twenty patients had no known liver disease when they developed the Grade 3 or Grade 4 bilirubin.

We're using the NCIC truncated grading system for bilirubin, so these elevations, even though they are Grade 3 or Grade 4 are not very high. This shows at least 20 patients, 8 breast, 12 colon. Here is a baseline bilirubin. The peak bilirubin is shown here. It usually occurred after being on treatment for about two to three months. These bilirubins occurred in absence of any change transamidine or phosphatase tend to be transient

and resolve easily with continued drug treatment.

Finally, I would like to present briefly our clinical benefit response data, which essentially is an attempt to look at the impact of capecitabine treatment on tumor-associated symptoms. To do this, I will show you the definition we used for clinical response, and our response rate in the overall population, and in those patients who

could respond.

The longitudinal analysis has also been performed by both our statisticians and the FDA statisticians. Since Masa(?), the FDA statistician is an acknowledged expert in this area, he will present this to you, and I will not.

The parameters of the clinical benefit response were daily pain assessment by the patient, a daily record of consumption of analgesics, and a weekly self-assessment of KPS by the patient.

To respond we used a priori definitions. These included a certain baseline threshold for the patient to use to have to be scored as a responder, a certain improvement, and a certain duration. For pain this was greater than 20 millimeters of pain on the DAS. They needed to improve by at least 50 percent. This improvement had to be sustained for at least four weeks.

Similarly, for analgesic consumption they needed to be taking greater than 70 milligrams of morphine equivalents per week at baseline. They needed to show a 50 percent reduction in consumption, and this had to be sustained for four weeks.

For KPS they needed to improve 20 points on the KPS performance scale, and sustained for four weeks.

The algorithm for taking responses from the individual categories for the overall clinical benefit response was shown here. The patients had to be positive at at least one parameter, with no negative parameters. Any negativity imparted a non-response category to the patient. If they were stable in all three, they were recorded as stable.

This is the graph that shows the overall clinical benefit response in the entire treated population, and in the subpopulations of those patients who could response by the baseline characteristics. The overall clinical benefit response in the entire treated population on whom we have information was 20 percent.

In the patients in the individual categories, 51 patients could response in the pain category; 47 percent of those patients did response. In the analgesic category 74 patients could respond, 34 percent did respond. In Karnofsky 80 could respond, but only approximately 4 percent did respond. In patients with ability to respond in any one of these three categories, the overall clinical benefit response rate was 30 percent.

When responses occurred, they tended to be durable. This is the mean pain score for the patients who

had responses in the pain category. You can see it improves down from 40, down to 10 to 15 by week 6, and this improvement is sustained after 24 weeks.

Now this may not be a fair comparison, but I'll just put this up for some perspective. Now these are comparisons across Phase II trials. Of course other drugs I show here were studied primarily in second and third line breast cancer, while capecitabine, as I have shown you, was studied in the third or fourth line. I just want to show you that we are in the same general efficacy category as these agents, both in terms of number of patients seen, overall response rate, duration of response, time to progression, survival on the median, and representative patients who are alive at one year.

So I would view this comparison with caution, but I do think it shows you that we are in the same general category of activity as a number of other drugs.

So in summary, in terms of risk/benefit assessment I think we have shown a response rate of 20 percent in a refractory patient population, with 40 percent of patients have stable disease. Duration response was 241 days, and median duration of survival was 12.8 months, with more than half the patients still alive a year.

We have predictable, manageable and rapidly reversible adverse events. The major ones were diarrhea and hand-foot syndrome. Dose modifications at Grade 2 typically allowed patients to remain on chronic therapy with a low incidence of adverse events.

We saw an overall benefit response in 20 percent of the entire population, and 47 percent of the patients with significant pain had a pain response. Again, as Dr. O'Shaughnessy mentioned this drug is compatible with oral, outpatient therapy, which is the patient's preference.

Agenda Item: Questions from the Committee

DR. DUTCHER: Thank you very much. Are there questions from the committee for the sponsor?

DR. SWAIN: Yes, I had a question about your patients. All your patients were previous treated with paclitaxel. You changed the minimum dose that was required during the study from -- I guess it was given, and then you changed it to 175. Did most of the patients get 175?

DR. GRIFFIN: I can explain that change. We had met with the regulatory authorities within the U.S. and New York and they made some suggestions. One suggestion was if patients received paclitaxel at the usual three hour infusion, they should be required to have a minimum of 175

mg/m^2 dose on that schedule. If they received paclitaxel in combination, or if they had received paclitaxel on alternate infusion schedules, for instance 24 or 96 hours, we did not require them to have 175 milligrams.

We do have a back-up slide that shows the percent of patients who received 175 milligrams or greater. In that population of patients who had the three hour infusion -- and I'm going to ask my colleague Dr. Alain Thibault to show that slide.

DR. THIBAULT: Alain Thibault, LaRoche Oncology Science.

This slide describes the dose intensity per patient in our 163 population. It shows that the vast majority of patients were treated on the high dose of paclitaxel of 175 mg/m^2. Several patients who received lesser doses were treated by continuous site infusion. So we would conclude here that nearly 80 percent of the patients were treated with high dose paclitaxel.

DR. SWAIN: Do you have the same data for doxorubicin?

DR. THIBAULT: We have the same data for doxorubicin, but I would have to look at my index for the slide.

DR. GRIFFIN: We did not require as a protocol requirement, any specific dose or minimal dose for doxorubicin.

DR. SWAIN: Sure, I was just interested to see how many patients just had 2040 or whatever for adjuvant treatment.

DR. THIBAULT: This slide here addresses most of the question. You have on the left column the categories of patients, whether they were resistant, failures, or exposed, but not having failed anthracycline as best as we could determine. This is the left-hand column. The median dose of anthracycline is measured here in mg/m^2. This is cumulative dose. The message from this slide is that the median dose of anthracycline administered to any category of patients was 240 or above. We had about 50 patients who had received more than 300 mg/m^2.

DR. SWAIN: Fifty patients you said? Five-zero?

DR. THIBAULT: Fifty patients, which is about one-third.

DR. SWAIN: I had another question about the safety database. I was interested in seeing more data just for the pivot trial. Like you had I think it was slide 67 that showed the percentage of all the toxicities for the

whole database, which I think is interesting, but two-thirds of the pool database were previously untreated, and most of them had colon cancer. So I would be interested in the specifics for just the pivotal trial in breast cancer.

DR. GRIFFIN: And again, the specific question would be the higher grade toxicities?

DR. SWAIN: All toxicities, like you have shown.

DR. GRIFFIN: There is no significant difference between the pivotal trial and the overall population, but I will try to find you the back-up to show that.

I apologize. I think we have it for Grade 3/Grade 4 between the pivotal and the entire population. We don't have it broken out for all four. We will check and make sure I'm telling you the exact truth, but I believe there is no big difference between them.

DR. SWAIN: Okay, that's fine. I had a question regarding that. You have in your safety update that about 50 percent of the patients had diarrhea, hand-foot syndrome, and I guess nausea. In your dose reductions or delays, those patients would require, even with Grade 0 or 1, to be delayed and maybe dose reduced. How many patients actually did have to be delayed or were dose reduced? Or maybe you can just show your dose reductions for all the patients.

DR. GRIFFIN: Can I have the back-up slide that shows the dose reduction? Because we did not reduce on Grade 0 to 1. Dose reductions were done on second occurrence in Grade 2, first occurrence in Grade 3 or Grade 4. We also interrupted for first occurrence at Grade 2. So if the patient developed at Grade 2 for the first time say on day 12, they would interrupt, and then resume a full dose. The second occurrence in the same Grade 2 would call for another interruption, recovery of 0-1.

DR. SWAIN: Do you have the data on how many patients in which that occurred?

DR. GRIFFIN: In the safety data pool, the percent of patients who have a reduction of any time during their treatment was 35 percent. The numbers who had dose reduction and interruption was approximately -- I'm going to ask my colleague Dr. Bruno Osterwalder to review this back-up slide.

DR. OSTERWALDER: Dr. Osterwalder, Quintiles.

Overall, 279 patients out of the 570 patients had either dose interruptions or dose reductions. This slide shows that 202 patients in fact had dose reductions; 129 patients had one dose reduction, and 79 patients had a second dose reduction down to 50 percent.

The dose reductions were triggers as seen in the schema before, mainly by the Grade 2 adverse events. Over 50 percent and an additional 37 percent were triggered by Grade 3 adverse events. So 90 percent had those reductions due to Grade 2s and Grade 3s.

We have carefully analyzed the effect of the dose modification scheme on the incidence and severity of the adverse events before and after those modifications, and that is shown in the third bullet. We can demonstrate a clear reduction on incidence and severity after dose modification.

DR. DUTCHER: Other questions for the sponsor?

DR. SLEDGE: I have a number of questions. I'm trying to get a little bit better handle on the group of patients who are being treated here. Perhaps I missed it, but I didn't see any data on percentage of patients who were steroid receptor positive in the trial.

DR. GRIFFIN: Yes, I did not present that, and we did not collect it on our primary case report form. We have now collected that, but it is being analyzed, and I do not have that data yet.

DR. SLEDGE: Similarly, your definition of resistance includes a fair number of patients who may have

responded to either anthracycline or taxol and then progressed after a response.

DR. GRIFFIN: Yes.

DR. SLEDGE: Have you broken down your data on responded versus never responded.

DR. GRIFFIN: I think our R3 category is essentially patients whose best overall response was progressive disease. So that would be the percentage of patients whose best overall response was progressive disease. That would exclude patients who had either a tumor response or stable disease as their best overall response.

DR. SLEDGE: From a toxicity question, if you look at patients who either had underlying liver disease or who developed hyperbilirubinemia, are these the patients who developed hand-foot syndrome, or developed diarrhea and dehydration? Are they preferentially lumped in that group of patients?

DR. GRIFFIN: Yes, and we have not seen any relationship between liver disease and development of other toxicities. I don't think it is a metabolic problem. Fluoropyrimidines as a class have great individual tolerances. I think that is what we are seeing here. So some people develop diarrhea. Some people develop hand-foot

syndrome. Some develop stomatitis, but I don't think there is a pharmacologic reason for it.

DR. SLEDGE: Do you have numbers on the number of patients who were screened for the trial versus the number of patients who actually entered the trial?

DR. GRIFFIN: We did not prospectively look at that, but we do have investigators here who could give you their personal feeling about patients who were potential for the trial, but did not go on the trial. We had a pain run in period of a week prior to going on trial to try to get stability to the CVR stuff. We did not lose any patients during that one week run period, except that one patient who showed rapidly progressing disease during the one week.

We did not exclude people during the first week of run in, but we did not critically prospectively look at screened patients at the sites who never went on protocol. I can ask Dr. Blum or Dr. LoRusso to comment about their own personal experience.

DR. BLUM: Joanne Blum. I'm a medical oncologist with Texas Oncology, and associate director for breast cancer research.

Our experience with this trial was that most of the patients who were off of the participation seemed to

wish to participate, those who had been anthracycline or taxane failures. We participated in this pivotal trial, as well as the subsequent taxane failure trial, as well as a Phase I taxol/capecitabine combination trial.

Overall, the interest in the trial was great. I don't remember having a patient who actually declined --

DR. SLEDGE: I'm sorry, that wasn't really my question. How many patients were excluded before you offered it to them?

DR. BLUM: We have at our center -- I can only speak to our center -- I believe 38 who were offered, and I think 37 participated at that interim trial. Perhaps I'm not answering your question.

DR. DUTCHER: Eligibility. Who met the eligibility.

DR. GRIFFIN: Again, I think the major point of the eligibility that was addressed in your question would be performance status, and we required a minimum performance status of 70, because we think that's the right group to use an investigative drug in.

If I can have the back-up slide in, I will show you the other trials. Recent large Phase II trials in breast cancer had very similar cut offs in terms of

performance status. So I don't think this was a highly selected population by a major clinical indicator, KPS.

DR. SLEDGE: Finally, could I ask Dr. O'Shaughnessy a question? Joyce, as a practicing clinician you and I both would have the same feeling if someone came up to you on the street and said, here is a drug that involves chronic administration, gives you hand-foot syndrome and diarrhea, and gives you a 20 percent response rate on metastatic breast cancer. What drug is it? The answer would be infusional 5FU.

Yet, basically you referred to only one study, whereas there is actually a fairly huge body of literature on infusional 5FU. Could you compare and contrast for us?

DR. O'SHAUGHNESSY: I actually thought about that and have a back-up slide. I think it's J-5.

I have listed here -- and again, George, it's not all of them -- a few more studies of 5FU/leucovorin, daily times 5 or weekly, and have shown some of the response rates here. I tried to find similar patient populations if I could. As I have described, these patient populations are fairly heterogeneous. It's a little bit of apples and oranges. I have listed some of the 5FU/leucovorin.

I think your question is right though. I think it

is continuous infusion 5FU, which is a relative comparator. I have again listed the Ragaz study, and the Regazzoni study is an interesting one, with Aaron Goldhirsh(?) from Switzerland. This was not so much of a prospective trial, but a treatment series from Switzerland of 106 consecutively treated patients, 80 of whom ended up having measurable disease, and they did find a 21 percent response rate in those 80 patients. This was also a heavily pretreated group of patients.

So I think there is clearly activity of continuous infusion. The thing about this is these data precede the introduction of paclitaxel or the taxanes into the therapeutic armamentarium. So the only study that really addresses that specific point is the last study. The Regazzoni study is one of I think the most promising in a heavily pre-treated group of patients showing similar -- but again, without the variable of paclitaxel being there.

DR. MARGOLIN: I have a pharmacology question, and then a response criteria question. It's a toxicity question about the hand-foot syndrome. You mentioned in the toxicity slide that all the clinical toxicities with the exception of the hand-foot syndrome resolved within a week. You have your toxicity-specific criteria. You also mentioned

separately that upon resolution you could resume. So I wanted to know about the time course.

The related question, is there any data levels of thymine phosphorylase in the skin that would suggest preferential accumulation?

DR. GRIFFIN: I will attempt to answer your toxicity question. In terms of the toxicity, the median duration of Grade 3 hand-foot syndrome when we did the analysis was 20 days. Now that may be an overestimate, because we had hoped in this study to determine duration of Grade 3 by asking the sites to record when the toxicity changed from Grade 3 back to Grade 2.

It usually wasn't done. They usually recorded when it completed resolved. So that may be an overestimate of the duration, but we don't know. We don't know how much of an overestimate. All the rest -- diarrhea, stomatitis, nausea, vomiting -- have median durations of less than five or six days, but hand-foot syndrome the median duration was 20 days in the pivotal trial.

I will ask Dr. Reigner to address the mechanism of hand-foot.

DR. REIGNER: Bruno Reigner, Hoffman-LaRoche in pharmacology.

So your question is related to the thymine phosphorylase related to skin?

DR. MARGOLIN: Right. Is there some pharmacologic reason that this drug should cause this syndrome having to do with preferential accumulation in the skin?

DR. REIGNER: Unfortunately, we do not have thymine phosphorylase formation about the skin. We are lacking this information.

DR. SCHILSKY: I had a couple of questions. I'm curious to know the categories you defined for refractory and failure, were those defined prospectively in the protocol?

DR. GRIFFIN: They were not defined prospectively in the protocol. The protocol was instituted prior to the publication from the European School of Oncology. What was done is information regarding best response to paclitaxel or anthracycline, time after progression on paclitaxel or anthracycline were obtained in a detailed manner on separate CRF pages, and then these criteria were retrospectively assigned by us.

DR. SCHILSKY: Did you make any attempt to have your external review panel try to actually verify whether these criteria were applied appropriately?

DR. GRIFFIN: The expert review panels essentially, aside from the availability of an oncology consultant or radiologist, so I don't think they would have helped us very much. We did provide the data in great detail to the FDA medical reviewers, so it has been looked at.

DR. SCHILSKY: You didn't get films though to document whether in fact if the investigator said someone was progressing on taxol, that they really were?

DR. GRIFFIN: No, we did not. We just asked for clinical information.

DR. SCHILSKY: One other question. Can you tell us something about how compliance with the oral dosing was assessed, and do you have any data about whether patients actually took the pills, or how often they didn't take the pills, or things like that?

DR. GRIFFIN: Yes, and again, we looked at compliance in our studies, and I think the most relevant group to look at are those patients who had neither a dose interruption or a dose reduction. I hope to show you a back-up slide showing the percentage of taken drug -- drug that actually passed into the GI tract -- compared to the planned dose. It is quite high.

Again, these are the 287 patients in the 570 patient safety pool who had neither a dose interruption at any time, or a dose reduction. You can see, this is received dose. This is planned dose. All the way out to week 24 it is in excess of 95 percent.

DR. SCHILSKY: How is received dose determined?

DR. GRIFFIN: These are done by pharmacy logs versus investigator planned dose.

DR. DUTCHER: By pill count?

DR. GRIFFIN: Yes, by pill count.

DR. SCHILSKY: I'm sorry, I just want to get clarification on this. When you say review of pharmacy logs does that mean that the dispensing of the drug from the pharmacy, or did you have some way of actually determining the number of pills that the patients actually took? What this tells me is that you had very good pharmacists. It does tell me much about whether the patient is taking the medicine.

DR. GRIFFIN: I can show you the methodology we used to do this. We asked all known information of drug agent take to be captured on the capecitabine treatment patient, the CRF, including any dose modifications, which would have been done on the basis of clinical symptoms, or

any historical evidence of noncompliance.

Then the capecitabine treatment page was carefully compared to the pharmacy drug dispensing log at the site. Returned pills and taken pills were measured. For patients with no dose modifications, we charted the figure I just showed you, which was a comparison of planned dose and received dose. We didn't do anything more detailed than that.

We do have a study nurse here who has treated lots of patients. Perhaps she would want to comment on why the patients took their oral dosing regimen.

MS. KROMELIS: Hi, I'm Priscilla Kromelis, and I have treated a lot of patients with capecitabine. I'm with Physician's Reliance Network in Dallas.

We did document when the patient came back for the next visit. We actually counted the pills and interviewed them very carefully as to missed doses. They actually were very compliant as far as taking their drug. They were anxious to be taking an oral medication, and they were anxious to be having this opportunity to participate in a drug, again, that was oral, and that possibly could have a response with the breast cancer.

So they were very compliant, and we did monitor

the drug very carefully when they came in for their follow-up visit.

DR. SCHILSKY: How many pills did the patients take per dose on the average?

MS. KROMELIS: It was dependent on their body surface area. It was 2,500, 10 mg/m^2. They took this in a divided dose. The IV comes 14 days. It was explained to them very carefully when they received their drug. The study nurse went over --

DR. DUTCHER: How many pills is that?

MS. KROMELIS: They came in 500 mg tablets and 150 mg tablets. They received the number of pills they needed to make up their total dose. So it was different with each patient.

DR. GRIFFIN: We had algorithms in the protocol for various body surface areas, the number of the pills. Capecitabine come in 150 mg and a 500 mg pill. The dose per day is 2,500 mg is the total dose, given in two equally divided doses. One of the reasons we decided to give it twice a day, we might have been able to give it once a day, but we wanted to limit the number of pills taken at one sitting.

You see here for an average patient, say with a

body surface area of 1.5 square meters, they would take morning and evening, two 150 mg tablets and three 500 mg tablets.

DR. SCHILSKY: Do the pills look different?

DR. GRIFFIN: Yes, they are different sizes.

DR. MARGOLIN: Just a small question. Either I missed it or it wasn't indicated in the documents. You have nine complete responders. I'm curious in both the definitions --

DR. GRIFFIN: I'm sorry, I gave you the wrong impression if you thought I claimed that. No, no. We have nine patients who had complete regression of their signal lesions, which were their biodimensionally measurable disease identified at baseline.

In breast cancer, once a patient has boney metastases, it's very hard to establish even between reasonable people, whether they are a complete responder or not. How much bone repair do you need before you can call them a complete responder?

Of those patients, we score three at time of submission as responders. I think the FDA has questioned two of those. We subsequently had another patient go on from a partial response to a complete response. But I think

a complete response in patients with widely disseminated breast cancer with boney metastases is a poorly defined category right now.

DR. MARGOLIN: That answers partially my question. The other half of the question was how partial response was defined vis-a-vis the bone scan component of partial response.

DR. GRIFFIN: The protocol specifically excluded bone lesions from any contribution to the response studies. They were not considered evaluable --

DR. MARGOLIN: So theoretically they could have -- it probably didn't happen of course, but they could have even progressed in bone while experiencing an objective response elsewhere?

DR. GRIFFIN: They could progress in bone on the basis of clinical symptoms or clinical judgment, but we didn't ask them to look for improvements in bone scan. We decided that it was just too unclear to make it worthwhile.

DR. OZOLS: Can you share with us any information yet about the randomized trial in colorectal cancer, 5FU versus capecitabine? Any toxicity, and when will that data be available?

DR. GRIFFIN: My statistician, Dr. Uli Burger, is

sitting behind me. I better not share any of that data, because the trial is still being conducted, but Uli may comment on it. We have a lot of data, but it is still ongoing. The accrual is completed, but the trial itself will go on for another six months, therefore we are reluctant to show any data on the trial.

DR. BURGER: Uli Berger, Hoffman-LaRoche, statistics. It will be available in the third quarter or fourth quarter of this year. We just finished recruitment in this trial, then we need a seven month follow-up to get a good evaluation of tumor response and progressive disease, and then these data become available. What we could present you is some information on the safety.

DR. SCHILSKY: Mild chemotherapy drugs it strikes me can be both a blessing and a curse. There are lots of good things about them potentially, but can you tell us something about how you intend to package and dispense this medication to guard against the possibility of overdose?

DR. GRIFFIN: I think we share your concern. I think an important component of the use of chemotherapy is patient education. We have tried to put an emphasis on patient education. We have a patient education sheet, which was essentially designed to provide a graphic representation

of the common Grade 2 toxicities on capecitabine. I show that here, because again, the patients are supposed to recognize their Grade 2 toxicities and interrupt their drug.

So this now has been translated into 16 languages, and we are using it worldwide. Again, I would suspect that Dr. Blum or Priscilla could probably comment on how this is used in the clinic.

DR. SCHILSKY: But that's not really my question. I'm sort of more interested in is the goal that the patient is going to get a prescription, and then they are going to get a bottle of pills, or two bottles of pills of two different sizes, and it's just going to have a label that says take two of these twice a day, take two of these twice and a day, and then they're going to have to be sure that they don't get them mixed up, and things like that?

DR. GRIFFIN: Yes, that is a goal. I think the experience has been, and we have done these trials in 60 different countries, multiple medical cultures, and cancer patients appear to be quite educable, and quite compliant with taking these drugs. We have not seen that as a major problem.

In terms of drug overdose, we have not really had a drug overdose. The drug in preclinical toxicology studies

has a very high LD50 as a single dose. It's a typical anti-metabolite. You can take a lot at one time without doing a lot of harm. It's more the chronicity of the exposure.

DR. SCHILSKY: One other question about additional medication. Is there any reason to be concerned about other things that the patients might be taking? Of course that is obviously very difficult to control, but patients take lots of things. Among them might be patients who like to stock up on folic acid, for example. Are there concerns about any potential interaction with a folate?

DR. GRIFFIN: Certainly we have looked for interactions in concomitant medications throughout our database. I will ask Dr. Bruno Reigner to add a comment on the potential for interactions with P450 active drugs. In terms of folic acid, I think I'll sit down and think that over and be right back.

DR. REIGNER: In terms of drug/drug interaction, certainly the combination with folic acid could potentially lead to some dynamic interaction. So this is certainly something that should be clearly avoided.

In terms of other drug/drug interactions, our drug has a low potential for drug/drug interaction. Our drug is metabolized by enzymes which are not enzymes which are

commonly involved in drug metabolism. For example, our drug is not metabolized by cytokine P450s. We have conducted experiments as well showing that our drug has no effect on different cytokine P450 isosimes(?). So based on these data, we believe that our drug has a low potential for drug/drug interaction.

We are currently conducting a series of population pharmacokinetic evaluations, and one of the main objectives of this population pharmacokinetic evaluation is to look at the issue of drug/drug interaction.

DR. GRIFFIN: In terms of the folic question, we did perform a standard oncology Phase I of capecitabine in combination with calcium leucovorin. Not expectedly, the MTD of the combination is lower than the MTD of the single agent. Of course those doses of calcium leucovorin were at 30 mg/m^2 day, and I think the vitamin dose of folic is 8 mg. So I don't think it would be a problem unless people were seriously overdosing themselves with folic.

MS. ZOOK-FISCHLER: As a patient representative I have concerns about the quality of life issues and adverse effects. I remember reading that the adverse effects were described as tolerable and manageable. I find those very subjective words. I would like some explanation of what is

meant by "tolerable."

The second thing was that I read that this treatment doesn't create -- the adverse effects are not any worse than other current treatments, but own experience is that the adverse effects on current treatments can be absolutely devastating. One that really concerned me was the hand-foot syndrome, which they said in many cases can be disabling. So I see that as a very important quality of life issue.

DR. GRIFFIN: I will try to address the first part of your question, but again, I think this would be best addressed by the clinicians and study nurse. In fact, I will ask both the clinicians and the study nurse to address this, because I think this is a major issue.

In terms of tolerability and manageability, I think tolerability to a certain extent certainly there were very few Grade 4 events, which are the life threatening events. So that's part of the tolerability. Certainly chronic therapy with this drug, we have patients still on this drug. The Phase I trials was out three years. For the breast cancer trials we have a number of patients out past 18 months. So this drug is consistent with chronic dosing.

In terms of manageability, that really refers to

the fact that we tried to titrate. If a person develops a toxicity, we do not tolerate that. We try to dose adjust to avoid redevelopment of the toxicity. As Dr. Osterwalder mentioned, we do have data that once the dose adjustment occurs, we do avoid, in the great majority of patients, recurrence of the toxicity. So we are not accepting the toxicity, we are trying to adjust it to avoid recurrence of the toxicity.

Toxicities, when they occur, are relatively brief in duration. But I do need to ask the clinicians, perhaps Joyce can comment on hand-foot syndrome and Joanne.

DR. SWAIN: Can I just follow-up on that? Does that mean when it stops, it goes away entirely and does come back, or do a lot of patients like we heard this morning describe, continue to have it throughout their course, the hand-foot syndrome?

DR. GRIFFIN: Again, what the dose adjustment schema calls for is interruption of the drug with the resolution of the Grade from 0 to 1. In Grade 1 hand-foot syndrome is essentially redness of the hands. When redness of the hands becomes a Grade 1 is really a judgment call.

Again, I think it would be best if the clinicians comment on the significance of the hand-foot syndrome in

terms of patient quality of life, because I think that is a very important question.

DR. BLUM: My experience in general has been that this side effect has been usually easily managed with holding those as temporarily for the Grade 1 toxicity. So that the patient will come to the clinic and often will have red hands or red feet without pain, and without desquamation. That is often the first side effect that they will have. With that, withholding doses, that symptom seems to subside.

My clinical experience has been that this has been the main experience; that the more severe toxicity, whether it is pain or desquamation has been a minority of patients. Even with that, that has resolved. My experience has been that this has not been impinged on aspects of holding things, turning objects, opening bottles, dropping things, and that patients have been able to wear their shoes, and able to ambulate without problems with rare exception.

When that has become a problem, if there has been a severe toxicity, a Grade 3, then withholding the drug, those side effects have subsided. So my experience has been that the toxicity has been transient and easily reversed with either holding drug, and then resuming again, or with

dose reduction.

MS. ZOOK-FISCHLER: My concern may be if you withhold the drug, I think the psychological anticipation for a patient, thinking that they will then have the same adverse effect a second time and a third time could result, it seems to me, in a patient choosing not to continue the drug.

The other question, when I asked about "tolerable," I really meant patient perception of what is tolerable, because I know it may not be life threatening, but three different patients may have a very different perception of what that tolerable limit is.

MS. KROMELIS: I can respond to that question. Patient education, first of all, I think this is the most important aspect of the treating the patients with oral capecitabine. When the patient initially comes into the office and we discuss the treatment plan with them, they are given a printed sheet with Grade 2 toxicities on it. We explain very, very carefully that if a patient experiences a Grade 2 toxicity, it is absolutely necessary that they call us, and that the drug is stopped.

If they stop it with a Grade 2 toxicity, we are usually able to resume the drug within two or three days.

We certainly try to prevent having toxicities go to a Grade 3. I think with time now we have stressed the importance of stopping the drug if they have a Grade 2 toxicity.

We also have some little therapies we use even if they develop a Grade 1 toxicity. We have some emollients and actually vitamin B6 that we are able to give our patients that seems to benefit them as well.

Again, patient education is so very important. I think they have realized that if in fact they do stop the drug when it reaches a Grade 2, that we will be able to resume the drug more quickly. If it has gone on to a Grade 3 or a Grade 4 and they are going to restart the drug, we do not restart the drug until it is back to a 0-1.

DR. GRIFFIN: We have looked at the 570 patient population. Eight patients were withdrawn for toxicity, which included hand-foot syndrome. Four of those eight though, had hand-foot syndrome. Other toxicities like diarrhea, nausea, vomiting, only four mentioned hand-foot syndrome as the reason for withdrawal. So that's less than 0.5 percent patients withdrawal.

DR. D. JOHNSON: Well, it would be interesting to know how many of these people do have hand-foot syndrome, who get that therapy interrupted, what that does to their

response. Don't answer that, though.

I do want to know though, since we are being asked to approve this product on the basis of the response rate, which seems to be similar to continuous infusion 5FU even in this group of patients as far as I can tell, although admittedly there aren't a lot of data there, what you showed me suggests as much.

So the alternative is the clinical benefit. I'm not sure I understood your slides in 79 and 80, so I want to go to those to make sure I understand those. Slide 80 is the clinical benefit mean pain for pain responders over time. You indicate that there is this drop, and there is this maintenance of improvement.

What I would like to know, is this maintenance of improvement, the way it states here is that it's the mean pain for pain responders, which would suggest that if you are not hurting, you are still on this curve, but if you are hurting, you are no longer on this curve, which means the curve will stay the same. Do you see what I'm saying?

I'm not sure this proves anything to me, except that if you pain goes away, you feel better.

DR. GRIFFIN: Again, I think this is probably an oversimplification.

DR. D. JOHNSON: It may be an oversimplification of a complicated area, but that's what you are asking us to approve your drug on. So you better be able to make it so we can understand it.

DR. GRIFFIN: Essentially what was shown here is the mean pain in responding patients. These were the patients who responded in the pain categories.

DR. D. JOHNSON: Responded in what manner? These are patients who responded objectively? If you are telling me their pain went away, and therefore they are a responder, then their pain responded. That's what I'm trying to determine.

DR. DUTCHER: Page 75 has the definition of pain score.

DR. D. JOHNSON: Right, I understand.

DR. GRIFFIN: An a priori definition of what a person would need to be scored a responder on our protocol. As I mentioned, they had to have three things. They had to have greater than 20 mm of pain at baseline. At baseline only 51 patients had greater 20 mm of pain at baseline. So they are the only ones who could score a response of any kind. Then they had to show this degree of improvement.

DR. D. JOHNSON: So all that curve shows me is

that 51 maintained their response. So the same thing might have been accomplished with codeine.

DR. GRIFFIN: Yes, and I think some of your concerns will be addressed by the longitudinal analysis, but I also ask Dr. Burger to present some more data on CBR. We can present data on the effect of dose interruption and dose reduction on the spots. I'll ask Dr. Burger to address both those questions.

DR. BURGER: When I understand you correctly, then you are concerned about the impact of missing values on these curves on these blocks over time. Certainly, I can agree to those curves. However, when we have extensively looked at the data, we have seen that patients which drop out, that they usually bump up with their pain score. They very often stayed up with the pain score being constant. So from that perspective, we haven't a big risk in showing these mean plots over time.

DR. D. JOHNSON: While you are looking for your slide, then that actually troubles me, because it suggests there is no correlation there to your drug. If they are progressing and you see that their pain score remains the same, how do you explain that? You are attempting to infer correlation it seems to me, with your compound. Isn't that

what you are trying to do?

DR. BURGER: I see your point.

DR. D. JOHNSON: Thank you.

DR. BURGER: Let me first address perhaps the duration, and then come back to the other one. What you see here is an intent of showing the duration of the pain response in a little bit different way. What you see here are the patient numbers with regard to pain. The yellow bar here means the duration of the response. The lower part is the onset. The other part is basically the drop out of the patient out of the study, or either when the response stopped. Stopping in this case was defined as two consecutive measures of pain greater than 0.75 percent of the baseline pain.

As you can see, actually many, many patients had a long duration of their response. The patients which were marked here with a star were the patients which were not sensal(?) at the end. So you can see that we had a few patients, when at their trial termination, which were really getting back to the baseline pain.

DR. MARGOLIN: Maybe a question would perhaps clarify that thing on what your answer is. If the patients that are starting at Week 0 on page 80, and those who

maintain the graph are the 50 patients from page 74 -- no, from whatever page it was that said that you had about 51 patients who had the pain as their clinical benefit response, page 79.

There are 51 patients in the pain subgroup. So those patients met the four week and the 50 percent pain score criterion. If those are the patients who went out to this 20 weeks, who, having gotten to the four week point, and therefore making it onto this line, that's a group presumably that may have such undulant disease that when they have progressive cancer, their pain didn't come back right when their cancer progressed on a scanner or on an exam.

DR. D. JOHNSON: I understand that.

DR. MARGOLIN: That may be the biological answer.

DR. D. JOHNSON: That may well be. I think it is very difficult to discern clinical benefit in a situation like this, but that's what we are being asked to assess. I would like to be convinced that there is some clinical benefit here. There are a lot of people who may not know what bag balm is, but I do, and I would just as soon not use bag balm on my hands in order to get through chemotherapy. This issue is, I think, a very important one about the

response and the duration of the pain.

Also just seeing your point -- go back to the slide you were showing me -- you required a greater than 75 percent increase over baseline in two consecutive assessments?

DR. BURGER: That was just an arbitrary definition of relapse. We required a 50 percent reduction in pain, maintained in four consecutive visits over four weeks to define a pain response.

DR. GRIFFIN: It's of baseline, not over baseline.

DR. D. JOHNSON: And during that time patients had their pain medication not adjusted?

DR. GRIFFIN: Again, we looked at that as separate score. Assume that they had their pain adjusted upward, it couldn't be a CBR, because of the negative rating category. The pain responders usually had decrease analgesics at the same time.

DR. DUTCHER: Can we take a break? Fifteen minutes.

[Brief recess.]

DR. DUTCHER: We will now have the FDA presentation. Dr. Alison Martin.

Agenda Item: FDA Presentation - Alison Martin,

M.D., FDA Reviewer, Masahiro Takeuchi, Sc.D., Statistical Reviewer

DR. MARTIN: Thank you and good afternoon. On behalf of the FDA I will be presenting the medical review. Dr. Masahiro Takeuchi will present the quality of life data.

I would like to acknowledge the rest of my colleagues in other disciplines for their work in reviewing this NDA.

The revisit the proposed indication, it is for the treatment of patients with metastatic breast cancer after failure of paclitaxel and an anthracycline-containing chemotherapy regimen.

The outline of my presentation will start with a brief overview of the regulatory history and some of the issues that this NDA presented to us. I will make some comments on the pivotal Phase II trial with regard to patient population and results, and then I will return for a summary of strengths and weaknesses.

As you have heard, the IND was filed in May 1994. The pivotal trial protocol was submitted the next year. Patient accrual was complete in a year. There was one amendment to the protocol after 63 patients had been entered, which provided for stricter definitions of

paclitaxel resistance, specifically taxol in adjuvant setting, a more formalized hand-foot syndrome, and clarification of the WHO criteria for progressive disease in that worsening of the fusions only would not be considered progressive disease.

The three issues that arose concerning this NDA were that the submission was based on a single trial, and this was an uncomparative trial; the only robust endpoint in the Phase II would be response rate, and that would be appropriate for accelerated, rather than traditional drug approval. We recognized that there was respective clinical benefit plan in the protocol, however, we advised it was very difficult to interpret this kind of data on an comparative arm. Also, the accelerated approval requires selection of an appropriate patient population.

If I could just spend a moment longer on this issue. The regulations with the following guidance that the patient population chosen has no adequate therapeutic alternatives, or if the population does, that the new drug product provides meaningful therapy benefit over the alternative.

Selection of this patient population is not always easy, because it changes over time as more drugs are

approved in an indication. While we recognize that this population is heavily pretreated, comparative trials can also be done on heavily pretreated patients. So in the questions we will be asking advice from ODAC on who the appropriate patient population should be. This is important to us in a number of ways, including advising other companies, especially with international harmonization.

Now I would like to try back to the pivotal Phase II trial. The primary objective was to determine the overall response rate of patients with measurable metastatic breast cancer failed previous paclitaxel chemotherapy was in the range of 20 percent. The statistical section from a stated hypothesis was that the response was less than or equal to 10 percent.

Secondary endpoints, which of we weigh less heavily in an uncontrolled trial were duration of response, time to progression, time to treatment failure, overall survival, and a clinical benefit response score similar to the one used with Gemzar/pancreatic cancer, using parameters of pain intensity, analgesic consumption, and performance status. Lastly, safety was to be evaluated by adverse event reporting and laboratory changes graded by NCIC from toxicity criteria.

To revisit some points in the eligibility criteria, either bi-dimensionally measurable or evaluable disease was allowed. It happened that 135 patients with measurable disease were entered. At least two, but not more than three regimens; and resistance to paclitaxel. The resistance to paclitaxel was defined I think conventionally, progression on therapy with or without an initial response. The amendment served to remove the possibility that paclitaxel could be given in the adjuvant setting. As has been mentioned, there were no eligibility criteria for anthracycline treatment.

A total of 163 patients were entered, and as one not dosed, the intent to treat population became 162. Most of the patients were entered from the United States, and 8 from four centers in Canada. As I mentioned, 135 had bi-dimensionally measurable disease. Enrollment per center ranged from 1 to 37. The largest accruer accrued 37 patients, and of these, 35 had measurable disease. This center also had multiple sites and multiple investigators accruing.

The demographics are shown for all patients, as well as those with measurable disease, since that was the specified population of interest for our response rate.

There is no significant difference in demographics between these populations. The eligibility criteria required patients were female. The median age was 56. The majority of patients were Caucasian, and Karnofsky performance status was 90.

Other clinical characteristics showed that the majority of the patients had at least three sites of metastatic disease, and that the predominant site was visceral as defined by lung/pleura, liver, and peritoneal.

Before I characterize the patients by their prior treatment status, I would like to revisit the definition provided in the NDA. As has already been mentioned, the protocol only defined resistance for taxol, and we accepted the definition as standard. The NDA added the further definition to resistance that relapse after an adjuvant regimen could occur within six months and a patient would be considered resistant.

The category of failure was also added in the NDA, and we are aware that there are many different definitions in the literature for what constitutes failure. These particular definitions here are weakened by the absence of a dose.

Using these definition in the NDA, however, we see

that the majority of patients with measurable disease or the entire population are resistant to paclitaxel, however, less than half are resistant to anthracycline.

This two by two table is meant to present a composite picture of drug resistance. Using the definition in the NDA, 42 patients are resistant to both drugs; 26 are resistant to paclitaxel and have failed an anthracycline; 13 are resistant to an anthracycline and failed taxol; and 10 have been exposed and are considered to have failed both drugs.

We looked at it in a slightly different way in exploratory fashion. We retain the definition of resistance as standard, and replaced failure with exposure. In the absence of specifying a minimum dose, we weren't sure why we wouldn't. This really could capture information on 26 additional patients who had received an anthracycline to see if they contributed data.

I did go back to the case forms and verify resistance, and I came up with 43 patients, which is essentially the same as the sponsor's submission. We beat the number who are resistant to paclitaxel and have received an anthracycline to 48. I will come back to this two by two table when I talk about responses.

Because it's a Phase II trial and the endpoint of interest is response rate, I spent a considerable amount of time trying to verify responses. As you heard, the sponsor submits that there are 27 responses for a rate of 20 percent, and there is 95 percent confidence interval of 13.6.

I looked at the independent review of these data in a different way. I looked at it as how many of the patients who were confirmed as responders by the sponsor, could they also confirm? For 18 patients who had radiologically identified indicator lesions, 12 of those were confirmed by the IRC. I will mention that the IRC reviewed 83 other patients, and in that situation 5 additional responses were noted by the IRC that were not noted by the investigator, so that inter-observer error went in both directions.

In the FDA's review we stood by the WHO criteria for protocol, and that meant that two of the three patients did not obtain a CR, because baseline disease was not factored in. We did, however, move them to the partial response group.

Our response rate is then 18.5 percent, with the lower bound of the 95 percent confidence interval again over

10. The next slide will go into differences in a bit more detail.

The IRC disagreed in six patients with the responders of the sponsors. In two of those cases, the measures of the IRC could be converted to partial response; 50 percent strengths in the indicator lesions if you factored in the clinical lesions that were not available to them.

In two other cases there was no explanation as to why there was a disagreement between the two. Both groups submitted their measurements. They were the correct time point and calculations were correct. There was no additional information from on the CR to clarify the situation. In that instance I accepted it as inter-observer variability and took the best response.

In the last patients on whom the IRC had a different opinion, I had their different opinion. So one of the patients became progressive disease and one became stable disease, although not for the same reasons as the IRC.

This two by two scale is an attempt to show response rate that might relate to composite drug resistance, and in the group of patients who were clearly

resistant to both the paclitaxel and an anthracycline, 11 patients out of 43 responded for a 25.6 percent response rate. There are responses in those subgroups.

We were concerned about potential biases on the part of the physician selection measurement changes in supportive care, so we did also try to look at ways to assess consistency. Of the 24 centers, four accrued than 10 patients, and the response rate in these large accruers versus the 20 center who accrued fewer patients was 20 percent. Lower bound of a 95 percent confidence interval for both of these groups is greater than 10 percent.

The largest accruer that had accrued 35 patients with measurable disease had a 17 percent response rate. This does not mean that there may not have been some bias, otherwise we were not able to see it. It may have been a system out.

Secondary endpoints -- for consistency's sake I will present these, although we weight these less -- are presented here for all patients, as well as those with measurable disease, so the denominator is either 162 or 135. We date duration of response by the time the first notation of response, rather than at the start of treatment, like the old WHO criteria do.

The duration of response is 154 days. The median time to progression for all patients or those with measurable disease is similar at 90-some days. Survival between these two groups is similar. For all patients the survival in months is 12.8; for those with measurable disease it's 10.2.

Looking at the most resistant subgroup, the duration of response stays the same at 154 days. The median time to progression remains about the same at 102, but survival does fall down to 8.5 months.

For the other efficacy parameter, quality of life, Dr. Takeuchi will present his analysis.

DR. TAKEUCHI: By using this opportunity, I would like to discuss some issues, and present our findings regarding the clinical benefit response in the study #014697.

So first of all I would like to describe clinical benefit response very briefly. Clinical benefit response was based on repeated measurements of pain, analgesic consumptions, and Karnofsky performance status. Positive or negative response required a four weeks of maintenance period.

This slide shows some issues involved in clinical

benefit response. First, the attrition rate was extremely high, preventing extended measurements of the three component of clinical benefit response. Secondly, we did not have a control group to compare. Third, the same cutting criteria first derived for the pancreatic cancer was applied so. So the question comes, is it appropriate to apply the same criteria for breast cancer, or that may be sensitive to those cutting criteria.

That is why we decided to use a longitudinal analysis. The purpose of this analysis is to characterize patterns of changes over time, and to investigate the effects of baseline covariates and dropouts on time trends.

The approach we took is that we fit polynomial growth curves describing the mean value of each component of the clinical benefit variable over time. We examined the mean response in each cohort. Those cohorts are based on the study designs, because each patient was examined every six weeks to determine whether she was responding or not, or examined at the time whether she was dropped out from the study.

Therefore, Cohort 1 consisted of patients who dropped out from the study between baseline and week 6. Cohort 2 consisted of patients who dropped out between week

7 and week 12. Similarly, Cohort 3 consisted of patients who dropped from the study between week 13 and week 18. Cohort 4 consisted of patients who could stay in the study beyond 18 weeks.

This longitudinal approach allows consideration of the individual component of the clinical benefit response, and treats the outcome as continuous rather than binary, and provides information on the temporal pattern of change. But I have to mention this caution. All analyses of clinical benefit response and its components are potentially biased, because of the dominating effect of dropouts. So those results should be interpreted cautiously.

This slide shows the sample size over time. So at the beginning of the study around 160 patients participated in this study. By the end of 18 weeks only 53 patients stayed in the study. That means more than 100 patients dropped out from the study during the treatment period.

This slide shows the results from the longitudinal analysis in pain score. Pain did not change over time in patients who were in Cohort 1. Those patients dropped out between baseline and week 6. Those pain scores stayed the same over the study. But pain score did decrease maybe around nine weeks, and started to increase for the patients

who are in the Cohort 2. That means Cohort 2 patients drop out from baseline at week 12, or the same time trend we found for the patients in Cohort 3, but patient score decreased until week 16, and started to increase a little bit for the patients who are in Cohort 4.

This slide shows the results from the longitudinal analysis in the analgesic consumption. Actually, the analgesic consumption did increase for the patients who drop out before six weeks. That means in Cohort 1. But analgesic consumption did not change over time for the patients in Cohort 2, 3, or 4.

This slide shows the results from the longitudinal analysis in the Karnofsky performance status. Performance status did not change over time for the patients in Cohort 1, 2, or 3, but performance status slightly increased over time for the patients in Cohort 4. That means if the patients can stay long enough, then the Karnofsky performance status increased.

So this slide shows a summary. For the patient who stayed in the study at least 18 weeks -- that means during the treatment period -- I had 50 patients. In these patients pain score decreased to around week 16, and started to increase a little bit after that. Analgesic consumption

stayed the same, so there is no change over time. On the other hand, the Karnofsky score increased slightly over time.

This slide shows the summary 2. For the patients who were resistant to both paclitaxel and anthracycline, we had 43 patients, as Dr. Martin mentioned. These patients' pain score, analgesic consumption, and Karnofsky score did not change over time, but please note that I had only 43 patients. So I had to use all the data. So I couldn't cut the data by Cohort 1, 2, 3, and 4. So I used all the patients. To make sure everything was okay, I just cut in the 12 weeks, but these all did not change.

This is kind of the conclusion of nonconclusion. This longitudinal analysis is an exploratory analysis. As I mentioned, we did not have any control group to compare. We faced a very high dropout rate. So it is very hard to draw any conclusions. This is my conclusion.

Thank you.

DR. MARTIN: Just a few more comments about safety. You have seen the more thorough presentation from the company. My only comment here is that I have included some of the total incidence of the most frequent adverse events, but it's not a statistically significant difference.

There is a trend that is consistent of an increased incidence in the patient population for consideration today, although the Grade 3/4 toxicities don't reflect that as much.

For the other frequent adverse events, hand-foot syndrome, paresthesia, and hyperbilirubinemia the same pattern is observed. The question mark is the total for the larger pool, because that is still under review.

For a conclusion I would offer a summary of strengths and weaknesses in this way, and I hope to hear some other comments. The NDA is based on a single Phase II trial, however, it is large and multicentered.

The primary endpoint that we are left with is response rate, however, it was response rate that had a 75 percent concordance rate by the IRC, and there appeared to be consistency across centers.

Although it was a heavily pretreated group, it was a heterogeneous population with regard to prior anthracycline therapy, yet 43 patients were doubly resistant, and responses conveyed in all subgroups.

The safety data is commensurate with other cytotoxics, although it is short-term safety data. We have a median duration of exposure on this just a bit over 12

weeks.

Although oral therapy is both a blessing and a curse, I kept going back and forth as to which column to put it in, I listed it under strength, but that would not be true for all individuals.

With that, I will conclude and take any questions if you like.

Agenda Item: Questions from the Committee

DR. DUTCHER: Questions for the FDA?

DR. SWAIN: I wanted to ask you about the hyperbilirubinemia. In your review you said that half of the patients on the little trial who had hyperbilirubinemia did not have liver metastases. Isn't that right? I think you had that in the very beginning, or maybe it was a different study.

DR. MARTIN: I think that information might have come in later, did it not, in the safety update, the analysis of who was at risk for hyperbilirubinemia. Yes, there appears to be something to that analysis.

DR. SWAIN: There are quite a few patients that do develop an elevated bilirubin, more than they should I think there today, who have no liver metastases in this study?

DR. MARTIN: Yes, I think it's also true that no

patients were taken off studies for laboratory analysis.

DR. SWAIN: It was said that it was transient. Does that mean that it was two days, four days, and you kept treating while patients had this elevated bilirubin?

DR. MARTIN: Treatment should have been dictated by the common toxicity criteria, where it was a laboratory parameter or not. Can the sponsor comment on duration of the hyperbilirubinemia once it occurred?

DR. GRIFFIN: The duration of the was somewhat heterogeneous. A considerable portion of the patients -- I'm unaware of a 50 percent incidence in the pivotal trial. I think it is still a small percent of patients without known liver metastases. Patient with progressive disease in liver, obviously it is sustained, and they would go off trial.

The patients who did not have a clear medical explanation, either hepatic metastases or a biliary tract disease, tended to have one or at most two elevations at any time on the drug. Those elevations would be either one day or two days. So it was very transient. In those patients without progressive metastatic disease, it would return towards normal even with continued drug exposure.

DR. D. JOHNSON: I'd like to ask Dr. Takeuchi a

couple of questions. I recognize this exploratory analysis you did led to no conclusions, so I would like to expand on those. Again, I'm having a very difficult time, and I'm trying to come to grips with this issue of you have selected cohorts here, and it seems to me a priori you selected cohorts that are destined to do well when you say they do well.

To me it's like selecting everybody that survived five years and saying, well, the five year survivors did well. I mean explain to me what you were attempting to do here.

DR. TAKEUCHI: For this analysis, since we faced heavy dropout, we call it a mixed effect model. In that case we must assume some missing mechanisms. To determine those missing mechanisms it is not ignorable. That means we cannot ignore the missing data in the cohort. That means I check the study designs. By designs, every patient was supposed to be examined every six weeks. If she responded or had stable disease, then she can continue on the study. Is that right?

DR. GRIFFIN: Right.

DR. TAKEUCHI: Otherwise, if she progressed, she must stop at that time. I'm a man, but if I say at 10 weeks

I don't feel good, so I would like to drop out, at that time also I must be examined whether I responded or not. So in that case, in that sense I saw by design a week interval which determined how people drop out. Then using those cohorts, how the trend is going along. Then if those time trends are the same, then I can put in all the data to get more precise time trends.

If the time trend is different, then we combine those cohorts, then I will be the biased estimate. So to avoid those biases, I just cut those cohorts that I think are derived by design.

DR. D. JOHNSON: Okay, I actually almost understand this. So I want to ask, let's look at Cohort 4. That is the only cohort that you indicate in your analysis had a benefit that I would recognize as a clinician as worthwhile, i.e., that's a group that had increasing performance status, and better pain control, correct? But no change in their analgesic use.

DR. TAKEUCHI: That's correct.

DR. D. JOHNSON: Now is there a way that I, as a clinician, looking at that specific cohort, might have identified that cohort at the outset of the therapy? In other words, is there something unique about that group of

patients, or is it a group that in fact had a high response rate --

DR. TAKEUCHI: All the responses came from that cohort.

DR. D. JOHNSON: All the responses came from that cohort?

DR. TAKEUCHI: Yes, 25 patients.

DR. D. JOHNSON: Now, the next question I want to ask you, one of you slides, "Summary 2," the group of people for whom the sponsor is seeking approval, that is, those individuals who have metastatic disease and have failed a paclitaxel and an anthracycline-containing regimen, your analysis of these 43 patients suggests that there is no change in pain score, no change in analgesic consumption, and no change on Karnofsky scores. Do we know specifically about the toxicity of that group of patients? Do we know specifically the response rate of that group of patients?

DR. TAKEUCHI: I think two patients responded.

DR. D. JOHNSON: Two of those 43 patients? But we don't have the toxicity of that group of patients?

DR. MARTIN: We have not correlated toxicity to dropout.

DR. TAKEUCHI: So did you get a conclusion?

DR. D. JOHNSON: I'm not conflicted any longer.

DR. SIMON: I also would like to ask a couple of questions about the longitudinal analysis. When you say there was a decrease, are you talking about a statistically significant decrease?

DR. TAKEUCHI: Yes. So for that analysis, my hypothesis parameter is 0 and out. That means, yes, there was a decrease.

DR. SIMON: You talk about a decrease here. It's essentially a model. You are talking about the average for the group is decreased, right?

DR. TAKEUCHI: Yes. So just I'm shooting for the population to make sure that from my point of view, I wanted to make sure I would get a robust result. So every parameter is tested by some estimator. So I just care about the standard error very much, otherwise no matter how we model, the parameter estimate is not biased.

I do care about the standard error to take care of those correlations, otherwise for those populations it is advanced. So either we see some clinical benefit. I do not expect too much, but if I see something there, I want to be able to detect it, so I use correlations, but the design must be robust.

DR. SIMON: Do you remember what percentage of patients had bone involvement? All these patients had bone metastases?

DR. MARTIN: Not off the top of my head, unless the sponsor has a slide, but a significant number. What would be your question?

DR. SIMON: I was wondering whether in this longitudinal analysis, if they didn't all have bone involvement, where any analyses were done in terms of using that as a covariant.

DR. MARTIN: Fifty-four percent. That's predominant site being bone. We didn't look at that. What we did focus on was making sure we knew who was put on the bisphosphanates for treatment, concomitant medications that might have not been captured by analgesic consumption such as anti-inflammatories, bisphosphanates, antidepressants. There were a significant number of patients taking those, but we couldn't see a pattern to it.

DR. SLEDGE: Actually, for my interest, did we see bisphosphanates in this trial?

DR. MARTIN: Sixteen as of when the study started, and some were on it before, and it carried on. So more than 16.

Agenda Item: Committee Discussion and Vote

DR. DUTCHER: Should we proceed to the questions?

DR. TEMPLE: The part of accelerated approval pertinent to us here is the one that says for serious and life threatening diseases without adequate treatment. We can rely on a surrogate endpoint, that is, reasonably likely to predict clinical benefit as a basis for approval.

The important distinction there is that reasonably likely is meant to mean a surrogate that we're less sure about usually. For example, durable complete response rates are a traditional basis for approval on oncology, but we feel very secure that those usually correspond to improved survival or something like that.

We are, for reasons that were shown this morning, less sure that partial response rates correspond to real clinical benefit, but it is not unreasonable to think they might. So the crucial matter is that it allows us, and says explicitly that for certain situations we will rely on a surrogate endpoint that is reasonably likely.

Surrogate endpoint here means something that is of no benefit to the patient per se, you don't benefit just from having your tumor shrink, you only benefit if that leads to dramatic improvement or better survival or

something like that. But that's what a surrogate means.

A separate program in oncology specifically said that for refractory disease without good treatment, we were prepared to rely specifically on partial responses as a base for approval. Accelerated approval comes with an ability of the agency to require as a condition of approval, the conduct of studies that will evaluate real clinical benefit.

A wrinkle that we added to that, because we thought it was important is that we have said that the clinical benefit studies might not necessarily be in the same stage of disease that was the one we approved the product for. In other words, we might approve it for refractory disease based on the surrogate endpoint and find the well controlled trials persuasively showing survival or some other benefit in an earlier stage of the disease.

That was reflecting what we thought would be the difficulty in doing well controlled trials in refractory disease, and our experience has certainly borne that out. It is very hard to get anybody to do it.

The condition is supposed to be applied when there isn't good therapy available, and when the new therapy appears to offer some advantage over available therapy. A little bit of that came up earlier. I guess the question

is, what constitutes available therapy? We have an inclination to think that that means something we have approved, but we try to be realistic about what is out in the world in addition.

So I saw the data Dr. O'Shaughnessy showed about the continuous infusion 5FU. It was a 35 patient study in people who are reasonably refractory. Whether that constitutes available therapy that is basically demonstrated, you need to think about. From my point of view, we haven't reviewed it. We don't know how many of those responses we would agree with. We don't know exactly how refractory was defined in each case.

So to my eye that means that the four people who were refractory to these two classes of drugs, it's not clear that there is other available there, but that's part of the judgment you all would have to make. The condition for accelerated approval means there isn't anything good to treat these people with.

DR. SCHILSKY: Just to clarify, Bob. I take it that there are no therapies which are indicated for use in this patient population at the present time?

DR. TEMPLE: In taxol/anthracycline resistant people that is right. We have a number of therapies for use

in people who are anthracycline resistant, notably taxanes, but nothing for this combination. As Alison said, this keeps changing as therapies come into the marketplace.

DR. SIMON: I'm just trying to clarify. So for that subgroup of patients, you could approve this drug based on response rate without an accelerated approval, is that right? Without any demonstration of patient benefit? I thought you said just based on response rate.

DR. TEMPLE: Well, no, our conclusion is that partial response rates are not the sort of endpoint we would use, at least not for cytotoxic drugs anyway, that we would use for a regular approval. We are prepared to use them under the accelerated approval setting. That means you are offering therapy where there really isn't any therapy, or isn't any very well established therapy. It comes with a condition that further studies be done.

DR. MARGOLIN: Another clarification question. Since traditionally, although this tradition seems to change with every meeting, even for accelerated approval there has been a sort of requirement for two well controlled similarly performed studies. Is it safe to assume that the two controlled studies were rolled into one here, because one endpoint was to be the surrogate for benefit, which is

response, and the other was to be the clinical benefit response that attempted to be carefully outlined?

DR. MARTIN: We didn't look at the quality of life endpoint as being able to be robust enough to really be a confirmatory endpoint. We looked at it as we could tell the company to do two Phase II trials, and chop this in half, and we weren't sure what benefit we would get in doing that, because this way there was one protocol. It was multicentered, and we explained we were looking for consistency of results, as we would for two separate Phase II trials.

DR. TEMPLE: The how many studies question is one that comes up all the time. When you are talking about a fundamentally uncontrolled series of observations, there is always a certain question of where one study starts and where the other study begins. The model for the idea of replication or substantiation of an observation comes from controlled trials, where you run them and there is a controlled group and you get a P value, and then you want to see if you can replicate the observation somewhere else.

Here you are looking at a series of people, and it is hard to say what constitutes a single study, but that is part of the judgment we would be asking you to make. It's

not unusual for example, to have several single site Phase II type oncology studies. Well, how different is that from a multicenter study of this kind? Not too, it seem to me, but that's part of what we are asking you.

DR. DUTCHER: So page 2. Study SO 14697 was a non-comparative, multicenter trial in 162 with metastatic breast cancer who had progressive disease despite treatment with paclitaxel. The primary efficacy endpoint was the objective response rate in patients with measurable disease. In the 135 women with measurable disease, the response was 18.5 percent with a median duration of 154 days. The response rate in the 43 patients who had disease resistant to both paclitaxel and an anthracycline was 25.6 percent, with a median response duration of 154 days.

1. Of the 162 women entered into the pivotal trial, 43 had disease that was resistant to both paclitaxel and an anthracycline.

a. In the 43 women with breast cancer resistant to both of those, is an objective tumor response rate of 25.6 percent with a median duration of 154 days evidence of a meaningful therapeutic benefit over existing treatments?

Comments?

DR. SWAIN: I think I would say yes to this, because even though we saw all the studies that Dr. O'Shaughnessy showed, none of those studies had patients that were so tightly put into the categories like they are here, with the paclitaxel and anthracycline resistant. Here they had one or the other, and usually when they were paclitaxel, they weren't progressing on paclitaxel.

So I think that we don't have any other data or any other anything to show that there is benefit in this group of patients. This is a fairly decent response rate, and like the FDA I would discount the benefit response data and just go with the objective response rate.

DR. SLEDGE: I think as Sandra has said, what you are left with here is a response rate, and that's all you've got. If you ask does this represent a significant improvement over what is existing, then you have to ask yourself what is existing? Well, in the community these patients are probably going to be treated with navelbine or they might be treated with continuous infusion fluorouracil.

As I asked Dr. O'Shaughnessy, this is a pill form of continuous infusion 5FU from a toxicity standpoint, and probably in general terms from a response standpoint. So I think in some sense we are being asked to approve something

that is already being used in the community, in a different form.

DR. KROOK: As a community physician, I agree. I guess I don't know what the existing treatments are. We out there, do a lot of things, just like you say. As I used to say, we cook it, we fry it, we do whatever to it, and we come up somewhere. I can't begin to tell you the response rate. It could be all the way from 5 to 30 if you collect the right patients and you have the right observers.

I agree with the statement, but I don't know what the existing treatments are. That's my problem.

DR. MARGOLIN: One attempt at a comment, which turns out to be sort of response to Dr. Krook is I'm a community oncologist in one of the academic centers. I can tell you, number one, these patients go straight to Phase II or the rare Phase II trials at our center.

Number two, I think the advantage of navelbine as an MDR drug, this is not -- and these patients often really lack IV access. One arm is gone forever more pretty much with these patients, and the other arm is used up. So something oral, which even if at the best it does substitute for a low dose chronic 5FU infusion I think is definitely welcome in our armamentarium.

DR. DUTCHER: All those who agree that this is evidence of meaningful therapy please raise your hand. Eleven yes. Any no? One no.

[Whereupon, Question 1A was answered affirmatively.]

DR. DUTCHER: Do you want to comment?

DR. OZOLS: I agree with everything that was said. I'm just still very disturbed that there is comparator. This clearly could have been done with a comparator. I think that the thing that George said, IV 5FU continuous infusion seems to me would do the same thing. So what I'm asking, is there established a benefit over existing treatment? I don't see how you can say that.

DR. DUTCHER: 1b. Are the other patients in the trial supportive of the response rate seen in this doubly resistant population? All those who agree? Twelve yes.

[Whereupon, Question 1b was answered unanimously affirmatively.]

DR. DUTCHER: Number 2, Patients who have received certain cumulative doses of anthracyclines and/or anthracenediones could be considered to be intolerant of, or poor candidates for further therapy with these agents because of the risk of cardiotoxicity with additional

treatment. On 3/17/98, we received data on cumulative doses of anthracyclines and/or anthracenediones received by each patient. In addition to the 43 patients above, there are 48 patients in the paclitaxel resistant and anthracycline exposed group, some of whom could potentially meet this criteria. We are currently analyzing the number of patients and objective response rates in the following groups:

a. In patients whose breast cancer is resistant to paclitaxel and who have received a minimum cumulative dose of 400 mg/m^2 of doxorubicin equivalents, would Xeloda represent a meaningful therapeutic gain over additional treatment with an anthracycline, assuming an overall response rate of 20 percent when these patients are added to the 43 resistant patients?

DR. SIMON: Excuse me, I don't have a copy of this question. I have a different question. Are there any other copies?

DR. MARGOLIN: While Dr. Simon is finding his copy, could we get some kind of clarification of what this means? Does this mean patients who are responding, who Dr. Swain would put on dexterous oxine(?) in patients who are resistant?

DR. DUTCHER: The entire group of people who

either failed or were resistant. I presume this means people who had failed, but weren't considered resistant? They weren't just taken off because --

DR. MARTIN: Failed or exposed, and actually represented a variety of patterns which couldn't be deciphered by prospective really by standpoint. I guess what we are asking is if cumulative dose -- the physician would have an option of going beyond. I guess we are asking in the patient who you might not want to go beyond -- in an adjuvant setting in the old doses, where the metastatic you got to 400 and they have stable disease; that patient.

DR. DUTCHER: So some of these were people that were taken off because of dose level, and not because of resistance?

DR. MARTIN: Reasons are not provided. That's retrospective data.

DR. JUSTICE: This is really a hypothetical question, because we're not talking about specific patients. We're saying assuming they got 400 mg/m^2 of doxorubicin equivalents, or I guess you would also have to consider some other cumulative dose with the addition of dexterous oxine. It gets complicated when you throw that in.

DR. SWAIN: I think it's a really difficult

question. Dexterous oxine hasn't been approved that long, and I think what you are talking about is this past data set basically, where maybe dexterous oxine wouldn't have been used. Physicians may have stopped treatment; have different levels of stopping treatment at 400 or 500 or whatever.

DR. JUSTICE: One answer to that question, assume no dexterous oxine was given.

DR. SWAIN: Well, then I think it is reasonable to stop at that level based on the data with the dexterous oxine, that you can get congestive heart failure in about 25 percent at 500 mg/m^2. So I certainly think it is reasonable not to continue after 400 mg/m^2, and not to give patients any more than if they have gotten adjuvant 400, and then in the metastatic disease setting, give that to them again.

Now even with dexterous oxine there is no data in that situation in which you have been treated with adjuvant therapy, and then you come back a year or two later and retreat with anthracycline. You may see a decreased response rate. There is absolutely no data in that setting. So even with the addition of dexterous oxine, you could say yes, this is a reasonable group to consider to use this product.

DR. SCHILSKY: I'm just trying -- like we all are

-- to get clarification on this. Isn't the real question whether capecitabine would be a reasonable therapy in paclitaxel resistant patients in whom the physician believes that further anthracycline therapy is no longer appropriate? Regardless of the cumulative dose or anything else, if the doctor doesn't think that that's an appropriate therapy to continue or to reintroduce, and the patient is paclitaxel resistant, and they meet these response criteria, would this be a reasonable treatment?

DR. DUTCHER: Does everyone agree with his version of the question?

DR. SLEDGE: It's still an amazingly mushy question, even phrased that way, is the problem. I don't think we should rephrase it. We have absolutely no data with adriamycin. We have absolutely no data with this drug. How can we answer this question rationally?

DR. TEMPLE: You have response rate data in the population, which seem to be applicable to that population. Now what you don't know is how sick they are going to get if you keep on giving them the anthracycline, but there is a fair amount of information about that.

DR. SLEDGE: But I don't think we can pretend as if zanosar doesn't exist. I think we can pretend that

doxorubicin doesn't exist.

DR. KROOK: I also think physicians are willing to push the dose higher with adriamycin.

DR. MARGOLIN: I think there are many, many reasons that we use clinical judgment to not give anthracyclines or more anthracyclines to selected patients. I don't think we're going to be able to come up with a clear cut recommendation coming out of this question that could go into a package insert.

DR. DUTCHER: So do we want to answer this question?

DR. TEMPLE: It is a little bit hot off the presses.

DR. DUTCHER: All right, let me try it one more time. In a patient who is resistant to paclitaxel and in whom doxorubicin may be inappropriate or may be contraindicated, or may not be considered, would capecitabine represent a meaningful therapeutic gain over additional treatment with an anthracycline?

DR. MARGOLIN: Remove the "over additional treatment."

DR. DUTCHER: I think we are not going to deal with this question.

DR. TEMPLE: I think Dr. Schilsky got it right. If the previous group is resistant to both therapies, the thought was people may or may not be resistant to the anthracycline, but for one reason or another, they shouldn't be any more because they are going to go into heart failure. Would this then be an appropriate therapy for that group? We know they respond in the same way as the others responded. That is the question.

DR. DUTCHER: All right, so instead of giving a dose, it would be patients for whom an anthracycline is contraindicated.

DR. TEMPLE: Yes.

DR. DUTCHER: That can be a clinical judgment. It doesn't have to be a number.

DR. SCHILSKY: Determined by the physicians, and not be inappropriate therapy.

DR. TEMPLE: If you wanted to label a drug this way, you could say for example, people who have already had 400 mg/m^2 or something like that as the cut off point.

DR. DUTCHER: Raise your hand if you think that this would represent a meaningful therapy gain over additional treatment in that setting of paclitaxel resistance, and a certain amount of hesitation or

contraindication to using an anthracycline. Would the use of this agent represent meaningful therapeutic gain?

If you think yes; we're voting. Six. How many would vote no? Five. How many abstain? One.

2b. In patients whose breast cancer is resistant to paclitaxel and who have received a standard adjuvant regimen resulting in a minimum cumulative dose of 240 mg/m^2 of doxorubicin equivalents, would Xeloda represent a meaningful therapeutic gain over additional treatment with an anthracycline, assuming an overall response rate of 20 percent when these patients are added to the 43 resistant patients and those described in 2a revised?

Comments?

DR. SLEDGE: My answer here would be no. The only possible exception would be the group of patients who had failed adjuvant anthracycline-based chemotherapy within six months, which would be another form of true anthracycline resistance. Absent of that, if someone relapses four years after four cycles of adjuvant AC, I'm still going to offer that patient adriamycin as a possible therapy.

DR. DUTCHER: Any other comments? How many people would use capecitabine in the setting of minimum cumulative dose of doxorubicin of 240 mg/m^2 in the face of resistance

to paclitaxel? All those vote yes, please raise your hand. Zero yes. All those who vote no? Twelve.

[Whereupon, Question 2b did not pass.]

DR. DUTCHER: Question 3, is the overall toxicity profile acceptable for women who have resistant disease after treatment with both paclitaxel and an anthracycline?

DR. MARGOLIN: Yes.

DR. DUTCHER: All those who would vote yes? Twelve yes.

[Whereupon, Question 3 was unanimously passed.]

DR. DUTCHER: Question 4, assuming an overall response rate of 20 percent, should Xeloda receive accelerated approval for the treatment of women with metastatic breast cancer:

a) resistant to paclitaxel and an anthracycline-containing chemotherapy regimen?

All those who would say yes? Ten yes. Those who vote no? Two. Any comments?

[Whereupon, Question 4a is approved.]

b) Resistant to paclitaxel and who have received a minimum cumulative dose of 400 mg/m^2 of doxorubicin equivalents? This is to vote for accelerated approval on that group.

DR. JUSTICE: You can amend this question the way you did the other.

DR. DUTCHER: Assuming an overall response rate of 20 percent, should Xeloda receive an accelerated approval for the treatment of women with metastatic breast cancer resistant to paclitaxel, and for whom an anthracycline is contraindicated?

All those who would vote yes? Eight yes. All those who would vote no? Three. Abstentions? One.

[Whereupon, Question 4b is approved.]

DR. DUTCHER: 4c) accelerated approval for treatment of women with metastatic breast cancer resistant to paclitaxel, and who have received a standard adjuvant regimen resulting in a minimum cumulative dose of 240 mg/m^2 of doxorubicin equivalents?

All those who would vote yes? All those who would vote no? Eleven no. Abstentions? One.

[Whereupon, Question 4c was not approved.]

DR. DUTCHER: 5. The sponsor has submitted a protocol for a randomized trial, "an open-label randomized Phase III study of capecitabine in combination with docetaxel (Taxotere) versus docetaxel monotherapy in patients with advanced and/or metastatic breast cancer."

Eligible patients would be resistant to, or have recurrent disease after an anthracycline-containing therapy or have relapsed during or within six weeks of adjuvant anthracycline-containing therapy. A total of 454 patients would be randomized to one of two arms. The primary endpoint is to demonstrate superiority in time to progression in favor of the capecitabine-docetaxel combination arm.

Would a favorable result with combination therapy in this study confirm the clinical benefit of Xeloda in patients with prior chemotherapy?

This is a trial in patients resistant to anthracycline, receiving a taxane plus capecitabine. Anybody want to comment?

DR. SWAIN: I think this is a population that is very resistant, and the taxotere data shows a 41 percent response rate in this disease, which is higher than any other drug that we have. If capecitabine adds to that, then I think it would definitely show the clinical benefits.

DR. SLEDGE: I'm a little bit more of a nihilist here. I think if we define benefit solely in terms of response rate and time to progression, we are missing what actually goes on in patients, which is toxicity, clinical

benefit, quality of life. So if the major endpoint here was superior in time to progression, you've got a statistically significant benefit of a month and a half, I would be unimpressed personally.

DR. MARGOLIN: I agree with Dr. Sledge, and I think that this is way too loose, this final statement. I think you would have to define it a lot more clearly before we could just say, yes, a favorable result would make us want to approve this.

DR. MARTIN: If we would get into another patient population, I agree that demonstrating clinical benefit is a much more complex decision.

DR. TEMPLE: Can you comment on what additional criteria you would like to add? The most obvious thing that is missing here is survival benefit, but that happens all the time nowadays. We are assured that everybody is going to cross over to effective salvage therapy. There is no chance of ever seeing -- for example, the people who are missing the capecitabine will be crossed over to it in the later parts of the trial. So that is the kind of thing that is regularly faced.

DR. MARGOLIN: I have more of a question than an answer on that. Does a post-marketing trial that serves to

convert an accelerated approval to full approval have to meet the same criteria that a full approval trial would in the first place? In other words, you can't use a surrogate to confirm a surrogate, right?

DR. TEMPLE: You have to do something that describes a clinical benefit. Time to progression I guess lives in a sort of middle range, but at least it has been considered a clinical benefit sometimes.

DR. SWAIN: What else would you ask for a clinical benefit in a study like this? We have seen so much quality of life data come before this committee, and it is always a problem. We really have a lot of dropout data, and we always end up saying it is not really helpful. I think time to progression is very helpful personally, and wanted to get your opinion about what else you would ask. We more than likely won't see a survival benefit.

DR. SLEDGE: Personally, if you combine two active drugs and you get a slightly longer time to progression, is that really an important or interesting observation for a patient with advanced breast cancer?

DR. SWAIN: What do you want then?

DR. SLEDGE: Realizing the difficult of quality of life data, this committee certainly has approved drugs based

upon quality of life data.

DR. SWAIN: That was when nothing else was available, like with gemcitabine.

DR. TEMPLE: When have we actually?

DR. SWAIN: Gemcitabine.

DR. TEMPLE: I think gemcitabine would not have been approved but for the survival advantage. I'm pretty sure I heard that correctly. You could say that esophageal -- that's sort of quality of life, you could swallow again. You rarely get something as neat as that. There are very few, if any examples, because the data is always so terrible.

DR. SCHILSKY: Since Alison has brought up the question of the design of the -- of course we don't know anything about what the design of the study, but I wonder if anybody could comment briefly on what the design is. For example, how are the two drugs proposed to be given together in this treatment plan?

DR. MARTIN: I don't know how easy it is for the sponsor to show their back-up slide. They have done a Phase I trial of the combination. The full synopsis is in the back of my review.

DR. GRIFFIN: I believe we cannot show any more

slides. That's my understanding, but I will ask Dr. Bruno Osterwalder to describe the overall design verbally.

DR. MARTIN: If you look at the medical review, it is page 62.

DR. OSTERWALDER: The slide shows you the objectives of the trial. As has been mentioned before, the primary endpoint is superiority in time to progression, but also see secondary endpoints, including superiority in terms of overall response rate, at least equivalent survival, safety profile, quality of life assessments, measurements of changes from baseline, medical care utilization analysis, and in addition, pharmacokinetics for a limited number of patients to add to the Phase I data that we have for docetaxel together with capecitabine.

The doses and the regimen, the docetaxel based on a standard Phase I combination trial, we have conducted the docetaxel dose is 75 mg/m^2 every three weeks, and capecitabine is given at the full dose 2,500 mg/m^2 day 1, 2, 14, with one week rest. So you combine the standard docetaxel regimen with the standard intermittent capecitabine regimen. We have done this Phase I trial and have not seen toxicities which would prevent us from doing this.

DR. SCHILSKY: So I would just comment. I don't know if any of my colleagues around the table would agree with this or not, but I would actually be somewhat skeptical about the ability of this particular trial design to demonstrate an advantage for the capecitabine arm. I suppose the reason I say that is because I think that in this patient population, if docetaxel is the most active therapy, I think you are going to have a difficult time demonstrating that adding capecitabine to a very active regimen is going to produce a meaningful additional, incremental improvement.

I think there may be alternative trial designs that have the potential to demonstrate that more convincingly than this trial sign would.

For example, I think one could for example, take this patient population, treat them with docetaxel as a single agent until the time of best clinical response, and then randomize them to continue docetaxel versus capecitabine. I think that design would have a much greater potential to demonstrate a benefit for capecitabine.

DR. MARGOLIN: I have a design related question. It's not a good idea like Dr. Schilsky, but maybe either Dr. Simon or Dr. Temple or somebody from FDA has. We often say

in randomized trials that if you allow crossover, that it pretty much neutralizes your ability to assess or to detect a survival benefit. Yet if there is a therapy that is substantially active, and we tend this and expect it in adjuvant trials for example, we really do expect the initial intervention to be responsible for a detectible survival benefit. So I just don't understand exactly where to put this concept into the design of trials.

DR. SIMON: I think when you are talking about a 20 percent response rate, many of which are probably very short responders, if you give the trial that was proposed, except use the survival endpoint, and you didn't see a survival difference, I would be very skeptical that the reason you didn't see it was that the crossover treatment had a survival advantage.

I think the reason you didn't see it was because it wasn't there. If you gave everybody at one progression, some other treatment, you still would not have seen it.

DR. TEMPLE: Well, we deal with this all the time. Rich may be absolutely right, the failure to find survival may be more fundamental than that you cross people over to effective salvage therapy. In a trial like this you would always collect survival data of course, even though people

are going to crossover, but on a lot of occasions, including things that have come before this committee, we have relied on time to progress as the endpoint.

DR. D. JOHNSON: I guess I'm sort of surprised that the sponsor wouldn't do a trial on a group of patients in whom they are seeking the approval. I understand the fact that they don't have to, but if we have a defined group that they believe that they have now convinced the committee that capecitabine is valuable, they also have data from the literature that was shown to us that the navelbine has a response rate in this group of patients, and continuous infusion 5FU does.

It seems to me that they could design a study to in fact prove their point. I challenge them to do it. I don't think they have the guts to do it, frankly. That's the bottom line. I don't think they can. My suspicion is that if they were to do it, that they would find that their drug doesn't work so well. That's my prediction. Now let's see if they've got the guts to do it.

DR. DUTCHER: Now what is your comparison?

DR. D. JOHNSON: I would use response rate, just exactly what they said today that they want us to approve it. Even Dr. Swain would agree with me they can measure

response rates, and just make a difference. Show us a difference in the response rates. You don't even have to do quality of life, although if you were to do that, you show an improvement in quality of life, I would be even more impressed by their drug. That's a prediction. I bet it doesn't happen.

DR. TEMPLE: The response rate data alone wouldn't fulfill the obligation --

DR. D. JOHNSON: I'm just telling you what I would be willing to accept.

DR. TEMPLE: Suppose they looked in a resistant population at navelbine with or without capecitabine. That would offer them a chance to show that they make a contribution even in that setting, so it's potentially win-win when we look at survival-type endpoints.

DR. D. JOHNSON: I would be able to accept that design, although I would less enthusiastic. I do want to accept that design, but I don't think they will do that either.

DR. DUTCHER: I think the other part of this study is that's the next drug. That's what people are looking at is docetaxel. So it's an accrual issue too, a study that will attract patients.

DR. SWAIN: Plus, I think we want to improve things and move it earlier on anyway. If you did see a benefit with such an active agent, I agree, I am skeptical too that they are going to see benefit. But unless you try it, you are definitely not going to see benefit. So I like the design, because it could mean an advance, rather than continuing in third line, comparing it to other third line drugs. We know the response rates are all 15-20 percent.

DR. D. JOHNSON: I don't see anything wrong with this design, what they are proposing to do. That's fine. I wouldn't be convinced. If the data show a benefit, fine, that's the case. I agree with Dr. Simon. I think a 20 percent partial response rate of short duration, no matter how you cut it, isn't going to show a clear benefit, perhaps in time to progress, but I tell you, that's a soft endpoint in my view.

DR. SLEDGE: Part of my skepticism with regard to this is as a result of the 1193 trial. In front line chemotherapy for metastatic breast cancer using an anthracycline and a taxane, the two most active agents that we have for the treatment of metastatic breast cancer as far as anyone knows, we got a two month improvement in time to progression. Do we really believe that further on down the

line, which is what this trial is, we're going to see better than that? I mean I think we have to be fairly skeptical about this. That was with no difference in survival, no difference in quality of life.

So if you are asking combination versus sequential therapy, which is basically what this trial is asking, we already know the answer to that question scientifically.

DR. SWAIN: The other issue with your trial is that patients stopped. It was an intermittent versus continuous therapy trial too, because the patients on the doxorubicin stopped at a certain dose level, all the doxorubicin arms.

DR. SLEDGE: Not really. They virtually all crossed over.

DR. SWAIN: But they had a set dose. They couldn't go beyond that. So it is a little different. There are a couple more studies that have come out looking at that issue, maintenance versus stopping at six months. So time to progression is longer in those studies where you continue it.

DR. TEMPLE: The skepticism being expressed must surely apply to the refractory situation also, where the response rate isn't any better. Are you expressing some

discomfort with the policy of approving treatments for refractory disease based on modest response rates without any evidence of actual clinical benefit?

DR. D. JOHNSON: Yes.

DR. TEMPLE: We probably should talk about that some time.

DR. DUTCHER: Any further comments? Are we voting on the last question? No, we have offered our comments.

DR. TEMPLE: That's okay. You have offered plenty to think about.

DR. DUTCHER: Thank you all very much. We'll be starting tomorrow morning at 8:00 a.m.

[Whereupon, the meeting was recessed at 4:55 p.m., to reconvene the following day, Friday, March 20, 1998, at 8:00 a.m.]