UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

74th MEETING

WEDNESDAY,
MARCH 12, 2003

The Committee met at 8:00 a.m. in the Versailles Ballroom of the Holiday Inn-Bethesda, 8120 Wisconsin Avenue, Bethesda, Maryland, Dr. Donna Przepiorka, Chair, presiding.

PRESENT:

DONNA PRZEPIORKA, M.D., Ph.D.	Chair
DOUGLAS W. BLAYNEY, M.D.	Member
OTIS W. BRAWLEY, M.D.	Member
JOHN T. CARPENTER, JR., M.D.	Member
BRUCE D. CHESON, M.D.	Member
THOMAS FLEMING, Ph.D.	Consultant (Viking)
STEPHEN L. GEORGE, Ph.D.	Member
DAVID P. KELSEN, M.D.	Member
SCOTT M. LIPPMAN, M.D.	Member
SILVANA MARTINO, D.O.	Member
MUSA MAYER, M.S.	Patient Representative (Voting)
GEORGE OHYE	Acting Industry Representative (Voting)
JODY L. PELUSI, F.N.P., Ph.D.	Consumer Representative
GREGORY H. REAMAN, M.D.	Member
BRUCE G. REDMAN, D.O.	Member
SARAH A. TAYLOR, M.D.	Member
JOHANNA CLIFFORD, M.S., RN, BSN	Executive Secretary

SPONSOR REPRESENTATIVES:

GORDON BRAY, M.D.	Ligand Pharmaceuticals
STEVEN HAMBURGER, Ph.D.	Johnson & Johnson Pharmaceutical
FRANCINE FOSS, M.D.	Consultant to Ligand
SUSAN KROWN, M.D.	Consultant to Johnson & Johnson
JAMES L'ITALIEN, M.D.	Ligand Pharmaceuticals
SURYA MOHANTY, Ph.D.	Johnson & Johnson Pharmaceutical
JAMES PLUDA, M.D.	MedImmune Oncology
APRIL TEITELBAUM, M.D.	Johnson & Johnson Pharmaceutical
ALEX ZUKIWSKI, M.D.	Johnson & Johnson Pharmaceutical

FDA REPRESENTATIVES:

RAMZI DAGHER, M.D.
ANN FARRELL, M.D.
PATRICIA KEEGAN, M.D.
GEORGE MILLS, M.D.
RICHARD PAZDUR, M.D.
QIN RYAN, M.D.
GENEVIEVE SCHECHTER, M.D.
ROBERT TEMPLE, M.D.
KAREN WEISS, M.D.
GRANT WILLIAMS, M.D.

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

8:10 a.m.

CHAIR PRZEPIORKA: On the record. Good morning. Welcome to the 74th meeting of the Oncologic Drugs Advisory Committee. The member of this Committee sit as consultants to the FDA. This is not a decision making body. The topic of the meeting for the next two days is actually to catch up on some of the accelerated approvals that have gone on over the past 10 years. We have some interesting discussion not only of the accelerated approvals process but some of the things that we have accomplished in the past and need to revisit. Let me start by asking Johanna Clifford to make the Conflict of Interest Statement.

SECRETARY CLIFFORD: The following announcement addresses the conflict of interest issues with respect to this meeting and is made a part of the record to preclude even the appearance of a conflict. To determine if any conflict exists, the Agency has reviewed the submitted agenda for this meeting and all relevant financial interests reported by the Committee participants.

The Conflict of Interest statute prohibits special Government employees from participating in matters that could affect their personal imputed interests. However the Agency may grant a waiver if the need for the individual service outweighs the conflict created by the financial interest.

Accordingly waivers have been granted to following individuals: Dr. Scott Lippman for serving on a competitor's speaker's bureau for which he has received less than $10,001 and for consulting for a competitor on an unrelated matter in which he receives from $10,001 to $50,000 a year; Dr. Thomas Fleming for serving on a competitor's data monitoring committee on an unrelated matter for which he receives less than $10,000 a year; Dr. Douglas Blayney for owning stock in the sponsor valued from $25,001 to $50,000; Dr. Sarah Taylor for owning stock in a competitor worth less than $5,001. A copy of these waivers may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 Parklawn Building.

In addition, we would like to note that

George Ohye, is participating in this meeting as the Acting Industry Representative. Mr. Ohye would like to disclose that he owns stock in the sponsor and in three competitors. He receives retirement pay from the sponsor. His wife works for the sponsor. Within the past year, he consulted for the sponsor.

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 participant should exclude himself or herself from such involvement and the exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

CHAIR PRZEPIORKA: Thank you. We would like to now go on to the open public hearing. We'll start by talking about the correspondence that has been received.

SECRETARY CLIFFORD: Thank you. The FDA

did receive letters with regard to this issue. In interest of time however they will not be read out loud. However they are available at the desk in the lobby and have been forwarded to the members for their review. These letters will be placed as part of the meeting record.

CHAIR PRZEPIORKA: Thank you. We have three speakers for the open public hearing this morning. I would like to call forward the first speaker, Katherine McComas.

MS. McCOMAS: Good morning. My name is Katherine McComas. I'm an assistant professor at the University of Maryland. I'm going to be conducting some research today with your assistance. It's a questionnaire called "Conflict of Interest in Federal Advisory Committees." I will be distributing this at a break time. I would be grateful if sometime today before you leave that you would complete the survey. It will take about 15 minutes and deposit it in a box marked "FDA Survey" in the lobby. This research is being conducted with collaboration of officials at the FDA. Your participation is voluntary but we'd greatly

appreciate if you would assist us. It will help us to understand more effectively how you understand and know about the Conflict of Interest procedures that the FDA uses to monitor the real and potential conflicts of interest of its advisory committee members. If you have any questions, I will be here all day. I will also be out in the lobby. Thank you very much for your time. We greatly appreciate your assistance. Thank you.

CHAIR PRZEPIORKA: The next speaker will be Steve Walker from the Abigail Alliance for Better Access to Developmental Drugs.

MR. WALKER: Good morning. My name is Steve Walker. I have the exalted title of FDA Advisor to the Abigail Alliance for Better Access to Developmental Drugs. Why I'm involved in this will become evident during my presentation. I have no affiliations with any pharmaceutical companies or anyone else involved in drug development. I pay my own expenses and I'm here today on my own dime. I would like to talk about something that is in part related to the subject matter today and also in part

related to our entire approval process and to propose a new idea to ODAC, the FDA and everyone in the room.

As you will hear probably all day long, accelerated approval is a part of a three-part process that was really intended since 1992 to make drug available much more quickly. You can't really talk about accelerated approval without talking about fast track and priority review. For what cancer patients wanted from this program and really expected to have happen especially after the Modernization Act, we expected or hoped for support of accelerated approval by both industry and the FDA, meaningful participation by industry, effective communication, good trials, regulatory acceptance of surrogate endpoints, realistic evaluations of risk-to benefit and clinical benefit, flexibility of the FDA which is something cancer patients don't see enough of, sense of urgency at the FDA which I think exists but at the institutional level may not, timely approvals and meaningful and implementable Phase IV trials for accelerated approval.

Just real quickly from the prospective of

a cancer patient advocate who has direct experience over the past few years of how this system works, there has been inconsistent support of accelerated approval. We are not seeing enough drugs come out. There has been meaningful participation by industry in all three of those programs.

Insufficient communication between FDA and industry, it's not always as open and real time as it should be. Clinical trial design, we're going to talk about that today. Limited regulatory acceptance of surrogate endpoints is a fact. There has been limited acceptance of that and too much emphasis on a overly restrictive definition of clinical benefit. There has been unrealistic risk versus benefit evaluations for end-stage cancer patients.

There continues to be a lack of flexibility at the FDA. At the institutional level, a sense of urgency doesn't seem to be there. We've had a few timely approvals and too many delayed approvals. We're going to hear more again about not only the usefulness of these trials but how implementable they are. It's difficult to test a drug in randomized and

placebo-controlled trials after approval. That's just a common sense problem.

Why has it under performed? In our view, we're relying too much on statistics and process instead of whether or not we have a good drug and whether or not that drug represents best available care for some population of patients. There's an overemphasis on adverse effects. In fact, we should be looking more at the adverse effect of not making a drug available rather than the adverse effect of making it available in a lot of cases.

We have failed to recognize at the technical level the right of Americans to decide how they want to try to live. That's a big problem for cancer patients by the way. We have as a result a pantheon of approval authorities that cancer patients look at as not having worked the way they should have. We're not seeing enough drugs come through the system. We have a big translation problem.

What we need is more acceptance and support for not just a letter but the spirit of accelerated approval which was to start capturing

these people that fall into this huge health care gap each year. Beyond approved treatments, we lose about 800,000 or 900,000 every year to cancer and they have nowhere to go except clinical trials which are too small and too restrictive.

The standards should not be moved forward to unattainable standards. They should be kept where they are or moved a little bit back. Lower hurtles. We need to redefine clinical benefit to be something more than just life extension because I have personal experience with surrogate endpoints being definite clinical benefit.

Defer more decision making to the physician and patient in the post-accelerated approval setting. Hopefully, you will solve the post-accelerated approval setting today. I don't know if you will but I hope you will and recognize the urgent need for timely approvals not just timely reviews.

Our message for today's meeting is we need Phase IV trials that tell us something that we don't already know. Maybe that is why it doesn't work for 90 percent of a patient population and does work for

ten percent rather than proving that it does work for ten percent.

Phase IV clinical trials should be ethical and enrollable. From cancer patient's standpoint and from a lot of practicing oncologists' standpoints, end-stage cancer patients shouldn't be going into randomized placebo-controlled trials. The oncologists won't put them in those trials. So you have a question of whether or not they are enrollable at that point which they probably aren't. It's going to be difficult to enroll at trial.

There is also a question of ethics. Challenges with designing post-approval trials shouldn't be considered a problem with the design of the trial all the time. It should be considered a problem with policy and regulations, for example, the definition of clinical end benefit. Survival advantage is not the only meaningful clinical benefit. We need to have everybody in this room thinking that these drugs need to be made available faster.

Moving beyond it, we think that the two approval mechanism we have now are good approval

mechanisms. We think that full approval needs to be the final goal for every drug that is approved in the United States. We think there should be Phase IV trials after accelerated approval but these two systems have left hundreds of thousands of Americans beyond approved options in what I call a health care gap. It is huge and I'm in it with my wife. It is horrible to be there. We need to fix it.

We need a new tiered approval system that adds a restrictive form of approval earlier in the process that is somewhat like a Treatment IND but is designed to serve this unserved patient population with appropriate restrictions because those investigational drugs represent best available care for those patients. The first one, Tier One: New Initial Approval, would become a first approval authority for new drugs for life-threatening diseases with unmet needs. It would follow along to Tier Two and Tier Three. Tier One and Tier Two would still be optional approval mechanisms for sponsors to pursue. They would be required after receiving Tier One to pursue the other two or at least full approval.

The way this would work is that this would be based on limited evidence of safety and activity from Phase I or Phase II trials. The marketing would be restricted to patients with life-threatening diseases, no approved treatment options and no reasonable access through clinical trials or EAPs which by the way is the majority of people in that health care gap. Informed consent would be required because the drug hasn't been fully evaluated. The sponsors would be required to continue diligent pursuit of higher tier approval. There are a lot of details that have to be filled in. We thought about all of those and I'm sure you're thinking about them right now but this will work.

This is my wife. She is 47 years old. We was diagnosed two years ago. She has Stage IV colon cancer. In September of last year, she had progressive disease in both lobes of her lungs, both lobes of her liver. She had extensive peritoneal implants. She had an extreme ascites problem requiring paracentesis every week to remove five liters of fluid.

The last drug that worked for her was the Saltz regimen. She had Saltz regimen, Xeloda, Oxaliplatin in the registration trial. Then because we had nowhere else to go and couldn't get into the ABX-EGF trial and we tried twice, she went through irinotocan and Xeloda. Her prior history did nothing but make her sick and her disease progressed.

She got into the single-agent Erbitux trial in September of last year. Two days after she started the trial, I asked her if she needed paracentesis and she said no. A week later, the fluid stopped accumulating. Two weeks later it was completely gone. At six weeks she had complete resolution of peritoneal implants. She had complete resolution of the disease in her right lung and she had reduction of the disease everywhere else. Eventually she reached stabile disease at about 70 percent reduction and tumor burden with CEA of 8.4.

She has since progressed and was taken off the study yesterday because after six months of extremely good quality life she was skiing two weeks ago in Utah. She was taken off study because of

progression in her liver only. We now have a plan for it that we wouldn't have had six months ago.

My message to you is if this drug was available the statistics for colon cancer patients would change. The reason I know that is because in our clinic where there are about 20 patients enrolled which is a targeted patient population that the partial response rate is very high, greater than 50 percent. It could be much greater than that in this targeted population. I don't have the official data. I can't get it. We want the FDA to find out what's going on with this trial and to act. If this is an example of a drug that would be a good candidate for Tier One approval. That's it. Any questions?

CHAIR PRZEPIORKA: Thank you for your insights, Mr. Walker. I just wanted to know. Will your slides be available on your website?

MR. WALKER: They can be, yes.

CHAIR PRZEPIORKA: Thank you. Any other questions? Our next speaker is Mr. Frank Burroughs from the Abigail Alliance for Better Access to Developmental Drugs.

MR. BURROUGHS: Steve, thank you so much. Steve Walker is the Abigail Alliance FDA Advisor and he has done a tremendous job for us. Thanks, Steve, for introducing our Tier One initiative. It's a really important idea. I've met some of you this morning that I know and that know the Abigail Alliance. For those of you who don't know me, I'm Frank Burroughs. I'm President of the Abigail Alliance for Better Access to Developmental Drugs.

I want to add a few things to what Steve said. This is the logo for the Abigail Alliance for Better Access to Developmental Drugs. Some of you know it already. It's my daughter who died in June 2001 after not being able to get access to EGFR targeted agents that had a significant chance of saving her life. If she was alive today, she still could not get those drugs. This is two years later.

We have Abigail as our logo because the Abigail Alliance and what we are about is about people. It's about tens of thousands of people in our country that need a better chance. This is important what I'm talking about. Abigail represents, our logo

represents tens of thousands of people who are dying of cancer and other life threatening diseases that don't have earlier access to development drugs.

Every agency in the Government or business or myself can be prone to not making change. We like things the way they are. It's working. It's our idea. For example, FAA, not FDA, had not made changes since the 1950's in airline safety, we would be having 100 times the number of commercial air crashes we have in this country every year. There has been a tremendous increase in air travel. If FAA hadn't made changes, we'd have 20,000 deaths a year in airplane crashes. The FAA made changes.

Of course the FDA over the years has made some tremendous changes. It's a fantastic agency. Don't get me wrong. But everybody, any of us, can make changes. I urge that we look close at Tier One approval, the concept we have here.

This is Peter Hallinan. He's no longer with us. He was denied access to cancer drugs that could have helped his brain cancer but they weren't approved yet. He didn't qualify for a clinical trial.

He couldn't get into the expanded access programs that were available. He didn't meet those criteria either. With Tier One, Peter would have had a chance at life. This is a solvable problem. Just think about it, if it were you. What if it were your wife or your daughter that had colon cancer, had neck cancer or brain cancer and couldn't get developmental drugs that had a significant chance of saving their lives.

I think we can speed this process with Tier One approval without jeopardizing the important review testing procedure. That's important. We need to field clinical trials as soon as possible. We can do all this, move a drug through the proper approval and review process but get drugs to people earlier.

This is Johnny Clark. We lost Johnny in November. He couldn't get EGFR inhibitors that had a chance to save his life. He's left two children and a wife. No one was listening to him. No one was giving him a chance. With Tier One approval, we could approve these drugs earlier for people who have run out of options like Johnny Clark, like Peter, like

Abigail and tens of thousands of other people.

Today we have drugs that have been approved that are saving tens of thousands of lives. Gleevac, Eloxatin, Herceptin and I could go on and on. You know the drugs that are saving tens of thousands of lives. Those programs had expanded access programs but those expanded access programs left tens of thousands of people by the side of the road. Some companies don't do expanded access programs.

With Tier One approval, we could get these drugs to people years earlier. We need to work together. We need to be bold. We need to think outside of the box. The real power here is not with me. It's not with anybody in this room really. It's with the cancer patients and the other people with life threatening illnesses. We need to help them better than we are. I want to thank you very much.

CHAIR PRZEPIORKA: Before you leave the podium, are there any questions for Mr. Burroughs? Thank you, sir. Are there any other speakers for the open public hearing? Hearing none, let us move on to the next item of the agenda. Dr. Pazdur and Dr.

Dagher will talk about the accelerated approval process.

DR. DAGHER: Good morning. Today I would like to summarize our experience with accelerated approvals from Oncology products over the last decade. Before summarizing past experience, I would like to outline the purpose of this meeting of the Oncology Drugs Advisory Committee which is three-fold: (1) to review past accelerated approvals; (2) discuss the current progress of associated Phase IV commitments; and (3) solicit input for improving the accelerated approval process.

I would like to point out that summary includes Oncology products approved in the Center for Drug Evaluation and Research as well as the Center for Biologics. As part of this presentation, I will provide some background on accelerated approval regulations, approvals based on control trials lacking a concurrent comparator, mostly single arm studies and those based on randomized trials.

A summary of accelerated approvals ultimately converted to full approval will be

provided. I will complete the presentation with a list of issues we would like the Committee members to keep in mind during the individual sponsor presentations. Finally, Dr. Pazdur will introduce some general issues about the accelerated approval program as a whole. These will also be presented to the Committee tomorrow in the form of questions for discussions after all the sponsor presentations have been completed.

Nineteen NDAs or Biologic applications for new treatment indications in Oncology have been approved involving 16 different products. Some of these indications were approved within 18 months of issuing invitations to this meeting and will not be presented by individual sponsors as they are too recent for a discussion of the status of Phase IV commitments. An additional four indications have been converted to full approval. They will be presented by individual sponsors over the next two days.

In reviewing the regulatory background, please keep in mind that reference to a drug also includes biologic products. In 1992, Subpart H was

added to the NDA regulations allowing accelerated approval for diseases that are serious or life-threatening where the drug appears to provide benefit over available therapy. Approval will be based on a drug's effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on the basis of an effect on a clinical benefit other than survival.

Approval will be subject to the requirement that the applicant study the drug further to verify and describe its benefit where there is uncertainty as to the relationship of the surrogate endpoint to clinical benefit or of the observed benefit to ultimate outcome. Post marketing studies would usually be studies underway to demonstrate that treatment with a drug is associated with clinical benefit.

The regulations state that the applicant shall carry out such studies with due diligence. If an applicant fails to perform confirmatory studies with due diligence, the Code of Federal Regulations describes a mechanism for removing the drug from the

market.

In general, we have considered an effect on survival or patient symptoms as evidence of clinical benefit. Objective Response Rate and Time to Progression have generally been viewed as surrogates reasonably likely to predict clinical benefit. In some circumstances where relatively non-toxic products are being evaluated such as hormonal therapies for breast cancer and some biologic products, Response Rates have been accepted as evidence of benefit. In the setting of hematologic malignancies, ?- responses have been accepted as clinically meaningful.

This slide and the following two slides summarize the approvals based on control trials without a concurrent comparator. As I mentioned, these are mostly single arm studies and in some instances there are studies where two different dose levels were being tested.

In 1995, Liposomal doxorubicin was approved for the second line treatment of Kaposi's Sarcoma based on response rate in a single open label study. In 1996, Amifostine was approved to reduce

renal toxicity associated with Cisplatin administration in advanced non-small cell lung cancer (NSCLC) based on results of a Phase II study. Docetaxel was approved for the second line treatment of breast cancer based on response rate measured in six United States and three Japanese trials.

Irinotocan was approved for the second line treatment of colon-rectal cancer based on response rate measured in three single agent studies using a weekly dosage schedule. In 1998 Capecitabine was approved for the treatment of refractory breast cancer based on objective response in a single Phase II study of patients who had failed prior Paclitaxel therapy.

In 1999, Liposomal doxorubicin was approved for the treatment of refractory ovarian cancer based on response rate in three single arm studies of women with metastatic disease most of whom had failed both Paclitaxel and platinum-based regimens. Temozolomide was approved based on the results of a single arm trial in patients with relapsed anaplastic astrocytoma who had failed

radiation therapy and many of whom had also received prior chemotherapy.

Denileukin diftitox was approved for the treatment of patients with persistent recurrent cutaneous T-cell lymphoma based on two arm study. Although analyzed, the trial evaluated to different dose levels of this product without a control arm and is hence listed in this category. In the year 2000, Gemtuzumab ozogamycin was approved for the second line treatment of AML in the elderly patients based on hematologic response in three single arm trials.

In 2001, Alemtuzumab was approved based on response rate and duration of response in one single arm study and two additional supportive non-comparative studies. Imatinib mesylate was approved for the treatment of chronic myelogenous leukemia in blast crisis accelerated phase or chronic phase after Interferon failure based on hematologic response in three single arm trials conducted in patients with Philadelphia chromosome positive disease.

The approval for gastrointestinal stromal tumors was based on objective response rate in a

single two arm study. Although many patients in this trial had not received prior chemotherapy, this was a population with metastatic or unresectable disease where chemotherapy has a less than five percent response rate.

Moving on to accelerated approvals based on randomized studies, Dexrazonxane was approved in 1995 for the reduction of cardiomyopathy associated with Doxorubicin administration based on three prospective randomized trials in which patients with breast cancer received a Doxorubicin containing regiment with Dexrazoxane or placebo. Left ventricular ejection fraction and the incidence of congestive heart failure were primary endpoints.

In 1999, Liposomal cytarabine was approved for the intrathecal treatment of Lymphomatous meningitis based on cytologic response in a comparative trial of Liposomal cytarabine versus cytarabine in patients with lymphoma. Supportive studies were conducted in patients with leukemia or solid tumors.

Celecoxib was approved for the reduction

of adenomatous polyps based on a randomized double blind placebo control study in patients with familial adenomatous polyposis. In 2002, Ibritumomab tiuxetan was approved for the treatment of relapsed/refractory low grade follicular non-Hodgkins lymphoma based on an evaluation of response in a randomized trial comparing Ibritumomab tiuxeten to Rituximab.

Oxaliplatin was approved for use in combination with 5-FU Leucovorin based on a randomized three arm study. Oxaliplatin combined with Infusional 5-FU Leucovorin versus 5-FU Leucovorin alone versus single agent Oxaliplatin in patients with advanced colorectal cancer refractory to first line treatment with Irinotocan and 5-FU Leucovorin. Approval was based on response rate and in interim analysis of time to radiographic progression.

Anastrozole was evaluated in a randomized double blind study comparing Tamoxifen alone, Anastrozole alone and Anastrozole in combination with Tamoxifen as adjament treatment of post menopausal women with breast cancer with disease free survival as a primary endpoint. Finally Imatinib mesylate was

approved for the treatment of newly diagnosed patients with chronic myelogenous leukemia based on time to progression in a randomized trial of the Imatinib versus Interferon.

If we examine the endpoints evaluated, we can conclude that in the setting of controlled trials without a concurrent comparator and in only refractory or relapsed patients, objective response rate was the main endpoint of interest. In the randomized setting a variety of endpoints from cytologic response to reduction in number of polyps were evaluated based on the indication being sought.

You may wonder why improvement in disease free survival or reduction in the incidence of congestive heart failure would not be adequate for full approval as opposed to accelerated approval. In the regulatory background, I mentioned that when there's uncertainty as to the relationship between benefit and ultimate outcome, the sponsor would be required to study the drug further.

In the case of products used for protection from cytotoxicity of cancer agents,

uncertainty as to possible existence of the tumor protective effect would exist. Hence although incidence of renal toxicity or cardiac toxicity was evaluated in the case of Amifostine and Dexrazoxane respectively, uncertainty about the possibility of a tumor protective effect necessitated approval under Subpart H.

In the case of Anastrozole although disease free survival was evaluated, patients had received only a median of 31 months of a planned 60 months of treatment. Hence uncertainty about ultimate outcome necessitated approval under Subpart H with follow-up of the same study as a Phase IV commitment. Similarly, the approval of Imatinib for the first line treatment of CML was based primarily on longer time to accelerated phase or blast crisis with Imatinib treatment and was supported by hematologic cytogenetic response. Confirmatory evidence of benefit would be provided by evaluation of time to accelerated phase or blast crisis and survival after a longer duration of follow-up.

I mentioned earlier that of the 19

indications of Subpart H, four have been subsequently granted for approval. These are listed here. Docetaxel received approval based on a randomized trial comparing Docetaxel to Mitomycin vinblastine and supportive evidence from a second randomized trial where Docetaxel was compared to Doxorubicin in patients with metastatic breast cancer.

In the case of Irinotocan, conversion to full approval was based on two large European trials in patients which failed first line treatment with 5-FU, a population less refractory than that examined in the accelerated approval setting. In the case of Capecitabine, the confirmatory Phase III randomized study evaluated the Capecitabine-Docetaxel combination versus Docetaxel alone in patients with advanced breast cancer who had failed prior Anthrocycline. Again it was a population less refractory than that examined in the accelerated approval setting. In the case of Dexrazoxane, we should point out that a planned confirmatory trial was under way at the time of accelerated approval. This was not utilized for full approval.

Although confirmatory trials were underway in these incidences at the time of accelerated approval in any indications that have not been converted to full approval, we have seen that approvals granted early in the history of the program were not usually associated with on-going trials. Whereas in the last two years, confirmatory studies have been underway at the time of approval in many instances.

Over the next two days, the status of Phase IV commitments for the following indications will be presented: Liposomal doxorubicin for Kaposi's sarcoma; Liposomal doxorubicin for metastatic ovarian cancer; Denileukin diftitox for cutaneous T-cell lymphoma; Amifostine for the renal toxicity associated with Cisplatin use in non-small cell lung cancer patients; Gemtuzumab ozogamycin for AML; Liposomal cytarabine for Lymphomatous meningitis; Celecoxib for familial adenomatous polyposis; and Temozolomide for refractory Anaplastic astrocytoma.

As you listen to these individual presentations, please keep the following in mind

regarding planned or on-going trials. For an on-going trial, has accrual been satisfactory? If not, what strategies can be used to address this issue? Have changing circumstances such as a change in medical practice impeded the conduct of a planned or initiated trial? If so, what alternative designs should be contemplated? At this point, I would like to turn things over Dr. Pazdur who will introduce some more general concepts regarding the accelerated approval program in Oncology.

DR. PAZDUR: I would like discuss three areas of Oncology Accelerated Approvals the first of which is the division's premise that these confirmatory trials are an integral part of a comprehensive drug development plan. Accelerated approval does not end with the approval of the drug. Hence the confirmatory trial should be discussed with the division early in the development process and be an inherent part of the total drug development strategy.

Secondly, I would like to discuss that patient population examined in confirmatory trials.

Frequently the division has allowed clinical benefit to be demonstrated in less refractory earlier stages of the disease than studied during the accelerated approval. Lastly I would like to comment on the merits of different trial designs specifically single arm versus randomized trials to obtain accelerated approval.

The preamble to the accelerated approval regulations comment that "Post-marketing studies would usually be underway" at the time of accelerated approval. Although we have not insisted that post-marketing confirmatory trials be underway which may potentially delay drugs to patients with life-threatening diseases, the division believes that these studies need to be carefully planned and discussed with the division early in the development plan preferably at or before the end of Phase II meetings. There needs to be continuous dialogue during the conduct of these confirmatory trials and strategies in place for alternatives if they fail.

The division envisions that a sponsor is committed to a comprehensive drug development program

which does not end with the receipt of the accelerated approval letter. We believe that these confirmatory trials to be an inherent part of the approval process. These confirmatory trials are equally important as the initial trials for accelerated approval. Confirmatory trials should be carefully integrated into the development plan.

There are reasons for the confirmatory trials to be considered as an integral part of the total drug development plan. Pragmatically the accelerated approval provides commercial drug to patients and may interfere with patient accrual in the confirmatory trial. Hence consideration must be given to measures that would ensure a timely completion of the confirmatory trial once accelerated approval is awarded. These may include additional sites or the expansion of the trial to geographic areas where the drug may not yet be approved.

Integration of the confirmatory trial early in the development plan allows further questions to be formulated and answered. These may include studying different doses or population pharmakinetic

investigations in the confirmatory trial.

As stated, the division would like a thorough discussion of the confirmatory trials early in the drug's development. We envision discussions at the clinical trial milestones, at the initiation and during the clinical trial. These discussions should focus on timely accrual, problems with the studies conduct and potential alternative trial designs and timely execution of new trials if accrual or the expected outcome is not likely to be attained.

The division encourages that these confirmatory trial be submitted to the FDA as SPAs or Special Protocol Assessments, a provision that is a binding agreement between the FDA and sponsor on an agreed-upon protocol. Both the FDA and the sponsor should have a clear understanding of the regulatory term "due diligence" with periodic review of timelines.

The division has allowed accelerated approval examining patient populations in refractory settings using single arm studies. One reason for this approach is that even small response rates in a

highly refractory population may identify a drug with a unique mechanism of action and bring novel agents to the clinic early. We have allowed the confirmatory trials to be conducted in an earlier stage or less heavily treated population than the initial accelerated approval.

Oncology drug development as expedited by the earlier introduction of promising agents to the first line and adjuvant settings. Accelerated approval may limit accrual into confirmatory trials in the approved indication. Allowing patients to be entered in less refractory settings may obviate this accrual problem. Nevertheless allowing the demonstration of clinical benefit in a different population may leave the question of clinical benefit in the accelerated approval indication unanswered.

Studying drugs initially in a refractory setting presents problems. Response rates may be progressively smaller in progressively more heavily treated patients. Hence a promising agent may be missed. Encouraging sponsors to study refractory patients can channel drug development to progressively

more heavily treated patients. This may lead to developing drugs in highly selected groups of patients with natural histories and responses that may not be easily extrapolated. In addition, studying patients with extensive prior therapies may pose problems in adequately characterizing toxicities because of chronic residual toxicities of prior therapies or progressive symptoms.

Accelerated approvals have been granted with the trial design using single arm trials in refractory populations as stated previously. These trials obviously allow more rapid trial completion and hence expedite drugs to patients with life-threatening diseases. An alternative trial design uses a randomized trial allowing accelerated approval on the basis of an interim analysis of surrogate endpoints, for example, response rate or time to progression. These randomized trials also allow additional endpoints other than response rates such as time to progression or time to symptomatic progression. At the completion of the trial, the clinical benefit endpoint of survival can be evaluated. Randomized

trials also allow a greater understanding of comparative toxicity.

Randomized trials also may optimize the evaluation of novel cytostatic agents by allowing an assessment of slowing or retarding or preventing tumor progression. This may simply not be possible with single arm trials. Randomized trials also allow "add-on" trial designs where the novel agent is added to standard therapy and then compared to standard therapy thus advancing standard and routine therapy's practice in the community.

Obviously randomized trials are more expensive than single arm trials and take more time. Nevertheless there are also other problems. Survival analysis can be complicated and confounded by cross over and subsequent therapy.

Although we have been discussing accelerated approval in Oncology, the other life threatening condition where this regulatory provision has been used in the accelerated approval of antiviral drugs in the treatment of AIDS. A slightly different strategy has been employed. Usually two randomized

trials each approaching 1,000 patients are required. The surrogate endpoint if viral load at 24 weeks which provides evidence for accelerated approval. Full approval is obtained with the same study by demonstrating the effect on the same endpoint at 48 weeks. The same trial provides support for accelerated approval and subsequently provides evidence for full approval.

A similar approach has already been discussed for Oncology drugs. Accelerated approval can be granted by an improvement in response rates and time to progression in a randomized trial. Full approval may be based on a survival advantage observed in continuing that exact same trial.

The goal of this meeting is to provide a constructive dialogue with sponsors on confirmatory trials aimed at demonstrating clinical benefit after initial accelerated approval is granted. The division wants this meeting and subsequent discussions to be proactive in assessing study design issues, endpoints, accrual problems and timely completion of studies. This is the first of what the division plans to be

recurring public meetings aimed at examining mandatory clinical benefit trials in the accelerated approval framework.

The mandatory confirmatory trials to demonstrate clinical benefits are equally important as the initial trials demonstrating an effect on a surrogate endpoint leading to that drugs approval. The subsequent confirmatory trials provides the demonstration of ultimate clinical benefit to the patient. Hence confirmatory trials must be an inherent and integral part of a comprehensive drug development plan and drug development strategy. Thank you.

CHAIR PRZEPIORKA: Thank you. Are there questions for Dr. Pazdur or Dr. Dagher? Dr. Martino.

DR. MARTINO: A basic question. During the same ten year period, many other drugs have been up for approval and denied. I need to understand a ratio here. It looks like we approved 19 during this ten year period.

CHAIR PRZEPIORKA: Dr. Pazdur.

DR. DAGHER: First of all, just a

clarification, you mean by "denied" meaning applications that were submitted for consideration for accelerated approval or in general.

DR. MARTINO: No, that is exactly what I mean.

DR. PAZDUR: I don't have those data just off the top of my head. I could get back to you with them.

CHAIR PRZEPIORKA: Dr. Temple.

DR. TEMPLE: Just before you leave, many of those have actually come to this committee and there aren't very many. One of the points I wanted to make is you might not know this from Mr. Walker's presentation. Accelerated approval is the way cytotoxic drugs come to the marketplace. Almost all of the drugs that are approved come this way.

The sample sizes in the databases are modest by most reasonable standards. A couple hundred would be quite typical with a ten percent response rate. You are seeing 20 responses. That is the usual way. Maybe that's not imaginative for some people but that reflects a total change in the way cancer drugs

are developed. You can argue about whether that's a good thing or bad thing. But it represents a vast change.

CHAIR PRZEPIORKA: Dr. George.

DR. GEORGE: A question about the HIV model and the use in Oncology. If I was following this right at least in two cases this has already been used in Oncology in the oxaliplatin and the anastrozole cases. Is that true? Are there others?

DR. PAZDUR: Those are the two primary examples, yes.

DR. TEMPLE: Can I say? But, Steve, oxaliplatin was unusual. You had to demonstrate the contribution of each component so you had really no choice but to do a randomized control trial.

DR. PAZDUR: But nevertheless the concept of having a randomized trial in place looking at an interim analysis of response rate and time to progression because obviously one is allowed to do that because of the randomized nature of the study and then letting that trial go on to completion to give you full clinical benefit. That's the point I was

trying to make. The hormonal therapy obviously was looking at the endpoint where we wanted additional confirmation that the effect on the endpoint was going to be maintained over a period of time.

DR. DAGHER: And that concept is also applied somewhat with the first line approval for CML for Gleevec that I outlined. So it doesn't fit that model exactly but it does fit the model of allowing to study further looking at the same endpoint with follow-up for more confirmatory evidence of that same endpoint.

CHAIR PRZEPIORKA: Dr. Cheson.

DR. CHESON: Models are nice when things fit. It's a good point in your policy that the confirmatory trials should be in place. But what happens when the confirmatory trials have already been conducted and they are negative?

DR. TEMPLE: The Committee obviously just saw a case like that. Nobody can tell you what the outcome of that is because it hasn't happened. Obviously in response to your question, if your idea was that was where you were going to do the

confirmatory trials, you are in considerable difficulty and you have to figure out how you can do them in the population that was in fact the accelerated approval population after the drug is approved. The difficulties of that are formidable. So nobody has a quick answer to that question.

DR. PAZDUR: You also have to analyze why the trials failed. Just because a trial fails does not mean that the drug does not work. There obviously could be methodological problems. Those really need to be discussed. Methodological problems could be inadequate power of the study, inadequate numbers of patients in the randomized trials, problems with stratification, a whole host of trials. Nevertheless I think that is perhaps a cogent questions and needs to be addressed in the discussions. We'd like to hear your opinions on that as we have general discussions on this.

CHAIR PRZEPIORKA: Dr. Blayney.

DR. BLAYNEY: What role does the unmet medical need play in the accelerated approval process? Once the confirmatory trial is done and perhaps in a

population where unmet medical need is not an issue, how does that play into that agency's thinking?

DR. TEMPLE: The accelerated approval only applies and can only be used for a serious or life threatening disease where the new therapy promises something different. That could mean it's first therapy in the class. It could mean it's effective in people who didn't respond. It could be a major safety advantage. Any one of those things. That's the only circumstance in which accelerated approval can be used.

The second part of your question is once you've approved something under accelerated approval what happens to other drugs. Is that what you are asking? I'm not sure if I understood the question.

DR. BLAYNEY: It was inspired by Dr. Cheson's remark about if the confirmatory trial is negative. Or Rick's remark on different study populations if that unmet medical need is not applicable in the confirmatory population.

DR. TEMPLE: The accelerated approval rule comes with a never used to-date accelerated

withdrawal. Instead of the usual elaborate hearing process, it would come before an advisory committee and that would be expedited. It turns out that it is fair to say that the circumstances in which things don't work out are always at least somewhat ambiguous.

When a drug has proved active in a setting where nothing else worked, you don't lightly remove it because a trial failed to show overall survival effect. Many trials fail to show overall survival effect. The details of what happens when it fails are hard to say. You are going to see some examples that will lead to a discussion of that. It's pretty obvious that you don't withdraw an active drug lightly. You try to do other studies. You think about why the studies failed. These are many of the things Rick talked about.

DR. PAZDUR: One of the issues that you bring up are twofold. The unmet medical need really has been the foundation that has allowed us to take a look at the single arm trials in doing these studies in refractory patients. It doesn't necessarily mean that you have to do it in a refractory population.

The other aspect of your question is if you have a drug that is approved for second line or third line colon cancer and you get the confirmatory trial of clinical benefit in the first line, what implication that has. We imply that clinical benefit has been made and that is a full approval and extends basically to that indication. So another drug under our current interpretations would have to go and examine if they wanted to examine an unmet medical need to the fourth line colon cancer population.

We are having some internal discussions now on this based on that exact subject of whether we want to look at randomized study in that exact indication if clinical benefit has not been met. Those are on-going.

DR. BLAYNEY: Is this unmet medical need constract? It seems to me there's a lot of moving around or permutations or difficulties with the sponsor trying to find a niche that may or may not be appropriate and does not reflect what I do every day.

DR. PAZDUR: That is a very big problem because what is my unmet medical need could not be

your unmet medical need. You could say the whole field of Oncology is one big unmet medical need. The issue here is the available therapy aspect does not necessarily mean approved drugs but it's usually approved drugs. If we're going to say that there is available therapy, we would like to have confidence that it is at least a generally accepted regimen or treatment even though it may not be approved., Something that would have some scrutiny that it could come in for example as a supplemental NDA, that type of level of proof.

Here again one of the major problems that we have that I tried to allude to is the fact that we have this game of drug X is in second line. Can we go to third line and then maybe we'll go to fourth line? That can get into a progressively more refractory population. As people know that sub-selects out very unique populations of people with unique natural histories. Their responses and that data may not extrapolated to the general first line population.

One saving grace for this obviously is once you do introduce the confirmatory trials to the

earlier stage, then these drugs are then used earlier. What was once considered a second line population for example in colon cancer Irinotocan treated patients that drug is now used in the first line setting with 5-FU. So the second line and third line keep on changing based on the introduction of drugs into earlier settings in combinations.

CHAIR PRZEPIORKA: Dr. Temple, you mentioned earlier that when you would consider a withdrawal that it would come before the Committee. Could you clarify please the Committee's role in the withdrawal process?

DR. TEMPLE: I'd have to read it again. Ordinarily if you want to withdraw a drug, you go through a Notice of Opportunity for Hearing. There is a hearing before an administrative law judge. In this case, the hearing equivalent is before the advisory committee which then advises us. The final decision is still made by the Commissioner but it's obviously a powerful role.

I wanted to make one more observation because you may want to discuss this. One of the

reasons one might think of doing the confirmatory studies in an earlier phase is that the response rated is modest say 10 percent there's a fairly good chance that you will not move something like overall survival with a response rate that low. We actually take the fact that the drug in different setting with a higher response rate can actually affect the clinical endpoint as evidenced that if you like a proof of concept that this is a drug that can have effects on the desired outcome even if you can quite figure out how to do the study to show that when the response rate is so low. You might want to discuss that reasoning because it's hard to prove but that is one of the reasons. From the beginning we've been satisfied with studies in other settings as providing that evidence.

DR. PAZDUR: And as I attempted to point out, in these heavily refractory patients they've already received all of the standard therapy that we would accept. The likelihood of exploring and finding unique mechanisms of action might be their novel agents. One would expect obviously the response rates

are usually lower in a more refractory population. As one moves them up to a first line setting, then there would be a higher response rate and a more easy time identifying and confirming clinical benefit.

CHAIR PRZEPIORKA: Another question for you, Dr. Pazdur. When sponsors give their presentations at these meetings, they go into a very detailed, in-depth literature review. But when the FDA gives their presentations, it sticks to the data. Once the drugs are out there, obviously there are some investigator initiated trials going on. At any point in time, do you ever take into account negative trials in the literature or negative investigator initiated trials for which you have data on other INDs when thinking about withdrawing a drug?

DR. PAZDUR: On the withdrawal of a drug, I haven't been in that situation to withdraw a drug so I can't comment on it. I don't know. Bob, do you have a comment?

DR. TEMPLE: We would if the trials of the company were negative and all the other trials were negative and it looks like there is no activity

anywhere. Surely that would influence. We might try to gain access to the detailed data because we like to do that. We would look at the entire database.

DR. PAZDUR: And that's true in making any regulatory decision. It's not confined just to those trials. It has to look at the totality of evidence in all trials and in anything that could support or negate a result. Just for clarifications, many times our presentations are somewhat abbreviated from the sponsors just to avoid duplication of material when we do present here. It may be a technical factor so that's why please read the full Medical Officer's review because those reviews have very comprehensive reviews of the literature on existing therapies.

CHAIR PRZEPIORKA: Dr. Pelusi.

DR. PELUSI: Over the few years that I've been here my amazement has also been as the drug come to us looking at the lack of information in terms of quality of life and in terms of symptom management. We see a fair number of patients leaving the clinical trials due to either side effects or disease progression. But we don't have a lot of the

information of what does it mean for those people to really experience that drug. If we manage symptoms better, would they be on it longer and would we see something different in terms of response? My question to you, Dr. Pazdur and your team, is when you are setting up those confirmatory studies, is that mentioned in terms of really looking at side effect management and quality of life studies.

DR. PAZDUR: Yes, for the demonstration of clinical benefit, that can mean several aspects. Although many people equate it only to survival that simply is not true. We have taken a look at disease related symptoms and have approved drugs on this basis. We do ask the sponsors to consider a time to symptomatic progression in many cases which we would consider evidence of clinical benefit. It is not simply a knee jerk reaction clinical benefit equals survival.

These areas of symptom benefit and quality of life are notoriously difficult. We've discussed this aspect in many ODAC meetings. They include methodological problems. They truly need a randomized

study. They have to be an integral part of the trial and not just an add-on as to a quality of life because somebody might like it. It really has to be an integral part. Very difficult to do.

DR. PELUSI: And I appreciate that. If I can just make one other comment about that. Clinical trials are difficult anyway but it really behooves us to really look at quality of life data. The other thing that concerns me in terms of quality of life is many times the only quality of life data that we see is only those who complete the trial. It becomes important for us to look out of the box to say we still have patients and families that went through that experience as well.

When we are looking at some of these confirmatory trials, whether the patient completes that we may need to put in a family quality of life. That tells us as that drug becomes available or not what is the impact on patients and families. Just for discussion.

DR. PAZDUR: Very interesting idea because obviously cancer does not only affect the patient but

the patient's family. As you can see by the public comments that we frequently have, it is not only the patient. It is the entirety of the family that experiences the disease.

CHAIR PRZEPIORKA: Ms. Mayer.

MS. MAYER: I still have a question about the issue of unmet medical need. Specifically in the case of adjuvant Anastrozole, it's not clear to me how that particular indication meets this criteria except insofar as there may given the interim data analysis on the ATAC trial be a slight improved benefit. Does this mean then that the sponsor involved in any randomized trial where there may be a slight improvement can come to FDA and apply for accelerated approval for that indication for their drugs?

DR. PAZDUR: First of all, that was not an unmet medical need because obviously in the adjuvant setting there is an approved drug for that. The issue is one where we have a situation where we were uncomfortable about the sustainability of the effect and wanting more follow-up data looking at that. If one does demonstrate an improvement over existing

therapy in a life threatening disease then yes it would be appropriate on the basis of a surrogate endpoint to look at accelerated approval or consider it.

But the unmet medical need issue, I really don't look at that as the inherent reason why that drug was given accelerated approval. It was primarily because of the plausibility of the endpoint which needs to further substantiated through follow-up. Do you have a different opinion?

DR. TEMPLE: You couldn't do it unless there was an unmet medical need because that's what the rule says. So we do interpret an advantage over existing therapy as meeting an unmet medical need. I guess you could consider that's not exactly what the word says but we do.

Can I make a comment about symptoms? We are very interested in people looking at symptoms and quality of life. A lot of money has been expended trying to do it with on the whole not such great results. I just want to make a pitch for something that we never see but comes up all the time. If

people could demonstrate an improvement in symptomatic time to progression, we would not consider that a surrogate endpoint. That would be considered a clinically meaningful endpoint. I have to tell you that you hardly ever see trials that even try to assess that. I just want to make a pitch that someone might want to do that.

CHAIR PRZEPIORKA: Dr. Redman.

DR. REDMAN: I have a question about the requirement for a confirmatory trial. Let me just say I'm a firm believer in Phase III trials. But in situations where the regulatory defined standard of care may not be the standard of care in the community or where there is no standard of care is a well-designed large Phase II registration trial that could be acceptable as adequate endpoints as a confirmatory trial.

DR. PAZDUR: A large Phase II looking at what type of endpoint though? You would have to look at a clinical benefit endpoint ultimately.

DR. REDMAN: A clinical benefit endpoint being one that got it accelerated approval response

rate, increase in symptoms.

DR. PAZDUR: Symptoms obviously but here again and we've discussed this with other applications demonstrating symptom benefit in a single arm study may be methodologically difficult. In some areas, we have looked at response rates to be clinical benefit. Those are leukemia for example because a complete response would correlate with a reduction in transfusions linked already to an improvement in survival in small cell lung cancer because of its very rapidly progressive nature. We've had a drug approved on the basis of looking at response rate with some symptom benefit.

DR. REDMAN: In a Phase II setting.

DR. PAZDUR: That was I believe in a Phase III setting. That was a randomized trial. But here again if we are convinced that there is a strong linkage there, then that could be a consideration.

CHAIR PRZEPIORKA: Dr. Fleming.

DR. FLEMING: Just a couple of issues to seek clarification. Is it appropriate to assume that the strength of evidence that we would expect for

establishing benefit when that evidence is obtained from post marketing studies after an accelerated approval would be comparable to what you would have required if you were looking at a full accelerated approval? That's question one.

Is it also true that we should assume that there is the same sense of urgency? We have a sense of urgency in drug development prior to an accelerated approval. Is it fair to assume we would have that same sense of urgency for how the timing of this assessment would need to be done after an accelerated approval as we're conducting those trials upon which we would ultimately hope to establish whether there is clinical benefit?

My sense is that the regulations assume there would be such sense of urgency, issues such it's assumed that usually these trials would be underway. Rick, these are your comments which are very well taken about how you can achieve this timeliness by having, for example, the randomized trial underway and maybe doing a interim analysis on a surrogate endpoint which also reflects the sense of urgency and the

document indicating that if the applicant fails to perform the required post marketing study with due diligence that there would be this accelerated withdrawal.

One more aspect to my question is that if this study that you planned is negative or at least is not conclusively positive what is the agency's philosophy on this. In the final document that you provided to us there's a sentence that says "A study that fails to show clinical effectiveness does not prove a drug has no clinical effect but it is a study that will lead to a withdrawal procedure because it has failed to show that the surrogate endpoint on which the approval was based is correlated with a favorable clinical outcome."

In wrapping all this up, what is your philosophy? Is it five years, seven years, ten years for a process of validating clinical benefit something that fits within the spirit of what was intended with accelerated approval? At least some of us think back to the beginning of time where this process was initiated in settings such as HIV-AIDS where we had

NIH sponsor trials that were nearing their completion when surrogate endpoints were used to get the accelerated approval where it was almost eminent that a full approval assessment could be made. It's philosophically unclear how much flexibility we are allowing for the timeframe once the accelerated approval has occurred and what we are doing to ensure that there is this sense of urgency to get a timely answer.

DR. PAZDUR: You've hit the nail on the head. That's why we are having this meeting. I want to instill a sense of urgency. It's very important and that's why I gave the presentation that I did that there has to be earlier discussions here with the agency. We're taking this as a serious aspect. This is equally as important as the response rates.

Remember with any program there is an evolution and a taking a look at history of the program. That's why we are doing it at this time. What are the lessons that we can learn from these applications to take forward and to improve the program. The success or failure of the program is

simply not whether Phase IV commitments have been met. There are many reasons why these commitments may have not been met and you'll be hearing them.

Nevertheless my reason for personally being the initiative behind this meeting is that I wanted the light of day on some of these applications and I want basically this to be a recurring meeting. For the sponsors that are not here because their applications are too early, we'll be seeing them again next year or in an 18-month period of time. This is not the final meeting on this.

Secondly, the reason why I wanted this trial initiated earlier, the truly successful trials that we saw that completed their trials in a very expedited fashion were those trials that were on when we approved the drugs. We really want to emphasize that to the sponsor. I don't want to get dogmatic here where we say I will never approve a drug unless the trial is on-going and has completed accrual because that may be counter productive in denying patients access to the drug.

Nevertheless I would like that to be the

exception than the rule. Over the past 18 months, the drugs we have not seen we have seen a commitment by most of the sponsors to have a greater commitment in fulfilling and initiating these trials in a more timely fashion. There is nothing more important than the sunlight of the day and the sunlight of public opinion to get people motivated to fulfill the commitments. That's why we are having this meeting.

To answer the other part of your question as far as level of proof, we have to be convinced that this drug works. It should be the same level of proof that we have for a full or conventional approval of the drug. There is no different evidentiary level of proof for accelerated approval of the drug.

DR. FLEMING: So just to summarize what I'm hearing the strength of evidence should be comparable. The second point is if I'm interpreting this correctly there needs to be due diligence. There needs to be a timely ascertainment of that level of strength of evidence. In the absence of that, then a withdrawal should in fact occur in the spirit of these regulations.

DR. PAZDUR: Yes.

CHAIR PRZEPIORKA: Dr. Cheson.

DR. CHESON: I would like to unfortunately go back to what we discussed a little bit earlier about unmet needs. Please take this in the spirit of someone who takes care of diseases that actually respond to chemotherapy and other forms of biological therapies.

The situation that we may have come into not too long ago and may come into again in the future is when you have the agency presented with two first-of-class compounds. At some point in time have agreed on a particular patient population. The trials go on with these two compounds. One of them gets approved and the other one comes up six or 12 months later. What happens then? There is no longer an unmet medical need. Both are let's say 60 percent drugs unlike what you see in lung cancer. They are both highly effective agents. How do you deal with that situation?

DR. TEMPLE: And your supposition is they are both accelerated type approvals. They don't have

a clinical outcome yet. Is that what you are asking?

DR. CHESON: Yes.

DR. TEMPLE: The answer to that will be coming fairly soon. We're working on that problem and agree that it is a problem. There is uniform agreement that the intent was not to kill off appropriately started drugs. We're looking at current regulations and guidance and I can't say more.

CHAIR PRZEPIORKA: Dr. Kelsen.

DR. KELSEN: Dr. Temple made the comment earlier that it's very difficult to withdraw a drug that's received accelerated approval on the basis of a surrogate endpoint. If the confirmatory trials are negative because they are very difficult diseases, there may be no obvious alternative to that particular treatment. It would mean to me that the surrogate endpoint should have been very strong at the beginning that led to accelerated approval.

As part of our discussion, it might help me if I had a better idea of acceptable surrogate endpoints or knowing that you can't write this into an iron. It also seems that it may be as we move forward

in the future that we're looking at small groups of patients who respond to individual treatments. We see that all the time. So there is some reason why they respond which hasn't been defined.

Maybe we could discuss this. I wonder if you've thought about when the drug comes for accelerated approval and we only see a 10 or 11 percent response rate if we require the sponsors to have a really plausible biological reason why that may occur or we include that in the confirmatory trial that they are required to demonstrate why those 10 people responded or did well and others didn't, understanding the challenges of that type of thing.

DR. PAZDUR: That's a problem. The way the regulations are written is the surrogate endpoint should reasonably likely to produce a clinical benefit. It doesn't say that has to be a definite surrogate for clinical benefit. It doesn't say that has to be a proven benefit. Reasonably likely in the eyes of the beholder. That's why we have brought many of these accelerated approvals especially when they tend to be on a more meager level of response rates.

It's a decision that is a clinical decision ultimately that has to be made on the stage of the disease, the refractoriness of the population. This is a difficult issue. It was written in such a way and Bob could comment on this far more appropriately than I can since he was involved with writing the regulation that there was this flexibility in clinical judgment to be entertained.

DR. TEMPLE: This was written at a time when certainly the Oncology community pretty much to a person believed that in refractory disease if you had something that successfully shrank a fraction of the tumors you had something that was promising. As endpoints go, shrinking tumors is not usually crazy. That is the tumor that's doing something and it isn't farfetched to think that's a reasonable endpoint.

One current development and we'll probably have to come back to on these matters is that as Rick said before shrinking tumors may not be the thing that a given drug does best. It may delay progression or something like that. It's very hard to establish in a single arm trial.

One of the things we've been certainly talking to people about is to make these early studies that are in fact randomized with a control group from the earliest beginning. That gives you in some sense two shots at finding something useful which also raises the question which we have brought to this Committee many times about whether time to progression is an endpoint that needs to be considered more seriously.

One of everybody's biggest problems is that it's extremely hard to keep people from crossing over. Whatever you think the effect of crossing over is it has to direct the study toward the null. It has to. Finding overall survival in these settings is increasingly difficult. We will come back to that again. The Committee has always said do survival but perhaps some modeling on the effects of what cross over does. We need to consider whether that's a surrogate endpoint of a somewhat more persuasive kind.

CHAIR PRZEPIORKA: I don't want to stifle the conversation here but I just want to point out that the more discussion we have the less lunch we

get. On the other hand, this is one incredibly detailed part of the law that we actually need a lot of information on. So I do want to go on with the questions. Dr. Martino.

DR. MARTINO: I need to understand a very basic issue here. Once accelerated approval has been given, you then allow the sponsor the opportunity to prove to you that there is more value to their drug and therefore to get full approval. Is there a timespan during which they have to do that? It strikes me that this is left as a somewhat extremely variable experience for them. I'm not sure that I'm understanding that in fact there are consequences to their not actually fulfilling their commitments.

In other words, how often does the Committee, the FDA, the group, actually then go back and say we're taking that drug off because you've not met your commitments? What degree of threat in reality not in concept actually exists?

DR. PAZDUR: Let me answer that question. First of all, the action to demonstrate clinical benefit as I was pointing out we really don't want

that to occur after the approval. That should be an integral part of the development process and be discussed with the agency while the drug is being developed.

We have seen this in the past, Silvana, where a drug basically comes to the Committee and should the drug receive accelerated approval or not. Yes. The FDA and the Committee or the FDA and the sponsor after the drug receives or during the labeling of the drug will discuss the clinical benefit trial. That is probably a situation that is suboptimal.

As I pointed and my purpose in giving the talk was that we are revisiting this program and this is the whole essence of this meeting as far as trying to bring this to light that these trials need to be an inherent, integral part of the program, discussed while the Phase II trial is on-going and before the end of Phase II meetings.

The preamble to the regulations state that these trials would be expected to be near complete enrollment. I have not been dogmatic because here again I don't want to deny therapies to people that

may benefit by just waiting for these trials to be initiated. We have allowed some degree of flexibility.

How much time does somebody have? It's defined relatively loosely again in the regulations and probably appropriately so. It states with due diligence. What does that mean? We're reviewing that. As I mentioned in my presentation, I want to have an on-going discussion on a periodic basis with sponsors regarding this definition and their interpretation of due diligence and my interpretation of due diligence here which may be different.

There are some diseases obviously that are going to take a long time to do. They are rare diseases. You will see some examples of this. We would not accept years to do a lung cancer trial. But for a very uncommon disease, there has to be some flexibility here.

DR. MARTINO: What about the consequence?

DR. PAZDUR: Consequences as Bob pointed out and as Ramzi did also, there is in the regulations a withdrawal procedure that can be initiated by the

Center director. It has to come back here ultimately. The indication, not the drug, can be taken from the sponsor after a well defined process here. This has not been done in Oncology to-date and I'm not aware of any of the AIDS drugs being removed.

Obviously the agency has removed drugs for toxic effects, unexpected toxicities, etc. Those are well known and well documented. I am unaware of one being removed because of lack of efficacy. I don't know if Bob wants to comment on that.

DR. TEMPLE: Many years ago a drug called Betahistine was taken off. It's comparatively unusual because we usually have a pretty good idea they work. The thread is there. The actuality would come down to the specific cases. We're clearly prepared to do that but you can imagine that there will be arguments about how definitive the negative study is. The absence of evidence isn't evidence of absence and all that stuff. So it would be a discussion. That's why we bring it to outside minds.

DR. MARTINO: So it strikes me that the threat is fairly minor in practicality. Is that what

I'm hearing?

DR. TEMPLE: No, I would say if somebody didn't flat out do them and there was no good excuse we would move on it. We really haven't encountered that.

DR. PAZDUR: "Past history need not predict future trends." E.F. Hutton.

CHAIR PRZEPIORKA: Mr. Ohye.

MR. OHYE: I think my question has been answered but I'd like to ask that you are not moving toward the requirement that patient accrual has to be on-going at the time of accelerated approval, are you? In other words, is that going to be a condition precedent?

DR. PAZDUR: No.

MR. OHYE: Because everyone knows, there are enumerable operational issues to get to that stage. As long as the sponsor is acting in due diligence to get the trial moving.

DR. PAZDUR: George, I made explicit comments that I thought that I would not want to do that because that would be ultimately unfair to many

patients who really need the drug to arbitrarily just say we need to have this trial on-going. So we have demonstrated the flexibility even though in the preamble it clearly states that it was intention that these should be on-going. I wouldn't mind. I would love it obviously.

But I would like and I don't think this is being overly regulatory to have really thorough discussions with the sponsor before that NDA is submitted about what is their confirmatory trial, what are your back-ups for this, what trials are being done. Please label your trials as these confirmatory trials so we don't get into a situation as we did a couple of months ago where there were Phase III studies being done and the sponsor saying these really weren't confirmatory trials. They have to be labeled and discussed.

Sometimes there's implicit understanding with the agency we thought. But that doesn't necessarily mean that this is what is in existence. We really want to have a thorough understanding before we even accept the NDA. I keep using these words but

this should be an integral part of a drug development strategy. It is not an afterthought. The drug approval does not stop with the approval letter.

MR. OHYE: Thank you.

CHAIR PRZEPIORKA: Dr. Reaman.

DR. REAMAN: Rick, you may have addressed it with the issue of back-up plans. But just for clarification in the setting of a negative confirmatory trial, if there are methodological issues which could in fact be a possible explanation for why the trial failed, what is the policy or procedure as relates to accelerated approval for permitting, encouraging an amendment or restructuring of that trial or the development of another confirmatory trial?

DR. PAZDUR: First of all, we would have to have demonstration of clinical benefit. Whether that occurs through reopening a trial versus a new trial, that gets really down to the science of the trial basically and the integrity of the trial if one would reopen it. But there is no wiggle room here. It's not that we would take a trial and say we think

you've demonstrated clinical benefit even though you have not met your endpoint. That goes back to Tom's question. It's the same evidentiary level of proof as we would want for a full approval of a new drug. If there is a problem then that becomes a negotiating point of what is good science as far as the reopening of a trial or looking at another indication.

It's important and one of the points that I want to get across is this is somewhat of a different situation for sponsors than basically gambling on whether a drug is going to be approved by the FDA. They already have a drug that is out there being marketed. Therefore I feel somewhat passionate here that they need to really put a full force in getting these approved even if it's multiple trials. The drug is out there. It is a drug. It isn't a hypothetical drug.

So they need to have one trial or two trials or three trials. I don't care how many there are but there needs to be an adequate commitment on the part of the pharmaceutical sponsor and their management that this is a real commitment and that it

should be handled with the same vim and vigor as they go after obtaining an approval of a new NDA to market the drug.

CHAIR PRZEPIORKA: Dr. Temple.

DR. TEMPLE: It's worth remembering the premise. The accelerated approval rule specifically accepted a lower than usual standard. Usually you are supposed to show that there is clinical benefit or have a surrogate that everybody believes is fully acceptable. This said we can use surrogates that are not of that quality that are more iffy than that for a particular reasons to serve an unmet medical need. Inherent in that was the idea that you would get the right answer. It's easy to forget that probably when the drug's out there. But as Rick says he feels very passionate that you are supposed to think of that from the beginning. It's the whole deal and not just this little piece of it.

CHAIR PRZEPIORKA: Any other questions for the FDA? Thank you. Now we are going to move on to the next item on the agenda which is actually we all know each other here and are very comfortable talking

to each other. But we need to introduce ourselves to the speakers. I want to go around the table and have everybody speak into the microphones so the transcriptionist can hear us and introduce yourself. Mr. Ohye.

MR. OHYE: George Ohye, Industry Rep. In the interest of full disclosure on conflict of interest, I also own shares in many of the competitors of Johnson & Johnson, some of whom will also present today.

DR. FLEMING: Thomas Fleming, University of Washington, Seattle.

MS. MAYER: Musa Mayer, Patient Rep, New York City.

DR. PELUSI: Jody Pelusi, Oncology Nurse Practitioner in Arizona and I sit as the Consumer Rep.

DR. REDMAN: Bruce Redman, University of Michigan Comprehensive Cancer Center.

DR. TAYLOR: Sarah Taylor, University of Kansas Medical Center.

DR. REAMAN: Gregory Reaman, Pediatric Oncologist, George Washington University Children's

Hospital in the Children's Oncology Group.

DR. CHESON: Bruce Cheson, Georgetown University, Lombardi Cancer Center.

DR. CARPENTER: John Carpenter, medical oncologist, University of Alabama, Birmingham.

DR. BRAWLEY: Otis Brawley, medical oncologist and epidemiologist, Emory University, Atlanta.

CHAIR PRZEPIORKA: Donna Przepiorka, Hematology, University of Tennessee Cancer Institute.

SECRETARY CLIFFORD: Johanna Clifford, FDA, Advising and Consulting Staff, Executive Secretary to this meeting.

DR. BLAYNEY: Doug Blayney, medical oncologist, Wilshire Oncology Medical Group in Pasadena, California.

DR. GEORGE: Stephen George, biostatistics, Duke University.

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

DR. MARTINO: Silvana Martino, medical oncologist from the John Wayne Cancer Institute in

Santa Monica, California.

DR. KELSEN: David Kelsen, medical oncologist, Sloan-Kettering, New York.

DR. DAGHER: Ramzi Dagher, Medical Officer, Division of Oncology Drug Products, FDA.

DR. RYAN: Qin Ryan, Medical Officer, CDER, FDA.

DR. PAZDUR: Richard Pazdur, FDA.

DR. TEMPLE: Bob Temple, FDA.

CHAIR PRZEPIORKA: Our first presentation is listed as Dr. Steven Hamburger from Johnson & Johnson Pharmaceutical, NDA 50-718 of DOXIL indicated for the treatment of Kaposi's sarcoma in AIDS patient with disease that has progressed on prior combination therapy or who are intolerant to such therapy. Dr. Hamburger.

DR. HAMBURGER: Thank you and good morning. My name is Steve Hamburger and I'm the Global Regulatory Strategic Leader for Oncology at Johnson & Johnson Pharmaceutical Research and Development. My goal is to provide you with some background information regarding the actions taken to

fulfill Phase IV commitments for DOXIL in the treatment for patients with AIDS related Kaposi's sarcoma.

We hope that this information will facilitate your discussions to provide guidance on the accelerated approval process and the Phase IV commitment trials that will allow conversion from accelerated to full approval. I will discuss some of the challenges we have encountered in conducting Phase IV commitment trials in patients with this disease. Some of these challenges may be applicable to other diseases and some may unique to Kaposi's sarcoma (KS).

With me today to answer any of your product specific questions are my colleagues Drs. George, Mohanty, Teitelbaum, Tonda, and Zukiwski. In addition joining us for this session is our consultant, Dr. Susan Krown, from Memorial Sloan-Kettering Cancer Center who is an expert in the treatment of patients with AIDS-KS.

DOXIL is indicated for the treatment of AIDS-KS in patients with disease that has progressed on prior combination chemotherapy or in patients who

are intolerant to such therapy. The design of the original Phase IV commitment trial was agreed upon with FDA before the NDA was approved. The design of this trial included input from the review division as well as ODAC members. We conducted this trial with due diligence and provided the results in a supplemental NDA soon after the data was analyzed.

Unfortunately the regulatory action was not conversion to full approval. I will discuss the reasons for this as part of this presentation. We are however committed to work with the FDA and others to design an appropriate clinical trial that will demonstrate the benefits of DOXIL in this patient population. Discussions are on-going with FDA and others regarding this trial design.

Since the original approval of DOXIL in this patient population and during the enrollment of the Phase IV commitment trial, the incidence of AIDS related KS has dramatically declined. While this is great news for patients infected with HIV, it is even more of a challenge to enroll patients in a clinical trial. This line represents the incidence of this

disease between 1973 and 1999 and identifies the sharp decline in incidence since the mid-1990s.

The introduction of highly active anti-retroviral therapy (HAART) during this time is most likely the predominant cause for the rapid decline in incidence. Despite this decline, patients with AIDS related KS continue to be seen and have severe enough disease to require immediate systemic chemotherapy. Such patients are a heterogenous group with respect to the status of their HIV infection.

Although some patients with advanced KS have well controlled HIV infection as evidenced by an undetectable HIV viral load and a relatively high CD4 count. More typically the patients who present with advanced symptomatic KS either fail to respond to adequately to antiviral therapy or intolerance of such therapy or have other barriers to compliance with therapy.

Another challenge in conducting a trial to document the clinical benefit of DOXIL is the fact that DOXIL is by far the most frequently prescribed chemotherapeutic agent used by U.S. physicians to

treat AIDS related KS. It has been estimated that 65 percent of patient AIDS-KS treated with chemotherapy in the United States received DOXIL either alone or as a part of combination chemotherapy. Whereas the next frequency prescribed, Paclitaxel, was prescribed in less than 20 percent of patients. The preferential prescribing of DOXIL and its commercial availability make it difficult to conduct an adequate and well controlled trial.

In September 1994, Sequus submitted the DOXIL NDA that contain safety and efficacy information obtained predominantly from four clinical trials. Efficacy information was available for 383 patients while safety data was available for 753 patients. In this submission and a supplement provided six weeks later, the FDA Medical Review focused on 77 patients retrospectively identified as having disease progress and prior systemic combination chemotherapy or being intolerant to such therapy. These patients were all enrolled in one study designated as Study 30-12.

On February 14, 1995, the ODAC recommended that DOXIL be approved under the accelerated approval

mechanism since the results of Study 30-12 represented substantial evidence of efficacy in a treatment of refractory AIDS related KS.

Following the NDA submission, there were on-going discussions regarding the design of the Phase IV commitment trial. In June 1995 during the NDA review, the sponsor and FDA agreed to the design of this Phase IV commitment trial. This was a double blind randomized evaluation of the clinical benefits of DOXIL in patients with AIDS related Kaposi's sarcoma randomized in a three to one manner to be treated with either DOXIL or DaunoXome. The start of this trial was dependent upon the commercial availability of DaunoXome.

In November 1995, DOXIL received accelerated approval for the treatment of patients with AIDS related KS. The Phase IV commitment trial designated as Study 30-38 was a double blind randomized trial. We contacted 50 U.S. investigational sites. Twenty-eight showed interest in performing this trial but only seven sites participated in this trial.

The first patient was enrolled in September 1996. It was approximately four months after the commercial availability of DaunoXome. Patients enrolled in this trial had AIDS related KS and could be either previously treated for this disease or chemo-naive.

As agreed with FDA, the primary endpoint was documentation of clinical benefit. The trial was not designed to test differences between DOXIL and DaunoXome. The FDA agreed that demonstrating superiority was not needed for the Phase IV commitment.

To be eligible for this trial, patients had to have AIDS related KS of a severity requiring systemic chemotherapy and one or more of the following systems. In addition they had to have five or more measurable mucocutaneous lesions. Efficacy measures was done by clinical benefit as well as tumor response utilizing the ACTG criteria. Investigators assessed tumor response and photographs of patients were also evaluated by an independent review blinded to patient treatment. The relationship between clinical benefit

and tumor response was also analyzed.

Clinical benefit was defined as improvement in one of the five symptom categories lasting at least four weeks in the absence of tumor progression or sever drug-induced toxicity. Patients assessed the five symptom categories using a questionnaire and rated the degree of symptom interference with daily activities on a four point scale.

In the left-hand column of this slide are the five symptom categories that we assessed. On the right are specific symptoms scored by the patients on the four point scale. To be eligible for enrollment in Study 30-38, patients had to have at least one of these symptoms. These symptoms may be debilitating, significantly altered normal activities of patients and justified the immediate use of cytotoxic chemotherapy. You should keep in mind that in some patients with less advanced KS may not have any of these symptoms and would not have been considered candidates for chemotherapy in general or this study in particular.

The efficacy of DOXIL and DaunoXome are measured by clinical benefit and tumor response as demonstrated in this study. Please recall that this study was not designed to show differences with treatment arms. The median time to objective tumor response was approximately 30 days for each drug.

The percentage of clinical benefit by each symptom category for each drug is provided in this slide which shows that both drugs provided clinical in each symptom category. This brief presentation of some of the efficacy data from the Phase IV commitment trial 30-38 was provided to you so that you can understand the basis for ALZA's submission of supplemental NDA (sNDA) in October 2001.

However in July 2002 the regulatory conclusion was that changes in anti-retroviral therapy confounded the FDA's efficacy assessment from Study 30-38. At the time of the original discussions with the FDA to design the Phase IV commitment trial, standard anti-retroviral therapy for patients with HIV infection consisted of single or dual nucleoside reverse transcriptase inhibitors.

During the conduct of Study 30-38, new anti-viral agents especially protease inhibitors were found to be effective to treat HIV infections. Thus new combinations collectively known as HAART were incorporated as standard treatments for many patients with HIV. Therefore many patients had changes made in the drugs used to treat their HIV infection shortly before or during their participation in Study 30-38. The protocol which was written before the introduction of HAART provided no guidance regarding HAART therapy.

We have conducted an extensive review of the literature on this subject. While there is no doubt that KS regresses in some patients treated with HAART, precise response rates are difficult to estimate. Dr. Krown is here and can address any of your specific questions regarding HAART or AIDS related KS.

In the fourth quarter of last year, we convened an advisory board of U.S. AIDS-KS experts. This was necessary as HAART therapy was an important variable that FDA required be stabilized for accurate assessment of the efficacy and safety of any systemic

chemotherapy including DOXIL to treat patients with AIDS related KS.

We submitted a Phase IV commitment trial protocol outline in November. There are on-going communications with FDA regarding a new protocol and development plan to confirm the clinical benefit of DOXIL in patients with AIDS related KS. In a February 3, 2003 meeting, we discussed potential clinical study designs with the FDA. As yet, however, we have not come to an agreement on the design of a trial that can be conducted in a timely manner.

In summary, although we continue in our commitment to provide convincing evidence for the clinical benefit of DOXIL in patients with AIDS related KS in 2003 there are significant challenges for protocol design and clinical trial implementation. The incidence of KS in 2002 has been estimated as about 1500 patients. Diseases of an incidence of this degree have been termed "ultra orphan diseases" and present special challenges for the design of clinical trials.

In practice when chemotherapy is

indicated, DOXIL has been the predominant choice for first line systemic chemotherapy of AIDS. This limits enrollment of potentially eligible patients into a clinical trial and as they have a choice to receive commercial drugs at the in-site of their primary HIV care rather than seeking treatment at a clinical trial site.

Many patients who present with AIDS and KS who require aggressive intervention are treated concomitantly with HAART and chemotherapy. The effect of HAART alone on AIDS-KS regression is not well documented. As we have described earlier, the literature contains some information but not from adequate or well-controlled trials. In some cases, the efficacy attributable to HAART has occurred during the administration of concomitant systemic chemotherapy.

Even when KS regression occurs after the introduction of HAART alone, the available data indicate that the time to response is months after the introduction of HAART and not the rapid reduction observed with chemotherapies like DOXIL. Finally the

on-going introduction of new anti-retroviral agents will further confound interpretation of future study results.

Not all patients with AIDS-KS require systemic chemotherapy. It is not acceptable to delay cytotoxic chemotherapy when medically indicated and such a trial design may not be executable. Thus based upon this information, it's difficult to conduct a placebo-controlled or active comparator-controlled trial in this relatively small patient population. For example, there was insufficient accrual in the joint ECOG, SWOG and AIDS Malignancy Consortium study comparing two approved drugs, Taxol and DOXIL in patients with AIDS related KS which recently led to premature study termination.

In conclusion, we are committed to design and implement with FDA agreement a new Phase IV trial as quickly as possible to convert this accelerated approval to full approval but acknowledge that there are substantial barriers to overcome. Thank you.

CHAIR PRZEPIORKA: Thank you, Dr. Hamburger. Dr. Pazdur, does the FDA have any comments

or questions that you want to specifically address regarding this product?

DR. DAGHER: I have a general comment. You mentioned in the summary that we've had on-going discussions and that different potential designs are being contemplated. Could you just in general comment on what kinds of trials you've been contemplating? I know that you may not have all the specifics but just in general the kind of trials that are being contemplated.

DR. HAMBURGER: We originally considered a single arm study comparison to baseline. That was not acceptable. There have been some other comments by the FDA but I would like Dr. Zukiwski to maybe answer those specifically.

DR. ZUKIWSKI: We've entertained a number of different trial designs with our FDA colleagues. I think those discussions are on-going and including things such as delaying initial cytotoxic treatment and seeing where the response will come in terms of time. At the present time, it is a very difficult trial to design. We're working very closely with our

FDA colleagues to come to a reasonable trial design which will demonstrate clear cut clinical benefit in this patient populations.

CHAIR PRZEPIORKA: Are there any questions from the Committee to the sponsor? Dr. Redman.

DR. REDMAN: In your slide presentation, I have two questions from it. You presented on use in the community of DOXIL versus Taxol. I was wondering how is that data accumulated, how accumulated it and has it been published.

DR. HAMBURGER: That data comes from a public database called Tandem. While the sample size is small, it's the only data that we can find regarding the utilization of any systemic chemotherapies to treat patients with KS.

DR. REDMAN: I'm not familiar with the database. Who does it?

DR. ZUKIWSKI: The data is obtained from a company called Tandem. What they do is perform market research. They look at trends and treatment. They take a sample of various treating physicians that have AIDS related KS in their practice. Mind you, it's a

limited sample because you can't blanketly canvass all the physicians in the United States so it is basically the trends in chemotherapy treatment for patients with AIDS related KS.

DR. REDMAN: Okay. The second question I had was related to your reference to an expert panel that was convened in the fall of 2002. What were the results of that regarding their thoughts and design of a trial and also who convened that panel?

DR. ZUKIWSKI: The panel was convened by Johnson & Johnson and Ortho Biotech. We had approximately 12 members, all who are recognized experts in the area. We sought advice from them and there were the seven or eight advisory board members to get their input in terms of the non-approval letter, the recommendations that the FDA had to try to come up with the most reasonable trial design which would be executable and demonstrate clinical benefit in this patient population.

DR. REDMAN: What were the results?

DR. ZUKIWSKI: We went through numerous different gyrations trying to come to a conclusion of

what the best trial design would be. The FDA has requested that we have patients enter into a trial that are stable on their HAART so they have stable anti-viral load, a stable CD4 count, etc. Looking at that patient population, we proposed one type of trial. We didn't believe we could execute a randomized trial because patients would not accept another treatment arm as evidenced with the previous ECOG-ACTG trial.

We recommended a straight forward simple Phase II trial using the patients as their own baseline with clinical benefit using the AIDS Malignancy Consortium questionnaire and using the patients themselves as their own baseline.

DR. REDMAN: That was the recommendation of the panel.

DR. ZUKIWSKI: That's what we came up with after numerous different discussions. There was consideration given to those patients who present de novo with the neglected AIDS, those individuals who were intolerant to HAART, who will not take it for various social reasons, who present with large volume

disease, etc. So that numerous considerations were given to potential trial designs.

CHAIR PRZEPIORKA: Dr. Hamburger, this is going to be a rather interactive session so if you wish to just keep your place at the podium, you may be more comfortable doing that. Dr. Fleming.

DR. FLEMING: I'd just like to have clarified. In your original letter on June 28, 1995, in your original Phase IV commitment, am I correct that it was in fact the 30-38 trial that was to serve as the basis of obtaining evidence to establish benefit? If in fact that's the case, my understanding was you weren't limiting yourself of course to survival.

You were also looking at disease related symptoms that certainly appear to be a very appropriate domain for establishing benefit. Yet you have said a couple of times something along the lines of you weren't expecting or needing to prove superiority. Could you clarify the exact basis that you were going to use these data to establish clinical benefit?

DR. HAMBURGER: The discussions with the FDA during the NDA review were that this trial would be sufficient and it was not because of the limited patient population in the three-to-one randomization that there the DaunoXome was just there to show the activity in the patient population. I would like Dr. Teitelbaum to help further answer your question.

DR. FLEMING: So at least the first part of my question seems to be implicitly answered yes. Study 30-38 was the basis for establishing benefit. Is that correct?

DR. HAMBURGER: That's correct and survival was not the primary endpoint, clinical benefit as defined and agreed upon.

DR. FLEMING: So then that leads to the second question which is the clarification as to exactly how we would judge clinical benefit.

DR. TEITELBAUM: Just to add to that. April Teitelbaum, Ortho Biotech. Reading from the letter from Sequus, the purpose of the randomized comparison was to enable a blinded comparison to minimize potential bias in assessment of clinical

benefits. That was why the DaunoXome was the comparator and was in the trial.

CHAIR PRZEPIORKA: Just to summarize here, we have a drug which looks like it has a very good response rate in these patients but the problem in completing the commitment or getting a protocol together to complete the commitment is that DOXIL appears to be already accepted in the community and no one wants to do a randomized trial. HAART may actually confer a benefit on Kaposi's but we're not certain about that. Dr. Fleming.

DR. FLEMING: Just to finish through this, it's still not clear to me then what was our prospectively-defined basis for judging whether this study was going to adequately establish clinical benefit. What was your target? What was your hypothesis? What was the threshold that had to be achieved in order to conclude adequately that we'd established clinical benefit?

DR. ZUKIWSKI: We need the statistical section of the trial.

DR. HAMBURGER: You know Dr. Temple was

the one at the meeting with the sponsor at that time. Maybe you have some comments regarding that.

DR. TEMPLE: It was a long time ago. Twenty years ago I would have remembered.

DR. ZUKIWSKI: Dr. Teitelbaum has just informed me that there was no defined threshold in terms of a statistical parameter on improvement in the clinical benefit score from baseline.

DR. MARTINO: Was this an equivalence trial because it numerically doesn't look like it was?

DR. ZUKIWSKI: No, there was never any intention to compare the DOXIL to the DaunoXome arm. It was basically there to have an active control to reduce any potential bias in evaluating the results.

DR. HAMBURGER: And recall this was a double blind trial so that was also important especially when one looking at symptom improvement or changes that has always been guidance that the FDA has given to sponsors.

CHAIR PRZEPIORKA: So essentially it was randomized Phase II trial.

DR. ZUKIWSKI: Yes.

CHAIR PRZEPIORKA: Dr. Kelsen.

DR. KELSEN: I'm glad to see that the problem is decreasing in incidence and I do understand that it's difficult to prove the point when there is only small groups of patients. Are there parts of the world in which AIDS related KS is still a pressing problem? Have you explored the possibility of performing a Phase IV post-marketing study outside the United States?

DR. ZUKIWSKI: Yes, that is indeed the case. There are areas throughout the world where KS associated with AIDS is continuing to be a problem. However in order to adequately translate the data that we would obtain in that population, we would have to have the same standard of care delivered, i.e. anti-retroviral therapy to make it applicable to the U.S. situation.

CHAIR PRZEPIORKA: Dr. Pazdur.

DR. PAZDUR: Can Dr. Krown perhaps comment on KS in Africa if that is even a possibility?

DR. KROWN: Actually a number of the consultants raised that possibility. Certainly to

unequivocally look at the introduction of HAART alone in a patient population that doesn't typically have access to those drugs and compare that to HAART plus DOXIL would certainly answer the question of what DOXIL adds to HAART but it is not really comparable to the situation that we encounter in this country.

There are also ethical considerations about bringing in HAART and DOXIL for the sole purpose in Africa of proving a point and then not having a health care delivery system that can continue to treat those patients. Although in an idealized world, that would be the place to do it and that's certainly where you see a high incidence of KS and a high incidence of very severe KS but it's not a practical solution.

CHAIR PRZEPIORKA: Dr. Kelsen.

DR. KELSEN: Just to follow that up, but isn't one of the points here that this agent itself offers benefit to patients if their retroviral therapy is not adequate or ideal? I understand that. Is not the argument that this agent helps people who have KS and if it helps people who have KS irrespective of their anti-viral therapy, would that not be an

important thing to know?

DR. KROWN: Of course it would be. You could take these data as evidence that it's the case. The agency has said that the introduction of HAART in some patients has so confounded the evaluation of clinical benefit that it can't be determined. But you could look at it another way.

CHAIR PRZEPIORKA: I do have one question. Was there any correlation between response in 30-38 and decreasing viral load?

DR. TEITELBAUM: Viral load was not looked at routinely. It was not captured if the individual sites did it.

CHAIR PRZEPIORKA: Would it be possible to go back and look at that data to suggest that if patients got a response without a change in their viral load then it was probably not the HAART?

DR. TEITELBAUM: We could attempt to do that but I'm not certain as to where those documents would be. It's not in the database right now. That information was not captured by the sponsor. So it would involve going back and finding the charts on

those individuals at those multiple sites.

CHAIR PRZEPIORKA: Dr. George.

DR. GEORGE: This example brings up at least two interesting issues, one of which is going to be common in the next couple of days. It is that the almost conundrum, the wish to do accelerated approval, can jeopardize the successful completion of the confirmatory studies which just emphasizes the point that was made earlier by Dr. Pazdur and others that it would be very desirable to have these studies underway.

In fact, I would even emphasize that it would be at the time of the approval but also have them be actually part of it. As in a couple of examples we heard, the accelerated approval is part of the study that then carries on to completion. That's a moot point for this but it's a theme that is an issue.

The second one for this particular example is a very unique setting. We should all be so lucky as to have the diseases we're studying drop incidence by 80 percent but it also creates the problem of course of small numbers but that the patients at least potentially dramatically different than originally

studied. My conclusion here is that this is a nearly impossible situation in this particular case. The first issue we're going to have to come to grips with more in the next couple of days.

DR. HAMBURGER: I'd like to make one comment. We agree with you that the conduct of the Phase IV commitment trials should be started before the approval. This study could have been started before the approval but it was dependent upon the availability of the other agent which wasn't approved until later. We started that trial as I mentioned earlier about four months after the commercial availability of DaunoXome.

CHAIR PRZEPIORKA: Dr. Pazdur, we talked earlier about one potential scenario being there's no way we're going to be able to ever prove what we need to prove under the current circumstances. Would it be just acceptable to allow the public to know that everybody really believes it but we haven't proved it yet and sign a consent form?

DR. PAZDUR: We're going to have some internal discussion on that point, Donna. I'm not going to answer yes or no to that. Let me just

emphasize this. Remember this was in the very early days of accelerated approval. One of my reasons of bringing this to you is not to embarrass anyone. It is basically to show that there has to be a learning curve with anything that is out there. Given the history retrospectively and being a Monday morning quarterback, it's obvious what should be done.

Our goal here is we're going to work with the sponsor. Probably we will be calling some of you to discuss further trial designs. If it is possible, we may have to come to terms with this. I'm not ready to make that commitment nor do I think Bob is at this time what our action would be on a situation where we couldn't make a decision.

The purpose of this is really as an illustrative example of exactly what I was making the point of. These confirmatory trials must be an integral part of a comprehensive program preferably started long before back-up plans on the line here not waiting until something fails five years after the fact. We have in fact served our purpose here.

Again we are using this as an illustrative

example of a past problem. Granted, it still is an active problem. By no means, am I trying to shove this under the carpet. But for us at this point in a 20 minute discussion to solve this problem that the agency has been grappling with over many meetings with the sponsor is probably not going to happen at this meeting.

CHAIR PRZEPIORKA: It's good to hear that there will continue to be on-going discussions and support in order to help the sponsor complete this commitment. Dr. Redman is the discussant. If you could summarize and give your insights regarding this problem.

DR. REDMAN: Thank you. I was going to go through the questions that the FDA asked and most of them have been answered. The document has accrual to on-going trials and satisfactorily allowing for timely study completion. I look at this as the study was done. Unfortunately the sponsor was hit with the fact of intervening therapy that brought up the question.

The initial study was done. It was done to the liking and specifics of the FDA. After the study

was done, something else had come and the baseline had moved on these individuals. I would like to hear what our Committee members feel about that.

CHAIR PRZEPIORKA: Dr. Brawley.

DR. BRAWLEY: I'm still stuck on how this randomized Phase study which is terribly underpowered - some people call it a randomized Phase II study - of DOXIL and DaunoXome, how you can do that trial and not compare the two but use that trial for approval for DOXIL. I'm still lost at that. Can you explain that to me, Dr. Pazdur? I realize that nobody from Ortho Biotech and nobody from the FDA was there in 1996 to make this decision.

DR. PAZDUR: You hit the button on the head but Bob was there.

DR. TEMPLE: But I don't get the blame for this. This is not the only trial done that way. There was a period of time when people did what you could call non-comparative comparative trials, specifically underpowered trials, where the control group was really there to show something about the population and what the overall response was and not to provide a formal

comparison. This was popular in the communities. This was not our invention.

I really think few statisticians would be happy with this because what it's actually doing is ambiguous. This is not the only one. Maybe Grant remembers. He's there chuckling at my discomfort. That's what the point of it was. The other drug tells you what's going on in case it helps define the population a little bit and that's it main function. Then you look at the results almost as a single-arm trial but with some assurance that you have an idea about the population. That's the best I'm going to be able to do because it's not my favorite design.

CHAIR PRZEPIORKA: Actually it is a favorite one of mine. The reason it is simply because of the situations like this where standard care, supportive care, all of that changes the natural history of the disease. If you power your Phase II study in order to look at an outcome theoretically based on some historical control, you may not get the right answer if your current population is not like that. So you can't go into a good Phase III trial

without that knowledge. This is an interesting situation where in fact the HAART did in fact change the natural history of the disease and the "compared to arm" showed us that responses were still good even with DaunoXome.

DR. PAZDUR: This has really demonstrated a lot of examples, the change of therapy, a learning experience. If we take as a learning experience of why to do these trials early, obviously there can be a change in therapy. That's even another reason. You could have the introduction of the agent when it becomes available commercially interfere with the study.

Here again I think two good examples of why this premise that we are trying to develop really hit home and enunciate and not to beat the drum any further of having these trials on-going clearly rings out here. Just to reiterate this is history. Going back is sometimes hard to construct. It probably is not something that we would go ahead with this trial design at this time in this disease.

CHAIR PRZEPIORKA: Dr. Blayney.

DR. BLAYNEY: Two things. The SEER data as I would take is striking evidence that HAART has influenced also in a preventive fashion Kaposi's sarcoma treatments as well as incidence. It seems to me as Dr. George has pointed out this is a problem to have. When the regulations were drawn, it wasn't anticipated that a cancer would go away as a problem.

My summary statement would be in this indication we ought to declare victory and move on with something to other problems that are more public health issues. Whether the regulations anticipate that phase that confirmatory trials will never be done, I would say okay but that's probably not important in this indication.

DR. REDMAN: But there is data that suggests that DOXIL is still being used out there even though the incidence of Kaposi's sarcoma, AIDS related, is decreasing. The information I have is that the drug is still being used. So it's still a problem. It may not be as massive a problem as it was 10 years ago or even five years ago but it's still a problem. Does DOXIL add anything or can it be proven to add anything

to the treatment of AIDS related Kaposi's.

DR. BLAYNEY: We have heard experts and I haven't seen an AIDS-KS in probably eight or 10 years. I used to see a fair amount. It's probably not a major public health issue and probably the study won't ever be able to get done.

DR. REDMAN: Any study or a Phase III randomized trial?

DR. BLAYNEY: I'll bet you any study. Unless something dramatic happens with HIV resistance to HAART, then you could conjure up a lot of possibilities that would make the underlying immunosuppression and cancer susceptibility different. It may never be doable. Any study.

CHAIR PRZEPIORKA: Ms. Mayer.

MS. MAYER: It occurs to me that there may be some future applications in a way of what we learned from this experience. If research proceeds as we would like it to in all cancers, we will be seeing more in the way of targeted cytostatic treatments becoming available. Yet there may still be a need for rapidly-acting cytotoxic drugs to get really aggressive disease

under control. I wonder if we can't think ahead about accelerated approvals for cytotoxic drugs bearing this in mind. This doesn't seem to me like a completely unique situation just in terms of how the disease behaves.

CHAIR PRZEPIORKA: Dr. Brawley.

DR. BRAWLEY: I suspect I'm going to be saying this quite a bit over the next two days. One of the things that perhaps we should consider which is a compromise in scientific principles is going and looking at the pediatric model or registration trials as opposed to the FDA use of the word for "registration trial" and maybe merging the two.

It would be interesting to have data on three to five hundred Kaposi's sarcoma patients who are all treated with this drug in the prescribed way. It would be interesting just to know what happened to those patients, how many of those patients had disease that regressed, how many of those patients had improvement in quality of life and on the other hand, how many didn't. Perhaps that's the only way that you are going to be able to truly assess the drug. Then of

course it's not going to be a true assessment because it's a Phase II type of approach.

There have been a number of things that we've done in American medicine over the last 100 years. Many of us would probably especially many of the more vocal of us bear to read some of that medical history about how things like bone marrow transplant for example which is not a drug but the use of a number of drugs for breast cancer seem to be working but ultimately in randomized trials did not work.

I'm always struck by the fact that we did the Halsted radical mastectomy for 75 years because it seemed to be the right thing to do. Only after the randomized clinical trials were completed which were very difficult to do that we realized that for 75 years we did the wrong thing to women. There's a whole long laundry list of things that seem to be the right thing to do after essentially a Phase II comparison that turned out to be the exact wrong thing if you were truly the advocate of the patient. But in this instance, we do need a large Phase II-ish, after-marketing registration trial in the pediatric model.

Thank you.

DR. PAZDUR: Just to add to Otis's litany, the Prempro example is the current one. You forgot it.

CHAIR PRZEPIORKA: Dr. Redman.

DR. BRAWLEY: How long did we give Premarin and Provera because it was good for women. Then after the randomized clinical trial, we found it caused heart disease. It prevents colon cancer but also causes breast cancer.

DR. REDMAN: I think Dr. Brawley brought up the very final point at least which is what alternative design should be considered. As one of the questions that I asked about the Phase II design, the cooperative groups have shown in this disease that they are not going to do a Phase III trial in AIDS related Kaposi's sarcoma. If the cooperative groups aren't going to do it, there isn't going to be a consortium of groups that are going to be able to do it. The sense I had from the expert panel that was convened by the sponsor was that some type of Phase II registry trial with defined endpoints would be valid. What those endpoints were with discussion with the FDA could be delineated and

become acceptable for final approval.

CHAIR PRZEPIORKA: Dr. Pelusi.

DR. PELUSI: Since we're throwing out just ideas and trying to brainstorm when you look at patient advocacy groups and you look at their tight network, the question becomes how can we involve them in whether it's looking at long term survival in terms of a registry and what data they may actually be able to have as well as looking at our own SEER registries and what is put into that. Now they are either alive or maybe they have the disease but again some of those other indicators may be helpful in trying to open that box and say where can we get data not only now but also long term.

CHAIR PRZEPIORKA: Dr. Fleming.

DR. FLEMING: I would certainly agree that one of the benefits of reviewing this experience is to learn how we can more effectively implement the accelerated approval process in the future. At the same time, we have to assess where we are today on this application and what is the proper interpretation and what are the proper next steps to be taken.

I would agree with the FDA judgment made on July 31, 2002 looking at these data that the role of DOXIL is unclear in the presence of HAART. Certainly in the nature of this trial and these results, I would arrive at that same conclusion. The question then is what will serve as a basis to allow us to in a timely way reliably establish whether there's clinical benefit. We're also hearing that there is considerable uncertainty about where we go from here.

What is the unmet need? Certainly the unmet need in 1995 differs from what the unmet need is today in this setting. The nature of this unmet need has radically changed, HAART being one of the major reasons for that not only influencing incidence but also overall consequences of Kaposi's. In addition to that, there have been two other approvals in 1996 and 1997 of Doxorubicin liposomal and Taxol.

So the question is what is the basis at this point for continuing the accelerated approval. If we look at the intentions in the spirit of the regulations, it was these procedures are intended when drugs provide meaningful therapeutic advantage over

existing therapies. It's also made clear later on that the fact that an agent is accepted is not a basis for continuing marketing. So we clearly have an accepted agent.

We have one for which there is a judgment that the data that was intended from a pivotal study does not provide adequately interpretable evidence to establish benefit on symptoms. We didn't just require survival. We looked at symptoms. We don't have an adequate basis to think of how we would get a reliable estimation of efficacy in a timely fashion. An unmet need has been radically changed. I would ask then in the spirit of accelerated approval how does one justify continuation and not withdrawal.

CHAIR PRZEPIORKA: Dr. Temple.

DR. TEMPLE: I didn't understand one thing, Tom. My understanding is that while the frequency of KS is way down there still are some people who despite HAART get it. Why isn't that the unmet medical need even though it's a much smaller population than you had before?

DR. FLEMING: The fact that people get an

agent doesn't in fact establish the relevance and importance of continuing to make its availability.

DR. TEMPLE: No, we're just talking about whether there's a need.

DR. FLEMING: Whether this can be studied and evaluated is another question but what I said is the nature of the unmet need has radically changed. Is there and to what extent would you judge it today to be an unmet need in view of HAART which has radically changed incidence and outcome and in view of two other approvals of other agents?

DR. PAZDUR: I would still consider that the nature and degree of that unmet medical need may have decreased. But to say that it's non-existent, I think would be inappropriate. Perhaps somebody that treats AIDS, Dr. Krown, could comment that. I feel somewhat incompetent to do that since I don't see the disease. To say that AIDS-KS is not an unmet medical need would be inappropriate.

DR. FLEMING: Let me just clarify the nature of my comment. It is that the level of unmet need in 1995 compared to where we are today has

substantially changed.

DR. PAZDUR: So it's a magnitude difference.

DR. FLEMING: It's a magnitude issue. Then the essence of my question is at whatever level of unmet need there needs to be a strategy, a timely ascertainment or evaluation, of clinical benefit. The study that was put forward we can criticize today as to whether or not it logically could have been on that basis of what the reality is today.

The FDA, and I would agree with their judgment in 2002, judged that this did not provide an adequate basis for establishing benefit. There isn't a clear cut plan in place to allow us to now move forward from where we are to achieve such a reliable assessment in a timely way. In the spirit of the accelerated approval regulations, is this not then a basis for withdrawing approval?

DR. KROWN: Dr. Krown would love to comment. Actually I would like to comment on a number of things. I would love to show you some pictures because there are a lot of people in the audience who

know theoretically what we're talking about but actually haven't seen this. In this case, sometimes the pictures are worth a thousand words. Clearly not all of the patients have disease of this severity. Why don't you move ahead to 117? I just want to show a couple of pictures.

I'm just going to show you pictures of KS that has presented in the era of HAART therapy. This is disease on the inner thighs of a patient who in this case was avoiding being treated for both HIV and KS. When he couldn't stand it anymore, he showed up for treatment. This was early enough on so that nobody had even reported KS regression with HAART but you can't say to a patient like that let's give you HAART and maybe in four or six months you might be better because we knew that we had a drug that was likely to help him. He received both HAART and DOXIL and did respond.

Move on to the next one. Other patients present having been on HAART but have been intolerant or noncompliant with their therapy in a poor control of their HIV infection and have advanced nodular disease that causing edema which you can see there and

ulceration and pain.

The final one. I hate to do this to people before lunch but this is actually the foot of a patient who just refused to take any oral therapy. He had his own reasons for this. I don't presume to tell him that he couldn't do that. He walked into my office with that foot. We treated him with DOXIL. The next slide after just a few doses shows what happened. I'm not saying that these are all the typical patients that presents with KS today but I'm saying that these are the patients for whom there is a need.

I would also like to address two other things, one of which is the reason why there is a preference for DOXIL in the community. Unlike the other approved agents, DOXIL needs to be given less frequently. Both Taxol and DaunoXome are typically given every two weeks whereas DOXIL is generally given every three weeks which is a convenience in quality of life factor for patients.

When you compare a liposomal Anthrocycline to a taxane, there is little or nothing in the way of neuropathy, little or no hair loss. There are many

important quality of life issues for patients that makes them even more than their physicians choose a drug like this compared to others that are out there in the community.

Finally what I would like to say is that we're dealing with an extraordinary heterogenous group of patients who present with far enough advanced disease so that clinical benefit can actually be assessed. Patients with lesser degrees of KS may not need chemotherapy at all or may not have specific symptoms other than I don't like the way my skin looks which is hardly something that you can assess in an objective way.

So we have patients who have never been treated for their HIV disease, patients who failed on therapy because they have a resistant virus, patients who are intolerant, patients who are noncompliant. Controlling for all those factors while at the same time evaluating the effects of a drug for KS is extraordinarily difficult. So this the challenge we are facing. But, yes, there are those patients still out there.

DR. PAZDUR: I want to come back to Tom's point because it needs to be addressed. One of our reasons of bringing this up obviously is to give public disclosure to what is going on with these accelerated approvals. You do represent a valid viewpoint. Obviously there are other viewpoints that we have heard from Committee members that do not necessarily correspond or correlate with your viewpoint.

This is going to be a point of on-going discussion. Remember this is a process. Your point is well taken. I'm glad that it has been brought out in a public forum with the sponsor hearing it. Nevertheless there are other viewpoints that have been expressed here.

CHAIR PRZEPIORKA: Dr. Cheson.

DR. CHESON: We're sitting here saying that 1500 patients is a tiny number when we have had drugs approved for diseases like GIST that's required far fewer numbers of patients. Those are really rare entities. What I'm suffering here is a lack of knowledge because I assume that there are certain subpopulations of patients who are not going to respond

to HAART for their KS. It's hard to approve a drug just for patients who refuse to take oral therapy or patients who decide to wait too long.

If we could identify based on whether it's this Tandem registry bank or what have you, a group of patients that either won't or can't respond to HAART and then do a Phase II trial in that group of patients. Then if there are enough of them around that we probably could get some useful information as to whether this drug is active or not sufficiently to meet the criteria to approve it.

We don't need a Phase III trial when we have situations like this. It would be impossible to do it but there are those patients out there and 1500 is not a small number when all you probably need is 100 of them. The AIDS activists have been very effective in the past in mobilizing patients to participate in clinical research. If we could get their help, perhaps we could get the study done.

DR. PAZDUR: And response rate with its ensuing cosmesis effect would be clinical benefit.

DR. TEMPLE: We've totally agreed that the

small number of people with the disease is not a basis to deny it. You can be an orphan and still have accelerated approval. That's okay and that happens and it's supposed to happen.

DR. CHESON: But the point was that not from your perspective of it but there are enough patients out there. Fifteen hundred is really not a tiny number. There are enough patients out there to do a trial. Just to say there are only 1500 a year, that's not justification for not doing a study because there are far fewer hairy cells and there are three drugs approved for hairy cell. Yes, remember those days. And GIST, etc. and the pediatric diseases as well from my friend here on my left, fewer patients have been required to approve drugs.

CHAIR PRZEPIORKA: Dr. Redman.

DR. REDMAN: Let me go back to the original confirmatory trial and just ask the FDA a question. I take the sense of the problem was with HAART. Was there a problem with their clinical benefit endpoints looking even back in retrospect?

DR. PAZDUR: Actual endpoints, no, because

we would expect a response rate with cosmesis in a cutaneous disease. We've done this not only for KS but cutaneous T-cell lymphoma, etc. to be a clinical benefit.

DR. REDMAN: So the endpoints are still valid here.

DR. PAZDUR: Correct.

CHAIR PRZEPIORKA: Dr. Temple, Dr. Hamburger, do you have any other questions for the Committee? Otherwise, I will let you all take a break for 10 minutes. Off the record.

(Whereupon, the foregoing matter went off the record at 10:44 a.m. and went back on the record at 11:01 a.m.)

CHAIR PRZEPIORKA: On the record. We're called to order here. If we could all take our seats.

DR. PAZDUR: I just want to bring a degree of clarification in the interpretation of the regulations here that is very important and could have gotten misunderstood or misconstrued. It is the idea of judgment that the regulations give us. That is the use of the word "may." The regulations state that we

"may" ask for these confirmatory trials. It doesn't say that we must. However when we ask for them which under my reign I assure you will happen, they are required to do them.

Also if the application or the clinical confirmatory trial fails to show clinical benefit, we "may" then move for an action to take the drug off the market or to remove the application. That issue is an area that gives us judgment so we don't need to have a reflex situation. You fail therefore you must come off.

As in any regulatory judgment, we have to take a look at the total picture. Obviously there are the clinical trials that are being undertaken for confirmatory trial. There are other evidence of a drug that are in cooperative groups, that are in single-institution groups, etc. that could come in to bear in making a regulatory decision. The principle that I want to get across here that might have been lost is this area of clinical judgment. It is not necessarily a knee-jerk reaction.

CHAIR PRZEPIORKA: Thank you. Going on to

the next session, we will start with the Conflict of Interest Statement please.

DR. FLEMING: Donna, could there be a question on this clarification? Is there time?

CHAIR PRZEPIORKA: A short question or a question that will have a short answer.

DR. FLEMING: Okay. The first "may" that you said I was not sure that I understood. The regs as I understand them say that if the approval is based on a surrogate endpoint, the applicant will be required to conduct clinical studies necessary to verify clinical benefit.

DR. PAZDUR: The rule actually says "may" unless you are looking at something different.

DR. FLEMING: I'm looking at page 3, section C, "Post Marketing Studies." We can come back to that.

DR. TEMPLE: I'll find it.

MR. OHYE: I think he's looking at the preamble and not the regulations.

DR. TEMPLE: The regulation actually says "may" but I'll check and make sure. I don't want to

tell you something that's not true.

CHAIR PRZEPIORKA: Ms. Clifford.

SECRETARY CLIFFORD: Thank you. The following announcement addresses the conflict of interest issues with respect to this portion of the meeting and is again made part of the record to preclude the appearance of a conflict. To determine if any conflict exists, the Agency has reviewed the submitted agenda for this meeting and all the relevant financial interests reported by the Committee participants.

The Conflict of Interest statute prohibits special Government employees from participating in matters that could affect their personal imputed interests. However the Agency may grant a waiver if the need for the individual service outweighs the conflict created by the financial interest.

Accordingly waivers have been granted to the following individuals: Dr. Douglas Blayney for owning stock in the sponsor worth from $25,001 to $50,000; Dr. David Kelsen for owning stock in two competitors each worth from $5,001 to $25,000; Dr.

Thomas Fleming for serving on two data monitoring committees for a competitor which for this unrelated activity he receives from $10,001 to $50,000 a year; Dr. Scott Lippman for serving on a competitor's speaker bureau for which he received $10,000 a year. A copy of these waivers may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 Parklawn Building.

In addition, we would like to note that George Ohye is participating in this meeting as the Acting Industry Representative. Mr. Ohye would like to disclose that he owns stock in the Johnson & Johnson and in a competitor. He receives retirement pay from the sponsor. His wife works for the sponsor. Within the past year, he consulted for the sponsor.

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 participant should exclude himself or herself from such involvement and the exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that all persons making

statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

CHAIR PRZEPIORKA: Thank you. If the new members of the division could introduce themselves to the panel and the sponsor please.

DR. WILLIAMS: Grant Williams.

CHAIR PRZEPIORKA: We'll start with the presentation by Dr. Hamburger of Johnson & Johnson regarding NDA 50-718, DOXIL for treatment of metastatic ovarian cancer in patients with disease that is refractory to both Paclitaxel and platinum-based chemotherapy regimens.

DR. HAMBURGER: Thank you and again good morning. For the record, my name is Steve Hamburger. I'm an employee at Johnson & Johnson Pharmaceutical Research and Development. My goal is to provide you with background information regarding the actions taken to fill the Phase IV commitments for DOXIL in treatment of patients with ovarian cancer. We hope that this information will facilitate your discussions to provide guidance on the accelerated approval process in the

Phase IV commitments that will allow conversion from accelerated to full approval.

I will discuss some of the challenges we have encountered in conducting Phase IV commitment trials in patients with this disease. Some of the challenges may be specific to this disease but others may be applicable to other diseases. With me today to answer your product specific questions are my colleagues, Drs. George, Mohanty, Teitelbaum, Tonda and Zukiwski.

DOXIL is indicated for "The treatment of metastatic carcinoma of the ovary in patients with disease that is refractory to both paclitaxel- and platinum-based chemotherapy regimens. Refractory disease is defined as disease that has progressed while on treatment, or within six months of completing treatment."

The original Phase IV commitment trial was agreed upon with FDA. This trial designated as Study 30-49 was on-going as a Phase III study before the NDA was submitted. Later in the presentation I will provide more details regarding this study as well as

its current status which is now complete and the planned final survival analysis is underway.

A second Phase IV commitment study referred to as SO200 is currently enrolling patients. The FDA has already informed us that this study will fulfill the Phase IV commitment to convert DOXIL from accelerated to full approval. The primary endpoints for both studies is overall survival.

There are some challenges surrounding the Phase IV commitment trials. The time to reach the survival endpoint in the original Phase IV commitment trial 30-49 was longer than estimated. For the second commitment trial, multiple parties were involved in its finalization and implementation.

There is competition for accrual to the second commitment trial. This was far less a challenge for accrual for the first commitment trial which completed accrual in 1999. Now there are other drug either approved for these patients, prescribed or being actively investigated in this patient population.

Finally U.S. physicians frequently prescribe DOXIL to treat patients with ovarian cancer.

Thus the commercial availability of DOXIL provides patients with an alternative source of drug outside the clinical trial setting.

In November 1998, DOXIL received orphan drug designation for this indication and this was one month before the sNDA for ovarian cancer was submitted to the FDA.

In June 1999, the ODAC recommended that DOXIL receive accelerated approval. Later that month, FDA approved the drug for this indication. The sNDA contained data from three Phase II non-comparative studies in patients with relapsed or refractory ovarian cancer. The primary endpoint was response rate and the dataset contained efficacy and safety information from 176 patients. In addition, data from the interim analysis of the on-going Study 30-49 was provided for review. In approval letter, FDA acknowledged that completion of Study 30-49 was the Phase IV commitment. The first patient was enrolled in Study 30-49 in May 1997 and the last patient enrolled was about two years later in March 1999.

This is a randomized Phase III trial of

DOXIL versus Topotecan in ovarian cancer. Topotecan had been approved in May 1996 about one year before the study started comparing it to DOXIL. The objective of Study 30-49 was to compare the efficacy and safety of these two drugs. The study population was patients with relapsed ovarian cancer following failure with platinum-based chemotherapy. The sample size was 474 patients.

The stratification was based upon platinum sensitivity and bulk of disease. In this slide you can see the two dose schedules for DOXIL and Topotecan. The primary endpoint of the study was time to progression. Secondary endpoints included objective response rate, response duration, survival and safety. The original design of this study was non-inferiority of DOXIL to Topotecan.

In June 2000, ALZA provided data from the planned end of treatment analysis. The timing of this analysis was when all patients had received a minimum of 24 weeks of therapy, six or eight cycles depending upon the treatment arm or disease progression. The analysis did not demonstrate superiority in time to

progression.

FDA requested superiority between treatments for conversion to full approval. However there was a significant survival advantage of DOXIL compared to Topotecan in the platinum-sensitive group. This was a subgroup analysis of a secondary endpoint. At this time about half of all patients were still alive.

This is the data for the primary endpoint proposed in the trial which was time to progression and the number of patients per treatment arm and their platinum sensitivity. As expected, time to progression for platinum sensitive patients is higher than platinum-refractory.

Now I present the results for the survival analysis at this time point. The 26 weeks improvement in survival in the platinum-sensitive was extremely encouraging. This is the data of the percentage of patients that had adverse events either Grade I, II, III, or IV for each of the treatment groups.

At the June 2000 meeting, FDA agreed to a final survival analysis to be performed when a

percentage of the 474 randomized and treated patients died or were lost to follow-up. Ninety percent events were chosen to provide adequate power for survival analysis on all patients enrolled in the study. Thus the protocol was amended to reflect this change. In addition, FDA requested a second protocol to prove the clinical benefit of DOXIL in patients with ovarian cancer be provided.

This protocol was submitted by ALZA one month later. The design was a comparison of DOXIL and carboplatin versus carboplatin alone in platinum-sensitive patients with recurrent epithelial ovarian carcinoma after failure of initial, platinum-based chemotherapy.

In the last quarter of 2000, there was dialogue between ALZA and the FDA regarding the protocol design of the second Phase IV commitment trial. Then in January 2001, discussions between SWOG and ALZA began for this to be a SWOG trial. These discussions included agreement with FDA on the design of the Phase IV commitment trial. The protocol was submitted to the FDA in December 2001.

Briefly SWOG SO200 compares overall survival as the primary endpoint between the two treatment groups. Secondary endpoints include progression of free survival, confirmed CRs, time to treatment failure and toxicity. Patients with recurrent disease or disease progression with a progression-free and platinum-free interval of six to 24 months after completion of first line platinum-based chemotherapy will be enrolled. The target is to enroll 900 patients.

This is a randomized, intergroup, open-label study comparing these two treatments. SWOG activated this protocol last August and the first patient was enrolled one month later.

I would like now to update you on the status of the original Phase IV commitment trial Study 30-49. As you recall, FDA agreed to a final survival analysis performed when 90 percent of the 474 randomized and treated patients had died or were lost to follow-up. We are currently performing the analysis of the final survival data. When that is available we will consult with the primary investigator and provide

this data to the FDA for their review.

I would now like to conclude with some of the issues or challenges with conducting the Phase IV commitment trials. After the end of planned treatment analysis for Study 30-49, the primary endpoint for was modified to become overall survival. A 90 percent event endpoint was chosen which originally was thought would occur about 12 months later. However the time to reach the 90 percent endpoint in Study 30-49 was greater than 3.5 years. Thus patients on both treatment arms lived longer than originally anticipated. This again was great news but did not allow for the rapid completion of this commitment.

Finalization and implementation of the second Phase IV commitment trial took some time. Multiple parties were involved in the finalization in design of this study. Again this is a 900 patient study. This is one of the largest studies in patients with relapsed ovarian cancer that had ever been conducted. In addition, there was some time delay when clinical responsibilities were transferred within our company.

Competition for accrual is always an issue. There are many on-going clinical trials competing for the same patient population. In addition, DOXIL can be prescribed to patients outside the clinical trial setting.

In summary, there are two pathways that could lead to full approval for DOXIL in treatment of patients with ovarian cancer. One is the original Phase IV commitment trial, Study 30-49, that started before the NDA submission and enrollment was completed prior to its accelerated approval. The design was acceptable for conversion to full approval. The planned survival analysis is underway and we will provide this information to the investigator and FDA when it is available.

The second trial is on-going and the study design is acceptable as a Phase IV commitment study. We are committed to completion of the analysis for Study 30-49, discussion with FDA and others including yourselves regarding the results from the final survival analysis as well as completion of Study SO200. Thank you.

CHAIR PRZEPIORKA: Thank you, Dr. Hamburger. Dr. Williams, do you have any comments for the Committee?

DR. WILLIAMS: I just want to provide a comment about the original Phase IV trial. This was an unusual circumstance where we did accelerated approval and then we looked at the trials that were on-going and noted that particular trial was in progress. We looked at the design of the trial. It was a direct comparison to Topotecan. It had the potential to show superiority in clinical benefit.

But in our analysis of its design as a non-inferiority trial, there was not sufficient evidence regarding the precision of the benefit of Topotecan to allow it to be a non-inferiority trial. We didn't know the confidence intervals of the Topotecan effect. So we did not believe that it would serve in that way.

Perhaps if we were to go back today and do it, we'd say okay go ahead and start another trial and then we'll look at this one too. But what we chose to do was to say if it shows superiority within the next year or so when the data were to come in, then we would

accept that for clinical benefit. But if it doesn't, then you need to go on and do another study. That's the way it happened. It wasn't necessarily identified as the accelerated approval trial when it came in. It was just noted that it was there and the results were to be available soon.

CHAIR PRZEPIORKA: If I can summarize the issues, they are that again DOXIL is already out there and people are using it. There are competing interests in new drugs coming out that will slow down accrual to the second protocol. The good news/bad news is survival in the first protocol is longer than expected or just waiting to get to the endpoint a little bit longer than we would expect to. Comments or questions from the Committee? Dr. Martino.

DR. MARTINO: Actually a question. Not knowing the survival results of the two trials but assuming that it does in fact demonstrate superiority, is there still interest for the SWOG trial to continue or how will you handle that issue?

DR. HAMBURGER: I'll let my clinical colleagues answer that question.

DR. ZUKIWSKI: We're committed to completion of the SWOG trial. It doesn't matter what the results are. That trial will continue and we will continue to support it and supply that data to the FDA as it matures.

DR. MARTINO: And that's an intergroup sort of design in participation rather than purely SWOG, I assume.

DR. ZUKIWSKI: Yes.

CHAIR PRZEPIORKA: Dr. Blayney.

DR. BLAYNEY: You are talking about a survival benefit on your 30-49 trial. The survival as we've heard alluded to can be influenced by crossover to another treatment. I suspect that's happened a fair amount on both arms. Are you capturing that data as part of the study?

DR. HAMBURGER: We are not capturing subsequent therapy.

DR. BLAYNEY: So it sounds like there's great danger that you may have a null result.

DR. HAMBURGER: There has been previous communications with other products regarding the effect

of subsequent therapy on the survival endpoint. I don't know if Dr. Temple or Dr. Pazdur want to discuss that. I know this has come up in discussions of the ODAC with other molecules about the effect of subsequent therapy on survival endpoint.

DR. TEMPLE: I'm sure Rick will want to comment more. The Committee when asked on several occasions has urged the overall survival be the endpoint. My own personal worry and we'll eventually come back to you with this is that if the thing you crossover to has significant activity, it has to be a bias toward equivalence. I'm just worried about what that means. It's not clear you can ethically prevent it and it's not clear what it does to the survival endpoint. But that's a longer discussion. I think we need to do some modeling and other stuff and see what it is but we are worried about it.

We've seen trials where there was a clear effect on time to progression and clearly less effect on survival. That's a predictable result if what you crossover to is active. So we are worried about it but don't have an answer yet.

DR. WILLIAMS: In general we would like the data collected. I'm not sure what we would do with it. I flirt when I heard the discussion back and forth but it would be prudent to collect the data. Obviously this wasn't your primary endpoint. Time to progression was and therefore it probably wasn't written into the protocol.

DR. FLEMING: Just a comment on this very point. I think we have to distinguish between crossing in to the experimental therapy versus what we might call crossing in which just means getting access to what would be both ethically and scientifically appropriate which is effective, supportive standard of care.

If in the SWOG trial which is carboplatin plus DOXIL versus just carboplatin if we cross in at progression on the control arm, that's problematic. In fact, many of us would argue that it's begging the very question we're trying to ask. That's answering a question immediate versus delay when we really want to answer the question treatment versus not.

On the other hand, if we are looking at for

example in the 30-49 trial DOXIL versus Topotecan and it's DOXIL followed by best possible management versus Topotecan followed by best possible management, I don't call it a bias if supportive care ultimately yields a result that suggests there's no difference. The strategy of initiating DOXIL versus the strategy of initiating Topotecan followed by best possible management in that case if it shows no difference is the truth.

DR. TEMPLE: I don't agree with that. I'll tell you why. You are the Oncologists so you can figure it out. In the long run all survival curves go to zero and you don't see anything. What you want to know is whether a response with this drug actually has clinical benefit. The fact that you can obliterate that by giving everybody the same good therapy afterward doesn't tell you that this drug doesn't have the desired effect on things. So I really do think you want to know. I'm not quite sure how you find out because you can't stop people from using and crossing over to a marketed drug.

DR. FLEMING: It's apparent that this

debate will have to be answered off line. It's much longer than just this time allotment. The immediate point though is the fact that curves go to zero is not relevant to the issue. It's how quickly they go to zero is the point.

Ultimately I would say I want to know what's the clinical relevance of a strategy starting with DOXIL versus a clinical relevance of a strategy starting with an alternative regimen. Ultimately, does that translate into clinical benefit for the patient, i.e. survival being one of those measures? We'll carry this discussion on later.

CHAIR PRZEPIORKA: Dr. George.

DR. GEORGE: I had a question of clarification concerning the data from interim analysis presented back in 1999. The accelerated approval. I'm just curious about how that works and how that fit into the decision at that time for accelerated approval.

DR. HAMBURGER: Let me clarify and say that the data I showed you in the treatment analysis occurred after the approval. There was interim data that was provided to the FDA during the review on 30-49

and it looks like Dr. Williams wants to address that one.

DR. WILLIAMS: We had the final analysis for the primary endpoint of time to progression. Right?

DR. HAMBURGER: That's correct.

DR. WILLIAMS: So in some sense, it wasn't an interim analysis. You are looking at survival after this subgroup analysis you believe. I just want to make a comment. It didn't seem that the subgroup had a superior time to progression just survival so that makes it more likely in my book that it's chance finding.

DR. GEORGE: Was this known? Is the first time anybody is hearing about this?

DR. WILLIAMS: You're talking about the subgroup analysis.

DR. GEORGE: Yes.

DR. WILLIAMS: Yes we did not buy that.

DR. GEORGE: The other issue I have is concerning the length of time until you get 90 percent of the events. Is it really surprisingly long? If you

had a median survival of one year and even if you started everybody at the same time, it would take almost three and a half years to get 90 percent of the events.

DR. HAMBURGER: I'd like Dr. Mohanty to answer that question.

DR. GEORGE: Is survival really better? It takes a long time to wait. It's just turning light bulbs and waiting until they all fail.

DR. MOHANTY: It was long but I don't think it is longer than what was totally unexpected. At the end of the planned analysis which is two years, at that time 50 percent events or deaths had happened. So it was expected to take long. It was a little longer than what was expected but survival takes a long time.

DR. GEORGE: Yes, I think it's a little misleading to say that survival is good. It just takes a long time. The extremes take a long time to observe.

CHAIR PRZEPIORKA: Dr. Blayney.

DR. BLAYNEY: Just to clarify Dr. Fleming's point. Best supportive care after failure of DOXIL often is Topotecan so there's a cross-in here.

DR. FLEMING: It's the opposite though. I have no problem with the experimental leading to standard. It's the opposite direction. It's the standard than having a cross-in into the experimental is the problem.

DR. BLAYNEY: Because of non-overlapping toxicities, women get the opposite treatment very commonly I suspect.

DR. HAMBURGER: Just remember that both drugs were approved at that time so they were available for patients to receive either drug as subsequent therapy.

CHAIR PRZEPIORKA: Ms. Mayer.

MS. MAYER: Just a question about the history of accelerated approval of DOXIL for this indication. What was it about the research at the time that caused you to bring this discussion to ODAC as I understand it was discussed here?

DR. WILLIAMS: Right. It met pretty much our standard setting for accelerated approval as a drug that has some activity in a setting where there is no available therapy. So it had a 15 to 20 percent

response rate. It was actually zero in Europe if I recall. They had a Phase II study in Europe that was zero but it was higher in the U.S. So it showed activity and was considered before the Committee to be reasonably likely to predict clinical benefit.

MS. MAYER: Yes, but you brought it to the Committee. There are some accelerated approvals you don't bring to the Committee and some you do. I'd like to understand more clearly what criteria you looked at.

DR. WILLIAMS: Of course there is the history. There are different division directors. There's different types of applications. At that time, we brought almost everything to the Committee. We're being a little more selective now because we're getting a few more "me-too" type drugs that really don't require the Committee's judgment. At that time, we were bringing essentially every application in and this was an accelerated approval. The setting accelerated approval lends itself in some circumstances where you have somewhat borderline evidence, then this judgment of what's reasonably likely by a group of experts fits well for the Committee in cases where it's borderline.

CHAIR PRZEPIORKA: Dr. Martino.

DR. MARTINO: A question to the FDA. If the first of the two trials demonstrate a survival advantage, at present does that then provide enough data in your mind for full approval or is the second trial still a requirement?

DR. WILLIAMS: The regulations basically state that the sponsor will supply evidence that the drug provides benefit. At the time that the FDA determined that there's sufficient benefit to meet our approval standard, then we would act at that time.

CHAIR PRZEPIORKA: Dr. Brawley is the discussant for this question and will give his comments.

DR. BRAWLEY: Thank you very much. So far and perhaps, Dr. Hamburger, you can help me if I were to summarize, you had three Phase II clinical trials that showed efficacy with the drug and that was used for getting accelerated approval. At the time of accelerated approval, Trial 30-49 was already enrolling patients. That was a trial that looked at DOXIL versus Topotecan in women who had been treated with just

platinum in the past.

The endpoints for Trial 30-49 changed over time. One question I have is did the purpose of the trial change. Was it initially started as a trial to show equivalence and then seems that it changed into a trial to look at the possibility that DOXIL might be superior to Topotecan?

DR. WILLIAMS: I could probably address that in some ways. The sponsor was planning to do non-inferiority studies. If I recall, there's a lot of back and forth about FDA's lack of comfort with the demonstration of Topotecan as an active control for an equivalent study or non-inferiority study. At the time it came up for accelerated approval, we told them that regardless of what you've planned we will only evaluate it as a superiority study. I think there was probably some back and forth.

DR. BRAWLEY: Thank you. That helps a great deal. As time progressed, the sponsor did start working on a trial which is now the SWOG trial. The SWOG trial just began accrual in the middle of last year. The next question I have is there any timeline

or projected timeline for the accrual of what really is a large number of patients, 900 patients. I know you are going through a number of cooperative groups. It's a intergroup trial that extends into Canada as well as the United States. Is there a timeline that's estimated?

DR. TEITELBAUM: They are estimating accrual of 150 patients annually.

DR. BRAWLEY: Six years of accrual.

DR. TEITELBAUM: 2007 is when we are anticipating according to their enrollment abilities and what they project.

DR. BRAWLEY: That's more than 150 a year. 900 total patients for 150 patients per year is six years of accrual. Then watching survival.

DR. HAMBURGER: In our response to the FDA, we provided them with a timeline and it's estimated the accrual will be completed in 2007 and we hope to have a supplemental NDA approximately 2009.

DR. BRAWLEY: Okay. The first question I'm supposed to address is has accrual to the on-going trial been satisfactory allowing for timely study

completion. My great concern and others may want to speak to this is that the trial that is outlined shows what really is very number of women every year who come into this situation.

It would be nice if the accrual entry criteria could be brought and I'm admitting I don't know how you could do that. Can other members of the Committee help me with this? Is it reasonable to wait until 2009?

CHAIR PRZEPIORKA: Dr. Carpenter.

DR. CARPENTER: Exploring additional sites particularly in Europe or some place where there are likely to be comparable patients where there may or may not as many competing therapies might be a way to get the number up. As I look around, everybody I see is uncomfortable with the study that going to take six years to complete accrual. If you were able to cut that time perhaps in half then it might be a study which is much more likely to succeed in its objectives.

CHAIR PRZEPIORKA: Just a logistical question to address that point. Because it's a SWOG study and SWOG centers don't exist in Europe, if they

tried to improve accrual by opening another protocol in Europe and then did an analysis based on the two protocols combined, would that be acceptable?

DR. BRAWLEY: Yes, that's been done before.

DR. PAZDUR: Yes. If it is prospectively done, we'd look at this. It's not out of the question.

DR. BRAWLEY: Yes, my greatest concern about getting the answer in 2009 and finishing accrual in 2007 is it's rare the trial that I see where accrual actually meets expectation. It's more likely that accrual to this trial is going to be finished in 2010 and results available in 2012. It's also very likely that another drug is going to come forth over the next five years and it's going to become even hard to complete this clinical trial. That's my advice for the day. Any comments from the Committee?

CHAIR PRZEPIORKA: Dr. Pelusi.

DR. PELUSI: I would just again want to throw out in terms of the difficulty of accruing people to clinical trials but I also think we really need to look at some creative ways of working with the patient advocacy groups to really have them understand how

important it is to utilize the clinical trials versus in community practice where it's already approved for just going forward. They are a true role in helping us make these determinations and what may be using them even more in terms of getting the information out and on that effect, saying how important these meetings are so that the consumer groups really begin to understand the difficulty of getting some of these Phase IV studies done and why their role is becoming more important.

CHAIR PRZEPIORKA: And again just to address the logistical issue that doesn't mean let the consumer groups go and find out what they were and get all the information. It means the sponsors being proactive, putting the packet together and getting it over to the advocacy groups. Ms. Mayer.

MS. MAYER: I just want to suggest that there may be times in which difficulty in trial accrual is essentially telling us something we need to listen to about the efficacy of the drug in the current environment and how that changes over time. I don't know what role patient advocates will play in

encouraging enrollment to trials of a drug when there are better alternatives available in the marketplace.

This is one of the real problems with accelerated approval as a way of moving forward. Unless withdrawal is enforced in some way, it leaves drugs on the market for indications that have no real proven efficacy. I don't know how we can address that but I just want to put that out on the table.

CHAIR PRZEPIORKA: Dr. Carpenter.

DR. CARPENTER: I would submit that there's not a better alternative out there than this study. The question is by 2007 whether it would be. Right now, this study is probably state-of-the-art. That's why efforts to get the accrual up and get it done so the answers will become available at a time when they are still pertinent to clinical practices what needs to be done with this study.

DR. BRAWLEY: Dr. Martino.

DR. MARTINO: Just some practical thoughts. I've been with SWOG for a long time and I know how the intergroup tends to function. It often functions well within this country and Canada where there are

established relationships and mechanisms. We're not particularly good at establishing mechanisms with Europe.

So it probably would be futile to think that the intergroup in this country and Canada could establish those relationships quickly enough to be of use for this trial. If there are thoughts to expand accrual, my personal advice would be I would ignore that pathway but rather establish another group in Europe or elsewhere which then could be used as a combination. That you probably can do much more efficiently.

The other possibilities could be the CTSU system which allows clinicians who are not necessarily part of the intergroup mechanism access to these trials. So there are some other pathways that are already established that can be used to enhance accrual to these large trials.

DR. TEITELBAUM: I just would like to say that it is a CTSU study.

CHAIR PRZEPIORKA: Thank you. Dr. Fleming.

DR. FLEMING: Dr. Brawley and others have

been raising some very relevant issues about the SWOG trial and its feasibility and timeliness. I'd like to step back though and just revisit how we got to that trial and focus on the interpretation of 30-49. But before doing that, one quick question. There's another trial 30-57 which is a randomized comparative study involving 214 looking at DOXIL versus Paclitaxel. We didn't hear about it but our briefing documents refer to it. If I'm interpreting it correctly, it showed a trend toward about 11 week longer survival on Paclitaxel than DOXIL.

DR. TEITELBAUM: This study was started in 1997 and planned to enroll 438 patients in order to obtain the 350 valuable patients. It enrolled a total of 214 patients from 33 sites throughout Europe. It was discontinued early because Paclitaxel had become approved as first line treatment in Europe.

When the study was started, it was DOXIL versus Paclitaxel in patients with relapsed ovarian cancer. The availability of the Paclitaxel in Europe made it virtually impossible to enroll any additional patients once the Paclitaxel was approved.

DR. FLEMING: Do you have a slide on the results? If not, I can just quote what was in the briefing document.

DR. TEITELBAUM: No, I do not.

DR. FLEMING: Basically it looks as though the response rates were four or five percent lower on DOXIL and median survival was 45.7 on DOXIL and 56.1 on Paclitaxel which I'm sure doesn't prove differences but suggests somewhat longer survival on Paclitaxel. The other data of course is the 30-49.

Just to follow up on Stephen George's comments which I agree with, the prudence of targeting follow-up in any trial until 90 percent of the events occurred is very questionable. I would argue in designing studies that if the median survival is three to five months, then I'm comfortable with the 90 percent truncation point. But when it's up around a year, it's much wiser to enroll larger numbers so that you are only having to follow until 75 to 80 percent of the events occurred. That's what we're running up to against in this trial.

More to the critical point though, what was

the intention of 30-49? I can see a definite maturation in the process between FDA and sponsors in how this accelerated approval process is being implemented between the early 1990s and now 1999. The letter here is much more explicit about what the expectations are.

For this study, it is very explicit. The likely evidence required to satisfy the Phase IV requirement would be to demonstrate superiority of DOXIL over Topotecan in either time to progression or survival with a supporting trend demonstrated for the other endpoint. That seems like a very rational criteria to put forward.

What I understand from the data that's been presented to us is numerically there is no difference in time to progression and numerically there is no difference in survival. So I'm perplexed. What was clearly laid out as a criterion for what would be an adequate basis for approval was not only not met because we had positive trends that weren't significant but the differences were trivial between these two arms.

Now there were subset analyses and we now get into and will be confronting later also in these two days how to interpret subgroup analyses. The subgroup analyses are interesting though at least this updated analysis that we're seeing here doesn't show a difference in progression, i.e. it doesn't show an interaction of platinum-sensitive for progression.

It does show an interaction for survival which is an interesting issue. Is this real or is this as most of us would anticipate in subgroup analyses more likely spurious due to excess differences that you see when you look in a lot of subgroup analyses? How is it that it would be likely that a two week difference in progression would translate into a 27 week difference in survival? This is what we might call a qualitative interaction because if you believe that there's a benefit in platinum-sensitive then you have to believe that there's an adverse trend in platinum-refractory.

There is an interesting hypothesis being generated here. In fact, this is what we're now coming to Dr. Brawley's question as to how do we confirm this.

We're confirming it with a study that's going to take six more years. Is this in fact the logical conclusion of now extending what has been a four year accelerated approval process here an additional at least six years unless we somehow can rapidly enhance the accrual rate when the target that was clearly specified in Dr. Temple's original letter was clearly not achieved in the primary analyses of that study and you have a 30-57 trial which is at least suggestive that there are better trends on survival of Paciltaxel?

DR. WILLIAMS: Tom, I was originator of the text that ended up in the letter. So I know that our intent was to note that there was a trial nearing completion which was not adequate to detect clinical benefit if it was there only if it appeared as Topotecan. Therefore we explicitly were not going to hold them to a negative study. That was our intent.

That's probably the only accelerated approval letter I've seen like that where we had an almost complete study and if they had shown superiority that would have been sufficient. If they did not show superiority, it would not be sufficient. We said we

would therefore ask for this other trial.

So it doesn't meet the requirement perhaps that you're thinking that we would have a Phase IV trial. It's a commitment. If you failed that Phase IV trial, therefore we will take your drug off the market. That was clearly not what we intended at that time.

DR. FLEMING: So just for clarification, at the time of this letter in June 1999, you were laying out criteria which if satisfied would lead to a full approval. If not satisfied, what explicitly was your intention?

DR. WILLIAMS: Wasn't that the next paragraph that says therefore if it is not met, we will expect you to meet with us and to plan a trial, etc.? That was in the next paragraph.

DR. FLEMING: Specifically you didn't have a specific expectation of what that would be and it wasn't the 30-57 trial I assume.

DR. WILLIAMS: It was a trial to demonstrate clinical benefit. It was a trial that would probably be an add-on design. If it didn't work, you might make the assumption that the drug didn't

work. So that was our thoughts at the time.

CHAIR PRZEPIORKA: Dr. Temple.

DR. TEMPLE: Grant, did they get caught up in our growing insight into non-inferiority trials? There was a time within my memory when if you showed that you ruled out the 20 percent loss and a hazard ratio that's 0.8, we said that was good enough. We came to realize that lots of times the control agent didn't have a 20 percent effect so you weren't ruling out anything at all. You weren't sure you were obtaining anything. A lot of attempts at non-inferiority got caught up in this growth of insight. Of course just to state the obvious, failure to beat the control agent doesn't mean it doesn't work. It just means it might not have been the best study design so that's why an alternative was proposed.

DR. WILLIAMS: I remember looking back but I don't recall directly if there was an agreement that this would be sufficient or not. You are correct that we have become much more attentive to the effect size proven in trials and the design. But at the time the trial was designed, it was not designed to be part of

the confirmatory trial for accelerated approval. It's one of the trials that comes in from the company as a Phase III trial. Then at the time of approval, we explicitly recognize the deficiencies of the study and said that we would expect the results soon and only if superiority would be satisfactory.

DR. FLEMING: Just to follow up on Bob's point, what's the lower limit of the confidence interval for the hazard ratio for survival? If you took a more lenient approach and said 0.8, does anybody know the answer to that?

DR. MOHANTY: The lower limit was 0.775.

DR. TEMPLE: But we didn't know what the control agent's effect was in any credible way.

CHAIR PRZEPIORKA: Dr. Taylor.

DR. TAYLOR: We should go back to our patient representative's comment. It's a good point in terms of trying to complete these trials. It's a very common perception in our society by both physicians and patients that new is better and that the older the trial becomes the more difficult it is to accrue to and that if it's a new drug it has to be better. Trying to

be part of the control arm is not something that patients necessarily perceive as better. They may want even a Phase II trial over doing something like this.

CHAIR PRZEPIORKA: Dr. Brawley, did you have more comments?

DR. BRAWLEY: Yes, in keeping with Dr. Taylor's comment, let's remember that this drug on clinical trial is competing against itself in the open market. So an individual who chooses to take Carboplatin alone or chooses to go into a trial that would randomize the Carboplatin alone versus Carboplatin and DOXIL could easily get Carboplatin and DOXIL off-study. Unfortunately many people do tend to think that more is better. Many women I suspect would opt for Carboplatin with DOXIL as opposed to a 50 percent chance of Carboplatin alone.

Also I'm very concerned about is it fair to patients to have trials that last so long. If there's any way to shorten it, we ought to. We've had some interesting discussions of ways to do it. Broadening entry criteria is something that I would really stress needs to be attempted. Going to Europe, Dr. Martino

talked about some of the problems with that which we've seen before.

One of the three questions that I was supposed to address is has accrual to an on-going trial been satisfactory and allowing for a timely study. I think that we've address that issue. Strategies that might be used in order to improve accrual. We addressed that issue. We've also addressed the issue and concern about changes in the marketplace that may make this current clinical trial even harder to do.

I will just conclude. I was asked to clarify a statement that I made in our first session this morning. I do believe that there are certain diseases where drugs like DOXIL would benefit from relatively large, long case series going to 10 or 12 institutions and trying to get every patient will allow the information as they get this drug to be collected into a database to look at trends and look at the number of patients who are getting DOXIL with HAART for Kaposi's or DOXIL alone or DOXIL having failed HAART. I don't believe ovarian cancer is one of them but Kaposi's probably is one of those diseases. It's a

very non-controlled study just collecting case series. It actually may be something that may be useful in figuring if some of these drugs actually do work in those Phase II like case series. I'll conclude. Thank you very much.

CHAIR PRZEPIORKA: Dr. Cheson.

DR. CHESON: We cannot forget that some of these decisions may be out of our control because since this is now a SWOG study it will be managed by a data safety monitoring committee. If accrual is suboptimal, that committee will have the authority to recommend to the chair of the group to shut it down. Unless it is accruing at a sufficient rate, it will be closed earlier than 2008, 2009 or 2010.

CHAIR PRZEPIORKA: The summary that I've collected from the comments today were to collect the treatment of patients post-relapse to make sure that if there is a crossover you have something to think about as to what happens with survival, work with the advocacy groups to get the information out regarding where the study is being done and why it's so important and consider a parallel protocol in Europe in order to

accelerate accrual and get this study completed as quickly as possible. Any other comments from the Committee? Mr. Fleming.

DR. FLEMING: Just to the first comment you gave about collecting, you are talking about the SWOG trial collecting data on crossover.

CHAIR PRZEPIORKA: Right.

DR. FLEMING: I guess my own perspective on that is that question that's being asked is a very relevant one if we believe the subgroup analysis is at least as sufficiently reliable to generate a hypothesis worthy of validation. Actually that is a reasonable interpretation. If that's your perspective, then it's answering a very relevant question. Can we improve survival by adding DOXIL to Carboplatin?

DOXIL at this point is not an established agent establishing effect in this setting. So ideally what I would encourage is that people if they are going to join the study sign an informed consent where they would realize that there is substantial uncertainty at least for them and their caregiver as to whether DOXIL is effective for them in this particular setting when

they're going to get Carboplatin.

If so, then I would hope that those people who are randomized to the control arm in fact wouldn't take DOXIL unless you believe the question of interest is immediate versus delay. That's a much more diluted question. Ultimately as a statistician we're not going to be able to go back and adjust out the fact that there are cross-ins on that control arm because if you censor them it's informative censoring.

The proper approach here is to say if you think you want DOXIL, then take DOXIL. You can get it. It's available from accelerated approval. If you are substantially uncertain in this setting whether it will provide benefit to you, then we have a trial that we would be interested in having you consider to be a part of. In which case if you randomize to the non-DOXIL arm, my hope is that most of those patients would use other supportive care approaches. If they take DOXIL, then you're presuming the answer that you already know it's a necessary component. Now you are only answering the question immediate versus delay.

CHAIR PRZEPIORKA: Dr. Brawley.

DR. BRAWLEY: Unfortunately, Dr. Fleming, it ain't that easy. Those of us who talk to patients and enroll patients in clinical trials our collected experience is that more patients are going to say more is better and DOXIL plus Carboplatin is more than Carboplatin alone. Therefore, I don't want a 50 percent chance that some computer is going to give me Carboplatin alone. I want both drugs.

Never mind, the fact that you and I can both name a number of instances where the added drug or added procedure has turned out to be the wrong thing. You saw some less than objective behavior earlier today.

DR. FLEMING: This gets right to the crux of the issue about accelerated approval and the practical implications of an accelerated approval. The control arm here, Carboplatin, isn't only Carboplatin. It's Carboplatin followed by best possible management of available therapies which I would argue that if we're trying to establish whether DOXIL should in fact be in that armamentarium then it shouldn't be one of those "available therapies."

If it's available from accelerated approval, I understand your point. It's now out there and the ability to ultimately establish whether or not the addition of DOXIL to standard of care whether that improves an outcome such as survival will now be forever compromised because people will have the option if they choose to get access.

CHAIR PRZEPIORKA: Dr. Carpenter.

DR. CARPENTER: It's just unrealistic to believe that this study is going to proceed any other way in the United States except for the people who got Carboplatin alone which preceded Doxil or relapse. It's probably one of the most attractive third line drug that will be in this setting. It's completely unrealistic to think that it's going to happen any other way. So any consideration of a study design which doesn't take that into account is just not living in this world.

CHAIR PRZEPIORKA: So basically what we are hearing is that survival may not be your best endpoint. If you are looking at clinical benefit, the best you could hope for is time to disease progression. Dr.

Redman.

DR. FLEMING: What I'm hearing at least is that all that's practical and what some people are saying is a strategy of immediate versus delay. Ultimately if delay provides part of the benefit what I'm hearing is we'll never know whether immediate versus not use is in fact going to show a difference.

DR. REDMAN: Just out of curiosity because I agree that the DSMB is probably going to recommend that the study be closed because it's not accruing, where do you go from that point?

DR. GEORGE: I think we'll come back here.

DR. PAZDUR: Back to the drawing board. But here again if you remember my comments, part of this whole process is basically that we'd like several options and plans for failure. Not every clinical trial is going to meet its objective and methodological problems will intervene and crossover will intervene. What are other plans? Here again we're looking forward of using this experience for other drugs.

CHAIR PRZEPIORKA: Dr. Temple.

DR. TEMPLE: We will be back for more

discussion of time to progression. I just need to mention that studies are typically sized for the time to progression and you hope that you get overall survival. If the benefit is the same two months, then a hazard ratio of 0.8 for time to progression becomes a hazard ratio of 0.9 even if you retain it all when you double the time. You start to get into trial sizes that are very different from what we now do. But we want to discuss all of that. I just want to put an advert in for the add-on study which at least has a chance.

CHAIR PRZEPIORKA: Mr. Ohye.

MR. OHYE: I'm going to defer my comments. Thank you.

CHAIR PRZEPIORKA: Dr. Kelsen.

DR. KELSEN: I was going to say that clearly we should rediscuss the issue of time to progression. We have a recent colon cancer trial in which this issue came up. This is not the time I guess but sooner or later we should spend considerable time on that.

DR. PAZDUR: Just to give a plug. As you

all know, we are in discussions with ASCO to start looking at specific diseases and endpoints. We're planning the first meeting on lung cancer to look specifically at endpoints which will be held in April. We plan on going on to other meetings.

Obviously these meetings with ASCO are not advice-giving meetings. They are meant basically for a discussion. The only people we could take advice from are you all so we will be coming back with the ASCO discussions to you on specific diseases. We plan on doing this over the next couple of years.

CHAIR PRZEPIORKA: May I ask? Will the members of this Committee be invited the discussions at ASCO?

DR. PAZDUR: There are members that have been either past or present. I believe past members have. One of the reasons why we wanted to have it separate is that there is a separate discussion and we included basically people that had specific disease interest in a disease.

CHAIR PRZEPIORKA: In that case, will individuals participating in the ASCO discussion come

here at a future time?

DR. PAZDUR: Yes, we plan on having this as a discussion where they would come with us to discuss these endpoints.

DR. WILLIAMS: The meetings will be open too so you can come.

CHAIR PRZEPIORKA: Any other comments or questions for Drs. Williams or Dr. Hamburger regarding this protocol? Thank you. In that case, the morning session is over and it is now noon. We will return at 1:00 p.m. for the afternoon session. Thank you. Off the record.

(Whereupon, at 12:04 p.m., the above-

entitled matter recessed to reconvene at 1:08 p.m. the same day.)

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

1:08 p.m.

CHAIR PRZEPIORKA: On the record. Thank you for joining us this afternoon. The first item on the agenda for this meeting will be the open public hearing. The speaker that we have for the afternoon session is Maryann Napoli from the Center for Medical Consumers. Ms. Napoli.

MS. NAPOLI: For the record, I'm Maryann Napoli from the Center for Medical Consumers in New York. We're a not-for-profit advocacy organization that's never had any pharmaceutical funding. Because our Center was founded to promote informed decision making, I spent a lot of time listening to cancer patients and helping them make cancer treatment decisions.

In 25 of the 27 years of our Center's existence, we've had a medical library that's open to the public. The people we attract are the kind of people who weigh and consider the evidence before going on a drug regimen. In the years that I've spent listening to people, I've been struck by the disconnect

between what oncologists say to people and what the patients hear. Oncologists when asked about efficacy frequently answer in terms of response rate but what the patient inevitably hears is survival rate.

I think that most people with cancer would be shocked to know how unreliable tumor shrinkage is as an endpoint and that it was the basis for accelerated approval in 10 out of 11 cancer drugs and the sole basis for 10 out of 55 given regular approval between 1990 and 2001. Consider what most cancer patients want from a drug, significantly prolonged survival and side effects that are too horrendous.

I applaud the trend towards making clinical benefit a required endpoint. I hope that this committee will continue to rethink and strengthen the accelerated approval process because it allows expensive minimally-tested drugs on the market to enjoy a long period of unearned hope and acceptance, drugs that have never compared to the standard drugs.

No matter what you decide to do as a committee, however, cancer patients must have a way of understanding the basis for drug approval be it

accelerated or regular. I've looked at the label for each of the drugs to be discussed today and concluded that the average intelligent consumer could easily miss their accelerated approval status when reading the Physician's Desk Reference which is the most popular book in our medical library.

Sure you can read the label and find mention of Phase II trials and partial and complete responses. But what does that mean to consumers? Yet people can go to the FDA website where they'll see a list of drugs given accelerated approval, but the explanation of accelerated approval is not readily understandable. Nor does it explain tumor response and how debatable it is as a good surrogate for prolonged survival or even symptom improvement.

Most manufacturers of drugs given accelerated approval have not completed the required confirmatory trials but you would be hard pressed to know that unless you read the "Wall Street Journal." The FDA website lists each drug's data of accelerated approval but not the status of those required confirmatory trials.

We advocates who write and translate and assimilate information for people with cancer need to know this information. We need to know how that due diligence is working out. We need to know whether companies are compiling with the regulation and how long it takes them to do so.

All cancer drugs should come with written information that's understandable to consumers who need a summary of the supporting evidence. In fact, there should be something like a black box warning to alert the consumer of a drug's accelerated approval status. I thank you all for your attention.

CHAIR PRZEPIORKA: Thank you, Ms. Napoli, for your excellent comments. Any questions from the committee? None. Thank you. Next is the Conflict of Interest statement by Ms. Clifford.

SECRETARY CLIFFORD: The following announcement addresses the conflict of interest issues with respect to this portion of the meeting and is made a part of the record to preclude even the appearance of a conflict. To determine if any conflict exists, the Agency has reviewed the submitted agenda for this

meeting and all relevant financial interests reported by the Committee participants.

The Conflict of Interest statute prohibits special Government employees from participating in matters that could affect their personal and imputed interests. However the Agency may grant a waiver if the need for the individual service outweighs the conflict created by the financial interest.

Accordingly waivers have been granted to following individuals: Dr. Douglas Blayney for owning stock in two competitors, each is valued from $25,001 to $50,000; and Dr. Scott Lippman for serving on a competitor's speaker's bureau for which he has received less than $10,001. A copy of these waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 Parklawn Building.

In addition, we would like to note that George Ohye, the Acting Industry Representative, owns stock in the sponsor and in three competitors. He receives retirement pay from the competitor. His wife works for the same competitor. Within the past year,

he consulted for the firm.

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 participant should exclude himself or herself from such involvement and the exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

I would also like to make an announcement on behalf of Katherine McComas. She was the woman who stood up in the open public hearing earlier. She did leave a survey and a box will be at the desk in the lobby.

CHAIR PRZEPIORKA: Thank you. On to our first presentation then, Dr. James L'Italien and Dr. Gordon Bray from Ligand Pharmaceuticals to discuss the Phase IV commitments on BLA 97-1325, ONTAK, for treatment of persistent or recurrent cutaneous T-cell lymphoma in patients whose malignant cells express a

CD25 component of the IL2 receptor.

We actually have a second person who wanted to make an additional comment, Ms. Mary Pendergast, if you can come to the podium to talk about FDAMA. I would ask that you provide your conflict of interest information prior to your comments. Thank you.

MS. PENDERGAST: Thank you. I would like to thank the chair for giving me the permission to speak very briefly. My name is Mary Pendergast. I work for Elan Pharmaceuticals, a bio-pharmaceutical company. While we don't have a dog in this particular fight that is to say one of your drugs is not being considered by this committee, I think you should assume that I have a conflict since I work for a company that may in the future seek to get accelerated approval for one of our products.

The reason why I'm talking here today is because I was formerly the Deputy Commissioner of the Food and Drug Administration and before that a lawyer in the office of the General Counsel at FDA for approximately 20 years all together. I participated in the drafting of the accelerated approval regulations

and I'm very familiar with something that hasn't been brought forward to the committee's attention yet in either the FDA's documents or in the discussion today which is a law that was passed in 1997 called "The Food and Drug Administration Modernization Act." That law was based in large measure on the activity the FDA had taken to speed drugs to the market through accelerated approval.

But it gave the agency additional authority, additional discretion to deal with the kinds of circumstances that the committee is being asked to face today. In particular, the Food and Drug Administration Modernization Act gave the agency the authority to waive the requirement for the Phase IV confirmatory trials and it gave the agency a discretion to decide to not withdraw the drugs should those trials be not completed or negative.

Let me just read to you from the law. As the law was passed in 1997, these kind of accelerated approval products are called "fast track drugs." Congress had told the agency that they should speed the development and approval of "fast track drugs." So

Section 506(b)(2) of the Federal Food, Drug and Cosmetic Act which was added by Congress in 1997 states

"Limitation: Approval of a fast track product under this subsection may be subject to the requirements."

Then "Requirement A: That the sponsor conduct appropriate post-approval studies to validate the surrogate endpoint or otherwise confirm the effect on the clinical endpoint." Congress used the word "may." The agency is not compelled to require those Phase IV trials. As Dr. Pazdur said I think mistakenly, the Phase IV trials are not mandatory. The FDA can choose not to require them. However should the agency choose to require them, then of course the company must do them. It says that it's definitely mandatory from the company's perspective.

Similarly the FDAMA provisions give the agency the ability to withdraw expeditiously an NDA if the sponsor fails to conduct the required post-approval study. But it does not demand that the agency pull the drug from the market. The law reads: "The Secretary may withdraw approval if: (a) the sponsor fails to

conduct any required post-approval study of the fast track drug with due diligence..." Then there are subsections (b) and (c) that deal with what if they do the study but the study is negative.

I bring this to your attention because in particular Dr. Fleming seemed to be under the mistaken impression that it was essential that all these Phase IV trials be done and that it was required that the agency pull the drugs from the market should the trials not get done or if the trials are negative. The law is quite clear that it's not the case. Thank you.

CHAIR PRZEPIORKA: Thank you very much. Are there any questions?

DR. CHESON: A point of clarification on the conflict of interest. I believe that Elan Pharmaceuticals does have a relationship with Ligand Pharmaceuticals. At least in Europe, they are co-developing several of the products such as the one that I'm discussing.

MS. PENDERGAST: Thank you and I know we used to have a relationship with Ligand but we got out of it. Like I said, consider me conflicted.

CHAIR PRZEPIORKA: Thank you. Other comments? Excellent additional information and clarification. Now on to Dr. L'Italien and Dr. Bray.

DR. L'ITALIEN: I'd like to begin this afternoon by thanking both the committee and the agency for the opportunity to present some of our recent advances in our Phase IV commitments for ONTAK. We'd like to actually divide the presentation today. Dr. Gordon Bray is going to be giving the presentation.

Let me also begin by saying I'm the Senior Vice President of Regulatory Affairs for Ligand Pharmaceuticals. Dr. Gordon Bray is our Senior Medical Director of Clinical Research. Dr. Andres Negro-Vilar is our Senior Vice President of R&D and Chief Scientific Officer is here to respond to questions as is Dr. Eric Groves, Vice President of Project Management and Dr. Francine Foss, Professor of Medicine at Tufts-New England Medical Center, who is acting as a consultant for us in our discussions today. Let me introduce Dr. Bray.

DR. BRAY: In the next 15 minutes I would like to review the structure mechanism of action and

clinical characteristics of denileukin diftitox or as it's currently known by its proprietary name, ONTAK. I'll review the clinical basis for accelerated approval of this product and some of the key milestones that have taken place in conjunction with its development.

I'll describe the outstanding clinical commitment upon which final approval is contingent and specifically I'll speak to the progress that we've made to date in completion of that commitment, some of the on-going efforts that we have undertaken to that end. In keeping with the request of the FDA, we are going to also discuss some of the challenges that we've encountered in our efforts to complete this outstanding clinical commitment. At the end of all this, I will sum up.

To begin with, ONTAK is a recombinant fusion protein that consists of the catalytic and membrane translocation domains of diphtheria toxin fused to the full length amino acid sequence for IL2. It's a protein that's designed the cytocidal activity of diphtheria toxin to tumor cells that express the receptor for IL2. Leukemic and lymphoma cells of both

B and T cell origin including cutaneous T-cell lymphoma for which this product is primarily indicated constitutively express one or more subunits of IL2 receptor on their cell surface.

This slide describes in a simplistic fashion the mechanism of action of ONTAK. It's helpful to begin briefly just by reviewing the structure of the IL2 receptor. As most of the members of the committee are no doubt aware, the IL2 receptor exists in a series of isoforms that vary with respect the representation of individual polypeptide subunits.

On the upper left-hand corner of the slide you will see a cartoon representation of High affinity IL2 receptor which consists of the alpha subunit or CD25, the beta subunit CD122 and the gamma subunit CD132. The intermediate affinity receptor for IL2 consists solely of the beta and the gamma subunits. Upon binding to either the intermediate or high affinity receptor for IL2, ONTAK will mediate signal transduction and internalization of the complex viracept mediated endocytosis.

Within the acidic environment of the

endosome, a series of furin mediated proteolytic cleavages take place that result in the liberation of the catalytic moi doi diphtheria toxin and its liberation into the cytosolic compartment. Within the cytosol, the catalytic moi doi diphtheria toxin potently inhibits protein synthesis by ADP ribosylating elongation factor 2 which ultimately results in the death of a cell by apoptosis.

ONTAK is indicated for the treatment of patients with persistent or recurrent CD25 positive cutaneous T-cell lymphoma or CTCL. It has been shown to have an acceptable safety profile. Its use is associated with minimal myelosuppression.

Accelerated approval for ONTAK was based on data in CTCL patients from two clinical studies. In a Phase I/Phase II dose escalation study, 37 percent of the patients demonstrated at least a 50 percent reduction in their overall tumor burden. In a Phase III dose comparison study, the overall rate of response which was the primary efficacy endpoint was 30 percent. Full approval of ONTAK requires completion of a three arm, blinded, placebo-controlled trial in CTCL which is

know as L4389-11.

I'm pleased to report that L4389-11 is on target for submission of a final study report in early 2006 consistent with prior communications with the agency involving the status of the trial.

Now this slide lists some of the key milestones that have taken place in conjunction with the development of ONTAK. In August 1996, the product received orphan drug designation by the Office of Orphan Products Development. In December 1997, a biologics license application was submitted to FDA by Seragen, Inc. In February 1999, the product received accelerated approval under Subpart 8 at which time Ligand Pharmaceuticals assumed all development responsibility for ONTAK from Seragen.

The next couple of slides I'd like to get into some of the specific designs elements for the L4389-11 study. Patients who are eligible for this study must have persistent or refractory CTCL and they must have disease stages between stage I(a) and stage III. Importantly all patients must have tumors that express CD25 on the surface of their tumor cells. The

reason that this is an important point is because only about 60 percent of patients with CTCL have CD25 positive disease. Similarly all patients must have had fewer than or equal to three prior therapies at the time that they present for enrollment in 4389-11. The primary efficacy endpoint of this study is the objective rate of response and the two secondary efficacy endpoints are time to progression and response duration.

Following discussions and correspondence with the agency that occurred during much of 1999, the study population for L4389-11 was increased from 120 subjects who were to have been randomized in equal numbers into the placebo arm of the study as well as into the two active treatment arms of the study to 195 study subjects which in essence would result in a randomization ratio of one placebo patient for every two patients in each of the active treatment arms of the study. This modification in the study population was felt to maintain the original size of the placebo group but it weighted randomization towards active study drug in an effort to encourage enrollment into

the study post approval.

Patients who present for enrollment in the study are screened for eligibility and CD25 status of their CTCL. Those who meet all eligibility criteria are randomized to receive up to eight courses of either placebo, 9 or 18 ug/kg/day of ONTAK on five consecutive days every 21 days. Tumor burden is assessed at baseline and at day one of each cycle of therapy subsequent to cycle one.

I'd like to talk a little bit about some of the progress that we've made since endeavoring to complete enrollment in this study. Subsequent to assuming responsibility for this clinical trial and adaptation of the 1999 amended protocol, enrollment in the study has increased progressively through the first quarter of 2003 during which time seven new study subjects have consented to participate in the trial.

Ligand has made significant efforts to increase enrollment in the study by bringing new study sites on line from various different geographies. What this slide shows is that in the year 2000 the number of study sites has increased from nine to 22 by the end of

2002. And by the end of the current quarter, we will have 28 active study sites enrolling patients from North America, Europe and Australia.

Just to sum up the current status of the L4389-11 study, we've now enrolled a little bit more than 50 percent of the total number of patients required to complete the trial. There are 28 active enrolling study sites in Europe, North America and Australia. There were seven patients who were enrolled in the first two months of 2003 which is a source of some encouragement to us. We estimate that approximately 29 of the 39 required placebo patients have already been enrolled in the study. We're on target for submission of a final study report for the trial in early 2006.

The agency has asked us to address some of the difficulties and challenges we've encountered in getting us to where we are today. I've actually listed those on the next slide: the small size of the patient population and the relative paucity of clinical research centers that have a seminal interest in this disease; certain practice patterns or standards of care

for CTCL as they impact eligibility for the study; impact of prior therapies on eligibility; and impact of the placebo arm. These have each had effects on our ability to recruit patients into this trial.

I'm going to spend the rest of my presentation going to each one of these in greater detail. To begin with, CTCL is an uncommon disease. It constitutes only a little bit more than two percent of all patients with lymphoma in the United States. It has an annual incidence of approximately four per million. So there are only a little bit over 1,000 new U.S. cases of CTCL reported per year. We've estimated that only approximately 400 CTCL patients were treated with ONTAK in the year just concluded.

I'd like to begin to get into some of the effects of practice patterns as they related to eligibility for the trial and how that has affected enrollment. To begin with, it's important to consider that most patients with CTCL are regarded as having rather early stage disease or late stage disease. Early stage disease encompasses Clinical Stage IA to IIA and these are patients who have exclusively patch

and plaque disease. Late stage disease is patients with Clinical Stage IIB. These are patients with cutaneous tumors all the way through and including Stage IVB which denotes extracutaneous visceral involvement.

Now it's clear that for early stage disease the standard of care involves the use of topical therapies either individually or in combination. I've listed some of those here in the left lower portion of the slide: topical Nitrogen mustard, BCNU, bexarotene gel, ultraviolet light, electron-beam therapy and also extracorporeal photophoresis. These are the therapies that are commonly used in patients with early stage CTCL.

It's not until patients begin to become refractory to these therapies either individually or in combination that the role of systemic therapies begins to assume greater importance in the management of this disease. So patients who become refractory to these topical therapies with early stage disease or patients who present with later stage disease are much more likely to be treated with agents like oral bexarotene,

interferon, ONTAK, oral methrotrexate, combination chemotherapy and purine analogues such as deoxycoformycin.

Now as I indicated earlier, patients with Stage IV disease are ineligible for L4389-11. And only patients with Stage I to Stage III disease can enroll and only patients who are CD25 positive can enroll. Taking all of these issues into consideration, it's apparent that patients with early stage disease are not going to be considered or have not been considered good candidates for this study because these are patients for whom topical therapies are considered the standard of care.

Contrary-wise, patients who are refractory to these topical therapies or present with late stage disease are often considered ineligible for the trial because by the time they present for enrollment, they will have received more than the maximum number of prior therapies required by the study.

We've observed the impact of the placebo arm in a number of different context that have involved patients, investigators and one example even opposition

to the study on the part of a governmental agency. Patients will often decline participation in the study because they often present with their primary disease and with recurrences with severe pruritus or ulcerations which have a debilitating effect upon their quality of life. Severe pruritus occurs in excess of 75 percent of patients with this disease.

I might add that systemic and/or topical steroids which are often used to manage the pruritus in CTCL are exclusionary in terms of eligibility for this trial. Also patients who have ulcerations, the ulcerations frequently serve as a portal for systemic infection which is a serious cause of morbidity and mortality in these patients.

Investigators are reluctant to consider a placebo control in this situation particularly insofar as patients may remain on placebo for up to eight cycles or until there's clearly demonstrable progressive disease. That's especially true for late stage patients where spontaneous remissions in this disease have not been known to occur.

Finally efforts in the year 2000 to involve

six study sites in France were rebuffed by the Ministry of Health when a clinical trials application was submitted and sought for in the conduct of the trial in that country. The French Ministry of Health declined the clinical trial application citing the March 2000 revised Declaration of Helsinki as the basis for declining the study.

So in summary, Study L4389-11 has been enlarged from 120 to 195 patients in order to encourage patient enrollment while maintaining the original size of the placebo group. It is a multicenter, international study that has been expanded to involve a total of 28 study sites in Europe, North America and Australia. We estimate that between 1.5 and 2 patients per site per year will achieve the goal of completion by 2006. Finally, I would just like to reiterate that we are on target for submission of a final study report for this clinical trial in early 2006. I appreciate your attention.

CHAIR PRZEPIORKA: Thank you, Dr. Bray. If you could keep your place at the podium for discussion. I would like the new members of the division who have

joined us at the table to introduce themselves please.

DR. MILLS: George Mills, FDA.

DR. SCHECHTER: Genevieve Schechter, FDA.

DR. KEEGAN: Patricia Keegan, FDA.

DR. WEISS: Karen Weiss, Center for Biologics (CBER), FDA.

CHAIR PRZEPIORKA: And Dr. Mills, do you have any comments on the presentation or specific instructions for the committee.

DR. MILLS: I defer my comments. Dr. Schechter or Dr. Keegan, do you want to go forth?

DR. KEEGAN: Our comments are really limited to the fact that this is a little different from some of the discussions this morning in that the trial that was going to be the confirmatory trial was underway prior to approval. What it really ran into was a lot of stumbling blocks in terms of continuing to accrue patients in that study. We see that as really a major problem in terms of completing this and getting full approval for this product.

CHAIR PRZEPIORKA: Dr. Fleming.

DR. FLEMING: Patricia, that does lead

right into at least what I see one of the key issues. I don't think we saw this as a slide but in our briefing documents on page 10, figure 3, it gives specific information on enrollment.

The good news is we are halfway there in total enrollment if in fact it's good news. It took us three years to do so. The other good news is we were underway before the accelerated approval. The bad news is if I understand this it looks like the enrollment over the last three years has been nine, seven and nine respectively. There is this recent accrual that has occurred in the last few months.

The first issue is if the extrapolation of what we've seen in three years to the future is a relevant extrapolation, it's not three years. It might be more like eight to ten years before we would finish this. That's the main issue but the second issue is it's been very apparent that this slow enrollment has been in place for quite some time. It would suggest to me that it's not an easy thing to fix or we would have already fixed it.

DR. KEEGAN: We've had two attempts to fix

it. There were so many patients already accrued at the time that we were reviewing this for accelerated approval. So there was the perception that we had good accrual rates that the sponsors themselves suspended the trial while we discussed ways to modify it to actually increase the accrual rates. There was a period of time where the accrual was suspended.

The perception was that if there were fewer patients randomized to placebo that it would fix the problem. Clearly that's not occurred. So the sponsors now made additional efforts to go outside the U.S. to seek additional sites. I'm not sure that we've had enough time under that process to know if that will address the issue or not.

CHAIR PRZEPIORKA: Dr. Redman.

DR. REDMAN: Just out of curiosity, what was the time period that those 70 some odd patients were accrued prior to the approval?

DR. L'ITALIEN: The time period was approximately three to four years. It was about 14 patients per year.

CHAIR PRZEPIORKA: Dr. Kelsen.

DR. KELSEN: This might apply to other trials that are accruing slowly so first it's a question for information I don't know. Is there a plausible biological reason why three prior regimens for topical therapy - I assume that's a part of a prior treatment - would in light of the knowledge that you have today if you have any new knowledge bar patients from entering the study? In other words, is there a reason to think that if they got UV or something else that it would make the drug that you are testing work less well? If it would then obviously that's the reason.

DR. L'ITALIEN: Sure. Yes, I have Dr. Francine Foss who is an expert in the treatment of CTCL here with us today. I would like to have her address this question.

DR. FOSS: That's a very important point and that's in my opinion one of the major issues that's forestalled accrual in this study. One of the issues is that when we actually started this study we didn't have available two agents that we have now that are in very common use in this patient population, mainly the

topical bexarotene gel as well as the oral bexarotene.

If you look at the way this disease is managed primarily early on in the course of the dermatologist's office, many of these patients get a succession of topical therapies and then perhaps oral therapies. Many of these patients don't even come to see the oncologist until they've already had multiple topical therapies as well as oral Targretin and in some cases oral methotrexate as well.

If you look at all of the literature out there and you exclude the IA patients which are the patients that present with less than 10 percent of their body surface area involved with patch or plaque stage disease and if you look at stage IB and above, historically that group of patients has not been a group of patients that's been cured using any of these topical modalities.

If you look back at some of the earlier literature where ostensibly there were patients who were cured with topical therapies, in fact almost all of those patients with topical nitrogen mustard and electron beam therapy had stage IA disease. Because of

the histopathologic confirmation of the disease was not in place in those studies and certainly it would be difficult to retrospectively go back and address that issue, in fact many of those patients may not have had mycosis fungoids.

If you look at studies that were done recently both at Stanford and at UCSF by Dr. Zackheim and Dr. Kim, there are 35 to 40 retrospective analyses, case control studies looking at patients with mycosis fungoids matched to normal population based on age and sex. You can see that patients who had stage IB or greater disease had a disease that impacted their survival. In other words, they had incurable disease. That's irrespective of treatment. Again most of these patients get multiple topical therapies before they move on to systemic.

In terms of thinking about the impact of therapy on this disease once you are stage IB, you have a disease that's going to impact your survival. You have a disease that's incurable. Most of these patients will go on and receive multiple topical therapies before they even get to a systemic therapy.

In fact if you look at the pivotal trial for ONTAK, the median number of therapies was between five and six. Similarly for the Targretin study as well. That's the group of patients that going to present to us in the oncology community for systemic therapy.

I personally don't believe and I don't think there's anything in the literature to suggest that topical therapy by itself is going to make any significant impact on the disease. Nor is there any suggestion that numbers of topical therapies versus a single topical therapy is going to make an impact.

I would strongly be in favor of basically not putting any limit on the number of topical therapies that a patient could receive but focusing more on number of systemic therapies if we want to select a group of patients that's earlier on in the course of the disease that's not beaten up by having received two or three courses of multi-agent chemotherapy.

DR. L'ITALIEN: Thank you, Dr. Foss.

DR. KELSEN: Can I follow up on that then?

CHAIR PRZEPIORKA: Sure.

DR. KELSEN: So my broader question which is being addressed to the agency was that when there are trials that are slow accruing in relatively small populations, there may be a point in which new knowledge or re-appreciation of knowledge that was available before would allow you to change eligibility criteria. It's clearly a tricky issue because you don't want to change the rules in mid-game too much. I'm struck by the fact that we're seeing this now a third time today that we might approach the issue of changing not crucial parts of a Phase IV study in order to get to the essence of whatever we want to get. If it's accrual that's a problem because of a technicality that's not as important as we thought, we ought to address that.

DR. L'ITALIEN: Right. One of the things that we need to consider today is that we have made great strides recently in enrolling new sites. These sites are just starting to manifest themselves by showing patients into the studies. The fact that we have seven patients in the first two months of this

year is already a reflection of the work we did in the last year to bring new sites on board especially in Europe and we're adding another six sites I believe this first quarter

We're certainly open to consideration of the number of prior therapies as a means of potentially increasing enrollment but we really first want to take a look and see what actually may be happening with the current sites and their enrollment. Then from there, certainly consider this as an option to discuss further with the agency.

CHAIR PRZEPIORKA: I have a question. Although the majority of the patients will be CD25 positive, is there any pre-clinical information to suggest that the CD122 positive patients should not also be participating in this study?

DR. L'ITALIEN: We actually do have a companion trial and perhaps, Dr. Bray, would you like to address this topic specifically?

DR. BRAY: All of the preapproval clinical data that is the basis for the accelerated approval is based upon patients who expressed CD25 on the surface

of at least 20 percent of their tumor cells. This was determined by an immunohistochemical assay. There was some earlier clinical work looking at antibodies CD122 as the basis for determination of eligibility. This is basically not including the studies that I have discussed.

There were a number of reasons why CD25 was chosen as the screening methodology. The antibodies were much more readily available. There was a good assay methodology in terms of evaluating patients for eligibility. That was one of the reasons why. Francine, do you have other insights?

DR. FOSS: When we did the Phase I study, the dose escalation study, we treated patients with Hodgkins, non-Hodgkins and cutaneous T-cell lymphoma. In that study, we did immunohistochemistry for both the alpha and beta components of the receptor. At that point, we really didn't have the antibody for the gamma chain.

When we went back retrospectively and did a correlation between the expression of the receptor isoform in clinical response, we really did not see a

strong correlation in that not all of the patients who expressed the High affinity form of the receptor namely at that point, alpha/beta responded at about 40 percent. There were patients who expressed only the beta component without alpha.

I can specifically remember two out of a denominator of 12 of those patients responded. Likewise, there were patients who expressed CD25 without expression of the beta component who also responded across the different histologies. That suggests that immunohistochemistry at least the way were doing it at that time for that study was not strongly predictive of who was going to respond.

Subsequent to that in my laboratory, we are doing a retrospective analysis, a PCR-based analysis, of those same specimens and all of the 73 CTCL patients that were treated on the pivotal trial. We're looking specifically to see if we can correlate the expression of the receptor isoform with response. I can't give you the exact data yet because we haven't done all the correlations but I can tell you that many of those skin biopsies from the CTCL patients in fact do express the

beta component of the receptor.

I don't the answer in terms of who is going to respond here is going to lie solely in the expression of the receptor isoform. Hopefully in the future if we do microarrays and other kinds of analyses, we may be able to predict better who is going to respond and certainly there are other factors with respect to how we deliver this drug. On the surface of it, we really don't have any good data to suggest that immunohistochemistry by itself is going to be a strong predictor of response.

DR. L'ITALIEN: Thank you.

CHAIR PRZEPIORKA: Dr. Cheson.

DR. CHESON: Although you're adding these additional sites, part of the problem is your old sites. You barely have a patient a year per site at these other institutions. Some of the sites you are projecting are in Russia and elsewhere. Do you have some idea of their track record in (a) participating in clinical trials and (b) in CTCL trials?

DR. L'ITALIEN: Yes, I'll ask Dr. Bray to address that specific question.

DR. BRAY: Yes, there are five study sites, four in Moscow and one in St. Petersburg. They're all large medical institutions referral facilities, most manned by oncologists. At one of the centers there's an academically oriented dermatologist who is the investigator. These are centers that have had a track record for the conduct of multi-institutional clinical trials.

In my view, they have been determined to be pretty medically sophisticated. I met with all of them individually. We have at this point in time a lot of confidence that they will be able to enroll patients in the study. The perspective generally among investigators outside of the United States has been that they are interested in the trial because the product is not approved in their jurisdiction and it represents another therapeutic option for their patients that they don't have access to.

DR. CHESON: Which raises another issue. Since you are targeting mostly oncologists, shouldn't you be targeting mostly dermatologists?

DR. BRAY: That's an interesting question.

As Francine alluded to, the disease is really cared for in the very early stages by community-based dermatologists and some academically-based dermatologists. Some academically-based dermatologists that have access to infusion facilities will often times administer systemic therapies to these patients including ONTAK. They virtually never administer cytotoxic chemotherapy. But therapies like interferon for example and ONTAK have been and are used by academically-oriented dermatologists and by clinical oncologists.

If you look at the distribution of investigators in the study before 1999 and after 1999, it's about a 50-50 split in terms of the number of dermatologists and clinical oncologists who are represented in the clinical study group.

DR. CHESON: Because if you could target and at least educate the dermatology community about the trial, they perhaps wouldn't be putting patients on three, four, five or six topical approaches before they sent them and rendering them ineligible for the study.

DR. BRAY: That's a really good point.

There's one initiative that we've basically embarked upon in Canada where one of our investigators is located. He has asked us if we could provide some information about the study to a group of community-based dermatologists in his catchment area which we are planning to do in the interest of essentially of eventually trying to facilitate referrals. When and as those kinds of opportunities do present themselves, we seize upon them if we can.

DR. CHESON: Of course, in essence we have what appears to be an active drug here based on a 30 percent response rate in two separate trials that's limping along for a number of fairly obvious reasons. It's slowly getting there. I agree with my colleague's skepticism based on the decreasing rate of accrual except for the recent period of time. If we could educate these sorts of population early, then we could hopefully increase the accrual to what is an important study. Now going through the prospectus here on the initial Phase III trial, could you review the differences between the two dose levels, both toxicity and activity?

DR. L'ITALIEN: Dr. Bray.

DR. CHESON: Since a three arm trial with trivial numbers of patients available is a real challenge anyhow.

DR. BRAY: The Phase III dose comparison study evaluated nine versus 18 ug/kg/day on five consecutive days very much like the Phase IV post-approval commitment confirmatory trial. The overall rate of response for patients in the 9 ug/kg arm was 23 percent. For the 18 ug/kg arm, it was 36 percent. There was no statistically significant difference between those two treatment arms but there was a trend towards significance in a subgroup analysis for patients with advanced stage disease who received the higher dose. With patients with Stage IIB disease or higher, the response rate was 38 percent for patients who got 18 ug/kg/day and it was 10 percent for patients who got 8 ug/kg/day.

DR. CHESON: And toxicity.

DR. BRAY: Basically my memory tells me that the toxicity was comparable for both arms of the study. There was really no apparent difference in the

incidence of Grade 3 or Grade 4 toxicities between the two study arms.

DR. CHESON: Then why a three arm study if the activities trending towards better even if not significant and the toxicity appears to be no greater in which you'd already have the study pretty much done with a two arm trial?

DR. FOSS: I was actually involved in those discussions and there was initially a concern with these earlier stage patients that perhaps we wanted to expose them to less toxicity. There is a slight difference. There is slightly less toxicity at the nine dose but it's not statistically significant and given the number of patients treated on that Phase III trial was small.

There was still a concern because there was no dose response relationship with this drug. There was a certain again to try to demonstrate in fact if there is no dose response relationship one could certainly use less drug and to just confirm the fact that the toxicity is the same in a larger group of patients. There you might see less toxicity. Those

were the discussions that I could recall. Pat, do you have anything to add?

DR. KEEGAN: One thing to remember is this study started a fairly long time ago in 1993 or 1994. At that time, the impression was that there wasn't much of a dose response relationship at the upper doses. It was trying to further explore whether that was a real conclusion or were there differences that were important to know.

Since I have the mike, I would just like to add another comment about the inclusion criteria. We haven't had a lot of discussion about modification of the inclusion criteria predominantly because as the company has said, they wanted to see how opening additional sites would enhance accrual. We open to loosening to some extent the inclusion criteria but we have to be careful about how loose it is because we still want to maintain a protocol that will accrue to a placebo control trial. There's a limit as to how far you can go.

We feel the placebo group is very important for some reasons that came out during the original

review. One of the toxicities of concern was infectious toxicities as a direct mechanism of attack of normal CD25 expressing T-cells and whether there was some risk in terms of infection that we would only be able to capture in a placebo control trial because of the high background rate. It's very important that we try and figure out a way to increase the accrual rate while still preserving accrual into a trial that really ought to be placebo controlled if we want to get an answer to that question.

DR. L'ITALIEN: I would like to emphasize further that of the 22 sites that we listed in 2002 approximately 10 or 12 of those occurred in the second half of the year. What we are seeing now within the last six to nine months is we've now accumulated these seven patients which we've incrued in the first two months of this year.

DR. CHESON: For how many sites?

DR. L'ITALIEN: That has been from the total of 22 sites.

DR. CHESON: How many patients from how many sites? Seven sites.

DR. L'ITALIEN: It's pretty much about one per site.

DR. BRAY: One patient was enrolled in Melbourne, Australia. Two in the U.K. Two in Germany. Two in Warsaw, Poland.

CHAIR PRZEPIORKA: Dr. George.

DR. GEORGE: I had a couple of things. One is something we haven't discussed up to now and I would like to hear a little bit about it. The primary endpoint of objective response rate in this particular disease seems to me to be somewhat difficult but maybe you can tell me otherwise. Has the definition and/or the determination or process for the determination of response in any way changed from the accelerated approval time to the current study? I'm particularly worried about the PRs and things being thrown into the objective.

DR. BRAY: The response criteria are virtually identical in comparing the Phase III pivotal dose comparison study and the Phase IV confirmatory trial. Partial response requires at least a 50 percent reduction in overall tumor burden. Clinical complete

response requires elimination of all clinical evidence of disease. Complete response basically equates with elimination of all evidence of disease with a documented biopsy of no abnormal cells. Those are the criteria that were used that have been used virtually adulterated in the studies that have been done pre and post approval.

DR. GEORGE: And you have a mechanism for verifying this.

DR. BRAY: For patients who have more than 10 percent body surface area involvement, there is a weighted severity index tool that is used that essentially weights the degree of disease severity for a tumor patch and plaque disease. For patients with less than 10 percent of body surface area involvement, we use basically five measurable lesions as index lesions in order to assess response. There's an independent data endpoint review committee that evaluates all of the results in a blinded fashion in order to confirm the validity of the responses.

DR. GEORGE: One other thing I'd want to ask about is a follow-up of Dr. Cheson's issue

concerning the logic of what we're doing here. Accelerated approval was based on an observed objection response rate of around one-third of the patients if you combine the two studies. This design was apparently set up and there's a real question about whether it should have been a three arm study because even the proposed analysis isn't really looking at dose response.

It has an interesting logic that you'd have to follow. It says first you do an overall test to see if there's any difference amongst the treatment. Then you start doing these contrasts. In other words, you compare the 9 ug to the placebo and you compare the 18. Then you compare 9 plus the 18 to the placebo. It's left unstated what happens hypothetically if you find the 9 is better than placebo and not the 18 but when you combine them maybe they are or maybe they're not.

You get into conundrums here and again this is retrospective but perhaps this would have been better done as a two arm study. I gather that the reason it's as small as it is in the design is because it must have been based on assuming that the placebo

response rate would essentially be zero or very low.

DR. BRAY: I know the answer. So the study is powered to didact a difference in response rate of 10 percent in the placebo arm versus 30 percent in best response rate in either of the active treatments.

DR. GEORGE: And you really don't expect much response in the placebo but as Pat brought out a key would be still you're worried about toxicity. So there is the safety issue. Just the way this flows, the logic is a little fractured to me. That's just a comment. I would have preferred a two arm study and made it cleaner.

DR. L'ITALIEN: I think we have to bear in mind that this study was initiated in 1995. There were certain objectives that were present when the study was initially starting to look at whether we did have a minimum effective dose to try to establish that which is why we had two arms. At the time of approval, we had 73 patients who had already accrued into the study. We felt that in spite of perhaps the flaws that you might have highlighted it still was perhaps our best chance at getting a rapid confirmatory trial. We need

to bear this in mind. We're looking at this now. It is often easy to go back and take a look and observe the flaws in the previous design.

DR. BRAY: One other important comment is that when this trial was initiated the results of the Phase III pivotal study were not known. In fact that Phase III pivotal trial wasn't concluded until the latter part of 1997. This study was already well underway for a two year period of time by the time in fact that the overall response rate of 30 percent in the placebo study was appreciated.

CHAIR PRZEPIORKA: Mr. Ohye.

MR. OHYE: Earlier we had a discussion of good news/bad news. I would like to emphasize that I find a lot of good news here. We see that the sponsor is getting a lot of instructive information from a hypocritical review. They have been extremely diligent in terms of trying to fulfill the Phase IV commitment. The good news is that we have a drug for an orphan product out there already and it's been accelerated approved I'd like to point out under the rule that requires that adequate and well controlled studies be

conducted that provide a likely benefit of the clinical benefit. I think I have that wrong but I think you all know what I mean.

When you are dealing with an orphan indication where you have probably less than 100 patients per month presented, they are doing their very best and they should be commended for trying to ramp up this study that was started way back in 1995 and the study they inherited from a previous sponsor.

CHAIR PRZEPIORKA: I have a question for Dr. Foss. Has there been a problem accruing patients to this protocol because of the placebo arm?

DR. FOSS: Yes.

CHAIR PRZEPIORKA: How would you address getting rid of that placebo arm?

DR. FOSS: I'm glad you asked that question because this study was opened at my institution and I enrolled a significant number of patients on it. But once ONTAK was approved, it was very difficult to convince patients to go into this study. One major issue even before ONTAK was approved is that patients are required to stay on the placebo arm of this study

until they have a documented progression. So we have to be able to document 25 percent or greater increase in their overall tumor burden.

At the same time, many of the patients actually were clinically not better. In fact their disease was progressing as marked by their systemic symptoms such as pruritus and other systemic manifestations. Yet we had to continue to treat this patients at the time obviously not knowing that they were on the placebo arm but we could not take them off the study because they didn't meet those criteria. To expect a patient to stay on a placebo arm where they are not clearly obtaining benefit for eight cycles is a lot to ask for these patients because again they are all symptomatic when they come into the study or we wouldn't be treating them.

In order to look at this issue critically in terms of why sites in the U.S. can't get patients on this study or unwilling to reopen the study, the major issues are the prior therapy as I mentioned before because everybody gets Targretin now. The other issue is if we could do something to change the placebo arm

not to eliminate it but perhaps to allow patients to roll off of the placebo arm if they have systematic worsening.

In terms of thinking about documenting that, in the Phase III trial, we used a pruritus score and a quality of life tool. Perhaps if we used those same tools in this study, we could allow an early exit for patients who clearly weren't improving.

CHAIR PRZEPIORKA: Yes.

DR. WEISS: I just also want to clarify with the sponsor. Because you are looking at having a question about using some kind of subjective outcomes, what are the unblinding effects of the product? Will people know and will that somehow influence perhaps the attempt to exit early from one arm of the trial?

DR. BRAY: I'm sorry. Could you please repeat your question because I only heard part of it.

DR. WEISS: It's just a question about the unblinding types of effects from administration of ONTAK.

DR. BRAY: When patients meet the definition of progressive disease as defined by Dr.

Foss or if they have stable disease after eight cycles of study drug, then there is the option for the investigator to request that we unblind the patient. If the patient when unblinded is found to have been randomized to placebo, they are then offered the option to enroll in a companion study that is an open label study that offers treatment to these patients at the 18 ug/kg/dose level.

I might also add that this study has as a secondary objective also an effort to identify a point estimate of response for patients with CD25 negative disease. It's basically an effort to have a one-stop shop for patients so that patients will commit to the screening process, undergo the biopsies knowing that if they have CD25 negative disease they have the option of presenting in another study. I don't know if that answers your question.

DR. WEISS: That's helpful but there's another half. Basically we have a placebo control trial but whether or not there are unblinding effects, infusional reactions and other kinds of things for administration of the product. There's a question on

the table about maybe people could withdraw early and that might help the acceptance of a placebo arm in the trial.

DR. BRAY: Now I understand. Many patients do experience infusion related constitutional symptoms with this product. It's important to emphasize that investigators cannot request that a patient be unblinded until they meet the objective definition of progressive disease. The reality is that there are certain infusion related constitutional symptoms and some hypersensitivity manifestations that might have the effect that you described.

CHAIR PRZEPIORKA: Dr. Fleming.

DR. FLEMING: I'd just like to return again to this issue of enrollment and where we are. I'm not really second guessing the original formulation of the trial that in fact looked like it was reasonably enrolling until such time as the accelerated approval occurred and then I have no question that the existence of placebo which was part of the trial before but no longer a requirement because patients could not get access to the agent without joining the trial has

negatively influenced the enrollment. I'm just trying to get a sense of whether there is the sense of urgency here that I uniformly witness from industry sponsors when we're in a preapproval mode.

We had in the year 1999 the hold that was referred to. Interestingly it was a hold to try to look at how we would increase enrollment rates. It's not exactly clear why we had to have a hold for that. Nevertheless there was a hold. Then in the year 2000 when there were just nine participants enrolled if this had been a premarketing study in my experience, sponsors would have been with the sense of urgency all over doing something immediately radical because at that level we would be 10 years away from finishing the enrollment. Nothing changed.

Then the next year when we again saw that same level of enrollment, then we doubled the number of sites although that was in the year 2000. We doubled the number of sites in 2001. But by 2002 we still hadn't increased the enrollment. Now what we are hearing is there have been further increases. There is more representation from Europe. What is the threshold

here? What's the target? What's the acceptable level?

We heard that there were seven enrolled in the first quarter of this year. If we maintain that, we will barely be at a level where we could finish this enrollment in another three plus years. What if we don't maintain it? What is the strategy here? What is the sense of urgency? What is an acceptable minimum to be achieved?

Then part of this question leads me back to what Drs. Cheson and George were saying earlier which brings us back to surely I would love to have information on the dose levels against control in an ideal world. If we stopped enrollment at this point to the nine dose level, we could reduce by 36 the number that would have to be enrolled. We would still have important clues about nine against placebo. We would obtain information about the 18 against placebo in at least one year less and at the current rate of enrollment maybe three years less. I keep coming back. Do we have a sense of urgency here that we would have if this were premarketing and do we have what is a minimum threshold here but we have to achieve to

continue the process?

DR. L'ITALIEN: I would start the response to this question by saying unequivocally we do have a sense of urgency to try to complete this trial. In the year 2000 as was presented in the briefing document and as Dr. Bray mentioned in his response, we did try to initiate six additional sites in France and had initial encouragement because those received local IRB approval which was subsequently reversed at the national agency level.

It's worth noting here that this is something because we are trying to recruit high quality sites that there is a significant investment in time in identifying and recruiting sites. Typically it takes about a year in advance for this to happen before you can actually bring a site on-line.

If you take a look at the attempts that were made in the year 2000 to bring on the six additional French sites, those were denied. We then sought to bring on additional sites. In the block diagram that we presented in the briefing document, you will note that we talk about active sites. The key

here is that while certain sites were also being brought on-line in 2001, there were other sites that were actually disengaging from the study because they were having a difficult time accruing into it. As a result of that, actually two U.S. sites dropped in that particular year.

In the second half of 2002, we had made substantial progress in bringing new sites on-line. Our expectation is and it was alluded to by several other committee members throughout the course of discussion today that you actually have to initiate the sites and we're going into sites that are purported to have a high number of CTCL patients. We then have to look at our accrual rates and then adjust. We'll add more sites if we need to.

At this point though, Dr. Fleming, it's worth noting that we can't really drop one of the active treatment arms for ethical considerations. At the current time given the overall randomization target of one to two to two, one being placebo, two being low dose and two being high dose relative ratio, we're actually enrolling at a ratio of about one placebo to

seven active treatment. 3.5:3.5 is the actual ratio to come up with the overall number.

Currently a patient enrolling has a seven in eight chance of getting active and a one in eight chance of getting placebo. This is what has been approved by the local IRBs. It is certainly our opinion it would be very difficult to go back now and retrench and ask them to go to a one to four randomization. We just don't think they would find that to be acceptable even in geographies where the drug is not available.

We have certainly thought through a number of the points that you have raised. We are making a very strong effort to accrue new sites. The other thing that's happened from this introspection about the study in the recent dialogue we've had with both the agency and amongst ourselves is that there may be some opportunities that have been discussed today to look at ways we could do further enrollment if our rates of accrual do not meet our expectation for completion of the study as outlined.

CHAIR PRZEPIORKA: Dr. Kelsen.

DR. KELSEN: I wonder if this discussion doesn't touch on the issue of a qualitative difference between a pivotal Phase III trial leading to approval and a post-marketing study. As I listen to this discussion, I'm struck that if this was a Phase III presentation and you brought it to the committee and said we changed eligibility requirements and the randomization design and added a number of centers, we would be wondering why we were be asking to look at that.

This is a Phase IV study. We touched on this a little bit earlier. I wonder if it doesn't apply to many Phase IV studies. There's one central point you're trying to get. You want to show that some crucial factor was true in your study that led to accelerated approval. Many of these other factors while desirable are less important. Some of that doesn't come out until the study is underway.

When I was listening to the discussion this morning, we talked about holding the Phase IV trial to the same standards as Phase III. I don't hear that this afternoon. I don't know how the agency feels

about that but it seems to me that it's reasonable to look at a Phase IV study in a bit of a different way than looking at it as a pivotal Phase III trial leading to full approval. But I understand that might be a controversial point.

DR. L'ITALIEN: As Drs. Foss and Bray have pointed out, there has been a certain evolution in the standard of care. There have been new topical therapies approved. Certainly at the time of the original study design, this wasn't contemplated because those other products weren't available. What we've talked about in terms of a redefinition of prior therapies is really an outcome of the evolution of topical therapies and also how this product is being positioned today by oncologists who are treating patients with ONTAK.

CHAIR PRZEPIORKA: Dr. Pelusi.

DR. PELUSI: With all respect and not sounding like having a major ethical issue here, we're going to see a same issue in terms of there are going to some countries that have already approved certain other drugs that are going to be here in this country

that other things are available. When we begin to look at that placebo arm and where we can really do the accrual for that arm or make it more conductive for people joining, the question becomes is there any thoughts in terms of the agency on looking at those placebo arms being definitely arms done in other countries. Again trying to be fair to everybody and looking at randomization but I think you can see where I'm coming from. If this patient issues continues to come up whether it's here or in France or perhaps they have that and we don't, can that be built into a trial?

DR. KEEGAN: Remember that the first 73 patients that were accrued on the study were accrued in the United States.

DR. L'ITALIEN: Yes, they were.

DR. KEEGAN: So it was not considered an unreasonable approach. The patient population was selected as those with symptomatic therapy might be a reasonable group in which another treatment could be delayed so that we could evaluate this with the opportunity to go on.

One other issue that I might remind the

committee of was at the time that we brought this product to the ODAC for the original discussion of accelerated approval and discussion of additional studies came up, they were aware of this trial that was on-going. There were also discussions of other trials that might be undertaken in more advanced disease and specifically in comparison to interferon or other products.

The sponsor has not come in with those sorts of proposals but I would like to hear some discussion if people believe that this trial is not going to be able to accrue and too much modification of the trial will make it unusable for terms of interpretation of the results of the trial. We were concerned when we made the modification to the randomization scheme and made it more unbalanced how that might affect looking at the results. There's a little trepidation there.

There is a thought that maybe there may come a time when there is so modification to the trial that it is no longer an adequate and well conducted trial. Could I hear some discussion from the committee

about starting afresh with a new trial?

DR. CHESON: Clearly what they are doing to increase accrual has to be the first step. That's increasing the number of centers that can provide high quality data hopefully and maybe targeting and educating the dermatology community. If that doesn't work then everybody needs to have another look at this study.

DR. L'ITALIEN: Certainly our intent is move forward with the current design. We are taking that very seriously to move forward and try to enroll sites and to go globally in the search for those sites to try to attract appropriate patients so that we won't have any major modification of the current study design. That has to be our first approach. That's what we are pursuing vigorously.

CHAIR PRZEPIORKA: Just to address your question about whether or not you'll end up with an interpretable study at the end. Because of the imbalance between the numbers to the placebo arm and the active arms if we don't keep the exclusion criteria over the vast majority of the arms, you're right.

Unfortunately the way it would pan out if change the inclusion criteria to include patients with more topical therapy or patients who receive 25 negative, you're going to be put disfavor in the treatment arms. Clearly if you still ended up with a significant difference, this drug could look actually pretty good rather than pretty bad. Dr. Brawley.

DR. BRAWLEY: I'm stepping back here and thinking about what we heard this morning and what we heard this afternoon. I'm not at all being critical of Ligand's efforts or Johnson & Johnson's efforts to accrue patients. I may even be sounding a little bit like the advocates here but I'm starting to worry about the ethics of the time it takes to get these answers. We just heard 10 to 12 years on this trial.

One of the ethical issues that I often worry about is some poor patient going on to a trial wasting his or her efforts in that trial trying to be a good patient in the trial and then we learn absolutely nothing from it. That's an insult to the patient.

One of the great problems here is that accelerated approval which was brought with the idea of

trying to get these drugs to patients earlier actually is competing with the clinical trials that ultimately help us figure out if these drugs actually do work. God help us if we approve one of these drugs and then actually perhaps by going to Russia or someplace else do the trial and do the trial well and find out that this drug actually hurts people. We actually have had drugs approved in the past that we ultimately found out had a net harm versus a net benefit.

We need to step back and look at this accelerated approval process. There is a point that was made earlier that once a company can make money - and I'm not criticizing Ligand or anybody else who's here - once the drug is available in accelerated approval and as Ms. Napoli noted most patients and I note I suspect most doctors don't realize the difference between accelerated approval and routine approval. Once a company can make money off of it talking about a conflict of interest, you can sell here or you can put someone into a trial where you have to supply the drug. You talk about a conflict of interest. We need to look very cautious at this.

DR. CHESON: Another problem with the system which should have been blatantly apparent to those who created it is the system itself can kill the drugs. You can have a drug approved by this mechanism, the accelerated approval, and because everybody is so happy to get it out there, no one goes on the clinical trials, the trials don't get done and therefore the drug gets yanked from the market even though it was an active drug because it was approved as some of them have been on some very skimpy data. At some point, the agency really needs to look at this accelerated approval and see if it has the potential to do more harm than good.

CHAIR PRZEPIORKA: Actually if I recall, Ms. Pendergest saying that the rule says "may" not "will" or "shall." So they've actually thought about that very carefully and I'm pleased to see that. Dr. Cheson, you're the discussant for this BLA. I just wanted to know if you could sum up your responses to the questions that have been posed for us.

DR. CHESON: I thought I was doing that before but I'll do it again. What we've heard is we

have a drug which is potentially valuable to a select group of patients with an uncommon disorder that appears to have benefit in about one-third of these patients. The Phase IV trial is having trouble accruing for a number of fairly valid reasons.

What we've heard is that virtually everybody would like the integrity of the study to be maintained for as long as possible and accrual accelerated hopefully by enhancing the number of sites which are hopefully high quality sites. If it comes to the point of having to modify eligibility criteria or any other factors, then we may have to reconsider what we do with the study but right now that has generated some interesting discussions about the process as a whole.

Even though it's going to be a ten year trial, hopefully it will get done. We have some encouraging news that there is a little blip on the accrual screen in the last few months. Hopefully that will be maintained. I don't know what else has been said.

CHAIR PRZEPIORKA: Dr. Redman may actually

answer that question.

DR. REDMAN: I don't know if I'm going to answer that question but I want to ask a question that has nothing to do with Ligand or anything. We are all dancing around the issue saying that because a drug is approved, everybody is getting the drug off trial and nobody is participating in the trial. In the year 2002 when seven patients were accrued to the trial, how much of the drug was sold commercially?

DR. L'ITALIEN: We did actually present that earlier. We estimate about approximately 400 patients were treated with ONTAK in CTCL.

CHAIR PRZEPIORKA: Dr. Blayney.

DR. BLAYNEY: I have three points but the last point I was going to make goes right to this issue. Having the ability to enroll patients on a trial does provide alternative access for patients who either can't afford the co-payment or can't afford these drugs so there is a mechanism for patients to get the active drug. I would encourage the trial to continue before Pat says to shut it down and rethink the design. So there is rationale even when the drug

can be obtained by prescription for this company to support this trial and for us as physicians enroll, support or refer to it.

Second point I would like to make is that the endpoint here is not survival but is objective and verifiable response and now the crossover problem which we discussed earlier. As Dr. Foss says taking patients allowing them to go off study earlier than completing the eight treatment may be a way to modify the endpoint which may overcome some of the reticence of study centers to be involved in placebo control.

Thirdly this is a rare disease that's usually managed. The patients I see have had a wide variety of topical creams and topical manipulations by the dermatologists. Perhaps opening up the inclusion criteria and perhaps not counting any of those topical therapies may be a way to get this thing rolling and getting an answer sooner. Thank you.

CHAIR PRZEPIORKA: Dr. Fleming.

DR. FLEMING: Just a few issues. Dr. Przepiorka, you had brought back the issue of the "will" versus the "may." The original terminology that

we were presented in the documentation coming into this meeting used the word "will." We've heard clarifications to "may."

In my own view, I don't know that's a profound change in the sense that I would surely hope and I believe the "may" terminology empowers the FDA to use its proper judgment as I would hope they generally be doing to safeguard the interest of the public and participants in trials. From my view, we are still in the same basic position that we would be whether we use the word "may" or "will." We have to look at whether or not we're doing studies in an adequately timely way that will provide answers to the questions ultimately as to whether this intervention provides clinical benefit.

When it comes to the issue of is there a way to streamline this trial to enhance the ability to get the answer in a timely way, we surely do want to think about whatever changes that we make in the context of whether it would reduce the interpretability. Just changing the randomization fraction does not in fact compromise the integrity of

the trial. You would though have to do a time stratification.

To put it simply if you started with the one-to-one randomization, then went to a three-to-one randomization, you can't pool the data. But you can pool the information stratified by the time periods when it was one-to-one and three-to-one and it becomes fully interpretable.

The issue against this which has also been stated is there may also be ethical issues against reducing this now to a two arm trial because it changes what fraction of the randomized participants would be on the placebo. If that's true, we have to revisit this ethics very delicately.

In general for study to be ethical, there has to be adequate equipoise to justify that a participant going into this trial is being randomized to two interventions where it's substantially uncertain whether benefit to risk of the experimental is better than the control. If one judges that's true and judges that it's ethical within the context of a five-to-one or three-to-one randomization, it's very difficult for

me to understand how ethical arguments would then reverse to say if it's now two-to-one or one-to-one it's no longer ethical.

There are practical considerations as to how rapidly we can enroll participants. A two-to-one or a four-to-one may give us an enhanced understanding about the safety profile of the experimental regimen. Bottomline here is it does seem to me that the FDA and the sponsor need to be thinking through all possible with all due urgency.

What are the most achievable ways for us to get the answers reliably addressing efficacy in a reasonably timely manner? One of those ways that I would at least encourage you to continue to think about is whether the randomization to the two arms could substantially reduce the time. We would still have information on that third arm during the time period up until now and it would allow us a much shorter timeframe to finish the study.

CHAIR PRZEPIORKA: Dr. Brawley.

DR. BRAWLEY: I was just wondering. I'm not sure that you can have equipoise in a drug that's

been approved, even approved through an accelerated mechanism such that you could have a placebo control trial in Phase IV. That worries me. That may be why the French decided not to get involved in this trial.

DR. FLEMING: It worried me in the very beginning, ten years ago, when the concept of accelerated approval was proposed. It was argued that we would be able to carry out then subsequent pivotal studies post-marketing to obtain the answer. I worried about that but I'm assuming anyone that in fact supports the concept of accelerated approval would say that there is the fine line here by saying reasonably to predict benefit isn't by any means reliably predicting benefit. Hence while it's reasonably likely hence justifying wider access during the time period that you are validating there is still substantial uncertainty hence making it ethical to continue randomized trials. It seems to me the logical conclusion if you don't accept that then the logical conclusion is you're not in the position where you can in fact do proper studies post-accelerated approval to validate whether or not there is clinical benefit.

CHAIR PRZEPIORKA: Dr. George.

DR. GEORGE: There's the rub. Accelerated approval unless we're talking this rarified atmosphere we're talking here needs approval. That's really why it's difficult. There is a fundamental disconnect between thinking about how we can do these trials after we've had the accelerated approval because I think maybe Dr. Cheson said this that it has the seeds of killing itself, apoptosis.

DR. CHESON: We call that pharmapoptosis.

CHAIR PRZEPIORKA: Dr. Martino.

DR. MARTINO: Part of the problem here is the actual word "accelerated." To most of us who don't sit on committees like this, acceleration means that there's a really good reason why you are allowing me to do something. In fact that's such a good reason that you quickly allowed me to do it.

The actual psychological implication and understanding of the word to most people is that there's actually probably a better reason why you have allowed me to use this drug. Those of us who realize that no one really understands this conception are

actually quite correct. Approval means approval. You allowed me to get there even quicker with this process. It must be a better drug. That's the assumption that most of us make and that's the struggle we are having. It's that people take it that way and act on it from that perspective.

CHAIR PRZEPIORKA: Dr. Weiss, do you have a comment?

DR. WEISS: I know you probably discussed it some this morning but certainly it seems like in oncology - and we were in a similar scenario just about a month ago that Dr. Fleming will very well remember with a different disease setting where we were talking about doing the confirmatory trial in a somewhat different population where the feasibility perhaps of doing a placebo controlled trial may be more palatable.

That is somewhat of the situation here. Even though it's very similar you are talking about a somewhat different population than the approved indication for ONTAK currently. I'm just wondering if anybody had any comment on that particular aspect.

DR. FLEMING: That's a very good point,

Karen. I personally do struggle with this idea of saying we believe there is enough evidence that we in fact want to make it available to the public. Then we think it's ethical to randomize unless we are in a setting where we think reasonable people will differ as to what level of evidence they think you need to have to justify use of the intervention hence allowing certain people to say I want to use it, certain people to say I don't want to use and certain people to say I'm uncertain. If that is the real world's scenario then it is ethical. It is possible then to enroll participants into studies like this even while the intervention is made widely available. Clearly in that scenario, it doesn't matter whether it's one-to-one, three-to-one or five-to-one randomization. It's either equally ethical or equally unethical.

Karen, the situation you referred to was a situation a month ago where there was a perspective that further advanced patients would benefit but intermediate advanced patients it was unclear. Those intermediate advanced patients then may well be willing to accept equipoise and be randomized. That is a

practical way this could be done.

CHAIR PRZEPIORKA: Ms. Mayer.

MS. MAYER: I just want to echo Dr. Martino's comments about patient perceptions about what accelerated approval really means. Even as an educated advocate prior to some of my preparatory reading for this meeting and prior to reading the data on the individual drugs involved, my perception in fact has been that we were talking about drugs that show unusual promise. That's why they are made available prior to the completion of clinical studies. This is a widely held perception that is perpetuated by the media and it's something that needs to be factored in.

CHAIR PRZEPIORKA: Dr. Temple.

DR. TEMPLE: I don't know for analogies help. Surrogates have been widely used in other areas besides oncology like lower blood pressure and lower cholesterol. Nobody has felt it's an ethical difficulty to confirm that lowering cholesterol really is good for you. Probably hundreds of thousands of people have been randomized into a placebo control trials to see what populations that's true in. That

was also true of hypertension until it became obviously that there really was a benefit when it did indeed become unethical. As long as there's a reasonable question among honest people about whether there's a real benefit, I think the ethics are fairly straight forward. The public perception is another matter. They may not want to be in them. That's more difficult.

CHAIR PRZEPIORKA: I would agree with you in that here's a situation that would be applicable to the principles that Dr. Pazdur mentioned earlier which is maybe the Phase IV commitment trials don't have to be exactly the same perhaps as in an earlier disease, maybe not placebo controlled but randomized against topical therapy earlier on.

DR. TEMPLE: There's no question. That's one of the reasons we have allowed that because you can get them done.

CHAIR PRZEPIORKA: Dr. Keegan.

DR. KEEGAN: Just another comment on the equipoise issue. In the original accelerated approval, there was exquisitely collected data on response rates.

It was actually one of the best applications I believe I've ever seen in terms of dealing with a difficult to assess disease. Photographic techniques were standardized. The grids. It was actually exquisite.

In addition, there was a number of things collected on that trial as are being collected on this trial to collect patient symptoms of a variety, pruritus, global severity assessment by physicians and concomitant medications usage. What was interesting was that although patients did in some instances report decreases in symptoms, we could not in most instances in most of the responding patients observe a documented decrease in use of concomitant medications to treat those symptoms which again led us to the concern about what are we seeing here.

There was some correlation in the patients with the most dramatic and complete responses but it was bordering on anecdotal in this entire dataset. Again the thought was it was hard to put that in context and a placebo controlled trial collecting the same kind of information would likely help us to put that concomitant medication in use context. I also

mention that because of the concern about using response rates as an endpoint in that collection of a lot of the patients' symptomology data in the concomitant medication use we expect will bolster that information and will provide us with an ability to put those response rates in the context of clinical benefit to patients.

CHAIR PRZEPIORKA: Dr. Pazdur.

DR. PAZDUR: I'd just like to draw your attention while everybody's laying crepe on this process to the successes of the process. Take a look, young man, West to where the four indications where we were able to basically demonstrate clinical benefit. There are some lessons that we can gain from there.

It's clear studies are better if they are on-going. We've repeated this. I almost sound like a machine saying this over and over again. The other thing that Donna brought out and I brought out previously was that most of these were being done in earlier or different stages of the disease.

For example if you take a look at the original Irinotocan trials, it was approved with a

10/15 percent response rate in 5-FU refractory diseases. Basically the study that the agency negotiated for clinical benefit was the first line trial. However in Europe there was best supportive care against CPT-11 in the same stage. We weren't even aware of those trials when the drug was approved I don't believe. I wasn't working at the agency but it wasn't widely known about the trials at the time of approval. The actual letter states that the first line trials were going to be the confirmatory trials. It's important that we keep in perspective that there might be other ways of addressing this issue.

Also as we lay crepe on this process here, it's important for us to understand that really an important part of this is to get these therapies out to people early. I don't think that we should undermine the benefit of people getting therapies early.

Remember the confirmatory studies are important. Believe me I'm the one that wanted this meeting. They are fundamental to the process but they're not the only way to spell success of a drug. Ultimately we want to know this answer. But to say

that these therapies are unsuccessful in a bigger picture here of oncology therapeutics in the United States would be really selling the process short.

I'm making an emotional plea here because I really think that one has to step back and take a look at the total picture not just has the confirmatory trials been done. Yes, I want them done but success is more than passing one test. Anyone that has any child or children know the answer that the success of a child simply isn't in their report card. Thank you.

CHAIR PRZEPIORKA: Thank you, Dr. Pazdur. I hope we're not giving the impression that we're trying to drape crepe on the accelerated approval process.

DR. PAZDUR: Well, you're doing a great job of it.

CHAIR PRZEPIORKA: This committee pretty much has a very good record of dealing with the accelerated approval of drugs that come here. We are happy to provide our insight into what should go into Phase IV commitments and if I speak for myself we are pleased with the way the division is handling Phase IV

commitments. Any other comments?

DR. CHESON: I can make one final glib comment. Reflecting on my two colleagues here who don't like the name accelerated approval because in fact it does suggest that you zipped it through and you are moving it fast, unconfirmed approval. Throw some crepe on that one.

DR. CARPENTER: Conditional approval.

DR. CHESON: Conditional approval.

DR. WEISS: There was actually some discussion about this. Bob Temple would remember. Wasn't there some thought that it was going to be called conditional at first but then there were problems with that?

DR. TEMPLE: That name turned out to be politically incorrect. And it's accelerated. We wouldn't have approved it without it so it is accelerated.

CHAIR PRZEPIORKA: Dr. Keegan or Dr. L'Italien, do you have other questions for the committee?

DR. L'ITALIEN: No, I just would like to

express our gratitude to the committee and also to the agency for some lively discussion today. Certainly it is our goal to bring these studies to conclusion as rapidly and successfully as possible. We pledge to work with the agency to keep on top of this and to try to complete these studies.

CHAIR PRZEPIORKA: Thank you. We will end this session and have a short break. Be back here by 2:55 p.m. Off the record.

(Whereupon, the foregoing matter went off the record at 2:50 p.m. and went back on the record at 3:00 p.m.)

CHAIR PRZEPIORKA: On the record. If the members of the division would like to take their seats we can get started please. We'll start with Ms. Clifford reading the Conflict of Interest statement.

SECRETARY CLIFFORD: The following announcement addresses the conflict of interest issue with respect to this meeting and is made a part of the record to preclude the appearance of a conflict. Based on a review of the submitted agenda for this meeting and all relevant financial interests reported by the

Committee participants, the Agency has determined that there is no potential for a conflict of interest at this meeting.

In addition, we would like to note that George Ohye is participating in this meeting as the Acting Industry Representative. Mr. Ohye would like to disclose that he previously served on the Board of Directors of the U.S. Bioscience, the developers of Ethyol prior to its acquisition by MedImmune. He has stock options in MedImmune.

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 participant should exclude himself or herself from such involvement and the exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

CHAIR PRZEPIORKA: At this time if we could ask the new members from the division to introduce

themselves please.

DR. FARRELL: Ann Farrell, Medical Officer.

DR. WILLIAMS: Grant Williams, Deputy Director.

CHAIR PRZEPIORKA: Thank you. Our next presentation will be given by Dr. James Pluda from MedImmune regarding NDA 20-221, Ethyol reduction in cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced non-small cell lung cancer.

DR. PLUDA: Thank you. As just stated, my name is Dr. James Pluda. I'm head of Clinical Oncology for MedImmune and I will be discussing the Ethyol Non-Small Cell Lung Cancer Indication.

First I would like to briefly review what I'll be discussing today at the meeting. I'll be presenting the mechanism of action of Amifostine and the indications for which it is fully approved followed by additional information regarding the accelerated approval for nephroprotection in non-small cell lung cancer patients receiving platinum.

I will then present the results of the

Phase III trial performed to meet the obligation of the accelerated approval strategy which although it did meet the nephroprotection endpoint did not meet the endpoint of demonstrating lack of tumor protection. Lastly I will discuss our continuing obligation to fulfill the accelerated approval and some of the issues involved.

This slide shows the mechanism of action of Amifostine. Amifostine is an organic thiophosphate developed by the Army initially to protect soldiers from the effect of radiation. It serves as a pro-drug being metabolized to its active form which is WR-1065 by membrane-bound alkaline phosphatase at the surface of cells. WR-1065 is a free-thiol which then is taken up into the cells and scavenges oxygen-free radicals and free radicals formed by chemotherapy as well.

Pre-clinical data indicate that there is a differential protective effect of amifostine in normal tissue compared to tumor tissue. This slide shows that amifostine is preferentially taken up by normal tissues compared to tumor tissue. I'd like to point out that the concentration over here is a logarithmic scale. As

you can see, Amifostine's highest concentration occurs in the kidney. In tumor tissue at 30 minutes which is typically when the chemotherapy, radiation therapy is given after the initial administration of Amifostine. There was a greater than two log difference in concentrations. Even as far as 90 minutes which is well after the end of the chemoinfusions or the radiation therapy, there is still greater than a log difference.

Amifostine has been formally approved for the prevention of xerostomia from radiation therapy in post-operative patients with head and neck cancer where the radiation field involves the majority of the parotid gland. In addition it was approved for the reduction of cumulative renal toxicity associated with cisplatin in advanced ovarian cancer patients.

Now U.S. BioSciences was granted accelerated approval for Amifostine for the prevention of cisplatin nephrotoxicity on the basis of a Phase II trial that contained 25 patients. This was in non-small cell lung cancer patients with locally advanced or metastatic disease stage IIIb/IV who were receiving

vinblastine, cisplatin and Amifostine.

In order to fulfill the accelerated approval, the requirement for full approval, a Phase III trial with non-small cell lung cancer patients administering cisplatin and Amifostine that demonstrated both nephroprotection as well as lack of tumor protection was required. This post-approval commitment was WR-0053 which was initiated by U.S. BioSciences in December 1994 and was on-going at the time the accelerated approval was granted.

This is a Phase III randomized control trial in the same population as the Phase II study locally advanced metastatics, Stage IIIB or IV non-small cell lung cancer patients. Patients received cisplatin and vinblastine with or with Amifostine. The co-endpoints of this trial were the demonstration of no reduction in anti-tumor efficacy with a reduction in Cisplatin-related nephrotoxicity.

Shown here are the results of the nephroprotection endpoint of the study. The nephroprotection by Amifostine and cisplatin treated patients was confirmed by this trial. As you can see,

the control patients had a 49 percent incidence of nephrotoxicity which was defined as a greater than or equal to 25 percent decrease in creatinine clearance from baseline. Whereas the Amifostine treated patients had only a 28 percent incidence of nephrotoxicity, a difference of 43 percent. If you look at nephrotoxicity two different ways, either by total cisplatin dose or by cumulative cisplatin dose to the onset of nephrotoxicity, there was still a significant difference between the control arm and the Amifostine arm.

This slide shows the results of two of the three parameters that were necessary to demonstrate no effective anti-tumor activity in the protocol. No difference was observed in the response rate or progression-free survival in the Amifostine patients compared to control. You can see that in the control arm there was a 32 percent response rate, 30 percent in the Amifostine arm. The median progression-free survival was 4.73 months in the control arm and 4.14 in the Amifostine arm.

This slide shows the results of the third

parameter, overall survival. The median survival for the Amifostine treated patients was 8.75 months. For the control patients, it was 9.93 months. Also shown here are Kaplan-Meier curves that depict that outcome. There's a slight separation at the end of the curves as you can see here.

Additional analyses were done of the data in order to see what factors might of influenced this observation. A covariant analysis on survival indicated that there was an interaction between treatment and performance status. This table here delineates those data. The biggest difference was between the Amifostine ECOG performance status zero patients and the control ECOG performance status zero patients. As you can see, the control was 17.2 months whereas the Amifostine was 9.8 months which was essentially identical to what was seen in historical controls. In the ECOG performance status one patients, the control and the Amifostine were the same and again were the same as in historical controls. The prolonged 17.9 months survival of the control performance status patients is clearly different from what might be

expected in the population and is likely responsible for what we saw in the separation in these curves.

What is depicted here is the collective experience with the Phase III Amifostine trial. The hazard ratio is in the 95 percent confidence intervals for all five Phase III trials including 53 which are up here. The turquoise bars represent the hazard ratios and the horizontal line represent the 95 percent confidence intervals. The hazard ratio is greater than one which is to the right of this vertical line and they all favor Amifostine. As you can see, all of the confidence intervals overlap one.

If we look at some of the individual studies, we see WR-0056 which is a study in patients with non-small cell lung cancer. It's the exact same population, IIIb/IV patients, as 0053. Although this trial didn't meet the endpoint of the trial which was hematological protection from carboplatin and paclitaxel, the survival data from this trial are instructive. In fact if you look at survival between the Amifostine control arms there is absolutely no difference between Amifostine control or even

historical control regardless of performance status.

WR-0001 was the ovarian cancer study that was used in order to grant Amifostine its initial full approval for cisplatin nephroprotection. There are two other studies 0038 and 9001 that were studies that administered radiation therapy. This was the head and neck study that was originally used to get the positive approval for prevention of xerostomia as well.

Although these trials involve different patients with different treatments, we do not see anything here that would suggest that there is an overall or general survival issue with Amifostine. Be that as it may, the overall conclusion that can be drawn from the results of 0053 are that cisplatin nephroprotection seen in the ovarian and non-small cell lung cancer trial were confirmed.

Looking at the anti-tumor efficacy endpoint, two of the three parameters for demonstrating no effect on anti-tumor treatment were met: no difference in the response rate and no difference in the progression-free survival. The difference in median survival did not meet the protocol defined

endpoint and is the reason that the lack of effect on anti-tumor efficacy endpoint overall was inconclusive and that WR-0053 did not meet the accelerated approval obligation.

Now the guidance that we have received from the agency is that we still have an obligation to perform a new cisplatin-based study in patients with non-small cell lung cancer, demonstrating the co-primary endpoints of nephroprotection as well as non-inferiority of survival or a survival surrogate.

It is this non-inferiority endpoint that drives the sample size for such a trial. The assumptions for calculating that sample size are that non-inferiority would be determined by a one-sided 97.5 percent confidence interval and that also there would be the retention of at least the 50 percent of a treatment effect seen in the literature for the regimen that's being used in this study with Amifostine.

Based on these assumptions, if non-inferiority of a surrogate that is of survival response rate were used as the primary endpoint, the trial would take about 1,150 patients. If one had used the actual

survival as the primary endpoint, the trial would take approximately 2,600 patients. To demonstrate nephroprotection alone with 85 percent statistical power would take approximately 400 patients.

The main challenge in the current environment to the performance of another cisplatin trial in non-small cell lung cancer of this size is accrual. Now there's a changing pattern of cisplatin utilization in this population with the decreased use of high dose regimens. Carboplatin is being substituted more frequently for cisplatin in some of these regimens. There are a number of high priority therapeutic agents being evaluated in this same population that will compete for accrual.

Based on the design presented and with the patient pool of non-small cell lung cancer patients receiving platinum in the United States of approximately 700 per year and an accrual rate of 240 patients per year, this trial will take approximately 6.5 or more years to complete.

In summary, the nephroprotection from cisplatin toxicity by Amifostine has been established.

Conclusive proof of lack of tumor protection by Amifostine has not yet been established. Therefore a definitive trial demonstrating lack of tumor protection in patients with non-small cell lung cancer receiving Amifostine/cisplatin is required.

We are currently confronted with the challenges of meeting that obligation and look forward to any comments or guidance that the committee may have to offer us. Thank you very much.

CHAIR PRZEPIORKA: Dr. Williams, do you have comments for the committee?

DR. WILLIAMS: Yes, thank you. One of the problems with this application in terms of tumor protection is that our approach and our knowledge about this field has progressed over the years. Tumor protection is one issue and non-inferiority studies are another issue. Both of those have become issues of concern to us.

Our first experience with this was with Zinecard. We brought that application to the committee twice. The first time there was a P-0.001 difference in response rate in breast cancer with Zinecard which

led to a very heightened concern that the possibility of tumor protection is there especially when you're not quite sure why the drug would protect the patient and not the tumor. So we have a heightened concern.

With the first approval in ovarian cancer, it was on a very small study by today's standard. It honestly didn't really rule out tumor protection. It was a little before we developed our current sophistication.

With this next accelerated approval, we began to apply our current standards to say you really do need to prove that you're not protecting the tumor at least in one tumor and do it well. That's why we stuck by our guns on this and not said that we're going to go ahead and convert approval without a really good proof by today's non-inferiority standards that there's no tumor protection.

The other difficulty is the lung cancer drugs are only marginally effective. So that the effect size you see from these drugs is so small that to show non-inferiority becomes a big challenge. Those are the issues that are behind our insistence to pursue

this exercise and to try to insist that this drug is proved in the clinical trial setting which I don't really understand why the drug should protect only the patient and not the tumor.

CHAIR PRZEPIORKA: I wanted to ask a question regarding trial design that I hope would engender some discussion but also because I am concerned about requiring a trial of 1,000 patients to prove non-inferiority. The issue that came up in the first trial had to do with the secondary endpoint and a safety concern. In order to relay that safety concern, would a valid trial be one not to show non-inferiority but to show inferiority and then reject the null hypothesis?

DR. WILLIAMS: No, actually we're using the term "non-inferiority" here. That's glorifying the term a bit. As Dr. Temple can tell you, in the other fields when we use the term "non-inferiority" that means almost exchangeable. We're just saying is there some effect here when we do this sort of a comparison.

I can bring up another issue that relates to this that might in some settings allow a different

trial design. My personal view is that what we're looking at is tumor protection. We're not looking at some extraneous potential effect on survival that this whole issue is related to tumor protection. So my view is that one can look for the most sensitive indicator of tumor effect and try to show that it's not abrogated. That would be my approach.

Now this survival effect may just totally be another spurious thing that we saw earlier. But in view of it, that one should take note. The trial was not designed by current standards to demonstrate non-inferiority by any endpoint for the previous trial. Just because you didn't see a difference, that doesn't mean that you've established that the drug does not protect the tumor. It only means you didn't see a difference.

To demonstrate non-inferiority to that, you need at least to know what is the effect the drug has and can you be sure that if the drug wasn't there that you'd see a difference. That's the minimal standard. You did need statisticians to help you decide how many patients do I need to study to show that I've had any

preservation of effect. We're not really asking for a very strict non-inferiority here. We're asking for at least a gross indication that the effect has been retained.

DR. PAZDUR: One of the aspects I would like to discuss and maybe Gain (PH) could answer this question also if we look at another endpoint other than preservation of survival for example response rate preservation what would be the numbers that would be required?

DR. PLUDA: Yes, as I showed if we look at response rate it would be 1150 patients. For survival it would be 2600 patients.

DR. WILLIAMS: Did you mention time to progression?

DR. PLUDA: The calculation here, we only found one randomized control paper in the literature that compared the chemotherapy that we would be using as a singlet to as a doublet in combination with cisplatin. There was only one article. That was a vinblastine plus or minus cisplatin and they didn't give time to progression data in that article. We only

had response rate so that's why we didn't have the time to progression.

CHAIR PRZEPIORKA: I hate to beg the question but if in fact they chose to say let's do a study to show that Amifostine is bad rather than good and powered it to show that it actually decreased median survival by four months which is what the first study showed, would a negative study of that design be of any help?

DR. WILLIAMS: I think you are misunderstanding that first study. We're not just demonstrating that it's wrong. That isn't our goal. Our goal is to demonstrate that Amifostine does not protect tumor.

DR. TEMPLE: It's not what she's asking. You're asking whether if they could show that it didn't make a four months worse would it be good enough. Is that right? That goes back to the old days. I don't know what the effect of the drug without any Amifostine is. Let's say it's only two months. Then ruling out a difference of four months isn't really very helpful because four months is larger than the whole effect of

the drug. So you get into these massive studies when you do so-called non-inferiority designs.

Just as a general rule, we try to calculate what the effect of the control agent is and then we take some fraction of it like 50 percent and say we want to rule out a loss of that. Because if you lost all of that, then you really wouldn't be doing any good. But it does produce these massive studies. I thought Grant was going to say that he thought looking at response rate was reasonable. Is that what you meant?

DR. WILLIAMS: Right.

DR. TEMPLE: Well, looking at response rate, the difference between no treatment and treatment on response rate is huge, compared to the difference in whatever you are looking, for example tumor-free survival. So it's a much smaller study. Was the 1100 patients based on 50 percent retention?

DR. PLUDA: Yes.

DR. TEMPLE: Yes. Well, that's tiny compared to what they have to do. So, one of the things that eventually we ought to all talk about is

with these tumor protectants how sure do we have to be. Would preservation of response rate be good enough, given that it's the same drug after all? That's worth thinking about because it can become impossible this way.

CHAIR PRZEPIORKA: Dr. Cheson.

DR. CHESON: I need help here from doctors, statisticians, Dr. George and Dr. Fleming. Here we have a series of randomized trials, one of which shows this potential decrement in outcome related to the drug and the others in one and the same disease -- others in different diseases -- fail to show any such suggestion of adverse effects. Can you speculate of some statistical quirk here that could explain this, short of doing a 2600 patient trial? Steve.

DR. GEORGE: Speculate?

DR. CHESON: Or whatever you statisticians call it.

DR. GEORGE: Right. Well, part of this is looking at the studies which are in different areas and different diseases and different designs. But it's hard to know in that case. It looks like they all

overlap the one. The issue though that is a fundamental problem here, I guess, in this type of study is you have something that you can show fairly easily perhaps that protects the toxicity but it's very difficult to show that it doesn't have a decrement in some other important --. It's very difficult in terms of just size and studies that have to be done. That's what Greg was getting at.

There's no easy way out of that, short of just loosening the standards that you would require. For example, if you looked at just these results, you might just say looking at response rates. I'm looking at one of these earlier slides. I don't know which one it is. There's the slide with response rates and progression-free survival.

If you look at those confidence intervals by sort of normal -- by common man-on-the-street kind of thinking, you ruled out a decrement of about 11 percent, even though the response rates themselves are virtually identical. You ruled out a bigger decrement than 11 percent but 11 percent -- if it's really that big -- that's probably too big for what you want. You

can do the same thing with progression-free survival.

So, in short -- but that's the kind of logic you have to use. If you are trying to protect yourself against the potential loss of any kind of effect, 50 percent is pretty big. And so you reach big numbers. I don't know an easy way out of that, short of loosening that standard. I don't know if you want to do that.

CHAIR PRZEPIORKA: Dr. Fleming.

DR. FLEMING: Bruce, your question about how to interpret the results of the 0053 trial in the context of the other studies is difficult. The 0053 was the targeted study. It was the primary study. It was in the indication in which we were focusing, and external data is always of some relevance. It's somewhat subjective how we weigh it in.

What is the relevance of what we see in head and neck and in other disease settings, relative to what we are seeing in small cell? Usually when we look at efficacy of platinum, we would establish the efficacy of platinum based on data in non-small cell, not whether there is or isn't efficacy in other

settings, unless we think there is a pathophysiologically related mechanism here that's sufficiently close that there's relevance. I would say that there is some relevance.

But ultimately it was prudent. The way this was being set up was to conduct a study of appropriate informativeness in this setting to understand whether we had the renal protection and that we didn't in fact compromise efficacy.

Donna, let me come back to your point, which is really a very important one. For me it's deja vu ODAC 1986, which is can we look at just saying we're not meaningful worse. I say that because in 1986 this committee was presented mitoxantrone in advanced breast cancer. Four small studies were done that showed we had three months less survival than adriamycin, but we weren't statistically significantly worse. And so there was a judgment that as a result approval should be given because we had equivalence, because we hadn't been proven to be worse.

Yet you step back and say adriamycin itself probably provides three months improvement in survival.

So for three months worse than something that provides three months benefit, even though we're not significantly worse, logic says we're the same as nothing. I can get rid of the cardiotoxicity, myelosuppression, nausea and vomiting of adriamycin by just stopping the adriamycin.

Here the fundamental challenge -- and it's not just because this is accelerated approval; this is always the case in chemoprotection trials -- what we have to ask ourselves is: okay, we can reduce from five in ten patients having significant renal toxicity to three in ten having significant renal toxicity. Presumably we could get that reduction by having some level of reduction in the cisplatin-based regimen in this setting.

If we did, how much less efficacy would we have with that level of reduction? Fundamentally, I want to be sure here that we're not giving sufficient levels of platinum-based regimens to induce renal toxicity in half the patients, and then we negate that in two of the five. So you still have toxicity in three of ten and not still have the benefits of that

regimen.

And so what we have to do then -- it's not good enough just to say, are we significantly worse -- do a small trial, and you will in fact not be able to conclude you're significantly worse even if you've lost all the benefit. It's not easy, but we do have to be able to have some level of confidence that we get the chemoprotection without the price of losing the efficacy.

So then we step back and say, how do we do it. It's not easy. When we look at this, is it enough to look at response rates? Well, response rates don't show much difference; but there is a difference in duration of response. The duration of response is one-third longer when we haven't given Ethyol. There are different small numbers. CRs are four versus one. And there's a difference of one month in survival -- or basically one and a half months in survival, and you have a relative risk of 0.83.

So when I look at all of this, I would say just the response data alone may not be capturing the nature of how we are compromising the benefit here.

Bottomline is, I think the FDA is right on target by saying that whether this is accelerated approval or not -- and I think we've heard that the fact that it's accelerated approval doesn't mean that we should have weaker standards for showing that we've established favorable benefit-to-risk -- in a chemoprotection study we have to show the chemoprotection and, as Stephen George says, that's the easy part.

The tougher part is to be able to show it selectively achieves such that you couldn't have been able to achieve that same chemoprotection by just a dose-response dose-reduction of the active agent. Here we are protecting patients to ensure that when we actually have made it as hard as it is to get an advance here we have an advance. We have regimens that improve survival. Let's not lose that advance if in fact we are trying to do so with chemoprotection in ways that might cost us more of the benefit and efficacy than we are willing to give up.

CHAIR PRZEPIORKA: I just want to give comments on your question because there has been a drug before this committee in the distant past that I recall

that also had a quirk of randomization where the eligibility of criteria were heterogenous and where the control arm had a good prognosis population as opposed to the treatment arm. That's some of the data he was alluding to when he was showing his own data which was that the control arm had a better survival than the historical controls. That is just a fluke which is why I'm concerned that perhaps they're being held to a higher standard than they should be if they have to go and do an entire non-inferiority study instead.

DR. WILLIAMS: The database that's described here is difficult because it just so happens that one study is the one that is in the indication and with the drug that it was proved. Carboplatin has no proved indication. We're protecting nephrotoxicity so the data that comes from carboplatin may be you want to make that extrapolation or maybe you don't.

Radiation is another kind of treatment. Maybe you want to make that extrapolation or maybe you don't. Head and neck is another tumor. I don't think they are overwhelming supportive. Then the ovarian study is quite small if you look the size of those

confidence intervals for the other approved indication.

I understand what you are saying and we really do have to make the fundamental decision. We have and that's why we are applying this standard about what we are going to do with tumor protection agents. We don't do this for anti-nausea agents. It's a clearly extremely different mechanism where we don't expect that it's going to interfere with the tumor. What we don't understand with great confidence why it shouldn't protect the tumor then why shouldn't we require them to make sure that they are retaining at least a moderate fraction of the benefit from the drug.

CHAIR PRZEPIORKA: Dr. Temple.

DR. TEMPLE: Having said that and not disagreeing with Tom in any way about the importance of it, I would add to the list of things we ought to bring to you for further discussion which is now getting very large the question of whether there are some other things one could do here. For example given that it's the same drug, is tumor response more plausible than it might be in some other cases as an indicator of similarity? That's one. I'm not trying to say what

the answer should be.

The other is if you really think that a therapy might interfere with the anti-tumor activity of a drug, maybe tumors of several different kinds are relevant to that and it's worth thinking about all the data together even though you wouldn't do that if you were trying to make a tumor treatment claim in each of those. That might be relevant to the mechanism here. You think that if it interferes with one it might interfere with the other. Again I don't know that we know that.

Those things we're thinking about because it becomes extraordinarily difficult to develop a protectant. If you want to protect it in several different tumors, you have to do all over again in each tumor. It's harder than working up a drug for treating something. So you can make it so difficult that nobody bothers too and that's not a good outcome.

DR. FLEMING: I would say it would be equally hard to working up another drug that you would look at as a replacement drug where you had to do a non-inferiority comparison. If Agent A is established

and now you come along with B and you want to look at B replacing A, it would be equally as challenging as that setting.

DR. TEMPLE: Yes, but that's very challenging and very difficult. Those are two questions off the top of my head that we need more discussion on. I'm sure people will think of more.

CHAIR PRZEPIORKA: Dr. Blayney.

DR. BLAYNEY: Again I enjoyed your comment, Dr. Fleming. Perhaps you can help me with a question. If you have a 30 percent response rate like you do in lung cancer and you're trying to detect the non-inferiority adding a loss or protection with your protector, what if you move to a 95 percent response rate like one would have with testis cancer? Does that make the study size smaller?

DR. FLEMING: What really drives this more is what's the margin. How much less are you willing to have before you say it's a clinically meaningful loss? That drives the sample size more than anything else. In my view what saves us and we don't think about it a lot in a non-inferiority setting is if we actually

think we might be a little better. Then we can rule out that we're meaningful worse without taking a very large sample size.

I step back in this setting and I read the conclusion paragraph that we were given by the sponsor as the rationale here. The sponsor is saying "Cumulative renal toxicity may have a significant and negative effect on the efficacy of cisplatin administration because of dose response, dose reductions, treatment delays, treatment discontinuations, life threatening fatal renal toxicity," etc. If reduction is working and technically it's a surrogate in creatinine clearance, 25 percent, if this benefit does translate into these targeted benefits then logically doesn't it follow that with this chemoprotective agent that this regime ought to have an enhanced benefit because you're not having to reduce the effective cisplatin-based regimen.

In fact, there was a hypothesis in here that you might be better ruling out a quality or if we're the same ruling out we're worse. With a truly effective chemoprotective agent that's doing what you

want, isn't that an agent that gives you a better way to deliver the effective interventions more fully in which case we would expect in truth a somewhat better result? It doesn't have to be statistically significantly better but just modestly better. This allows you now to rule out you're meaningful worse with a much smaller sample size.

Part of what troubles me here is the aggregate data in which one trial could be a false negative conclusion show a negative trend even in the context of validated renal protection which should have I would have thought allowed us to more fully treat these patients. I would have thought we would have seen a positive trend. If truth is a positive trend, to answer your question, we can rule out a negative trend without an inordinately large sample size.

DR. BLAYNEY: But your remark is predicated on a dose response in lung cancer. With platinum in lung cancer, there's probably not a dose response. It may be four to six cycles.

DR. FLEMING: I was just quoting the sponsor's remark.

DR. BLAYNEY: Yes. I'm sorry. The point is that it does require either a dose response or a cumulative benefit. I don't think that in lung cancer anybody believes that's the case.

DR. FLEMING: The other argument that I would always make in a non-inferiority trial is the margin should in fact be a bit more flexible if we are truly providing tangible benefit in ways other than what is reflected by that endpoint. We really are providing important symptom relief for reduction of major important documented side effects. Those are out there and documented. My own view is that should allow for a bigger margin.

So we did see a surrogate here. What are some of the tangible things that we can add that we can say are documented to be better for this intervention group that got the Ethyol? To the extent that we can document ways that this group is better, I would argue to the FDA that a somewhat larger margin should be allowed. To the extent that we can't, then a more rigorous margin should be required.

CHAIR PRZEPIORKA: Dr. Kelsen.

DR. KELSEN: We focused on the ability of the agent to protect against nephrotoxicity at higher doses and want to preserve efficacy at higher doses. But sponsor noted that lower doses are much more commonly given. What data is there for using this agent as a nephroprotectant in lower doses? What's the magnitude of the difference there?

DR. PLUDA: The only nephroprotection significant data that we have is from the ovarian trial, the non-small cell lung cancer trials. Other trials with much lower doses of cisplatin have not as yet have been performed.

DR. KELSEN: So if you give cisplatin to a human whether it's for lung cancer or not if doses of 50 to 75 per meter square which would be used fairly frequently now, how well does this agent protect against nephrotoxicity in those patients?

DR. PLUDA: Those studies have not as yet been performed.

DR. KELSEN: If the magnitude of the difference is very small and you have any worry about losing efficacy, the balance shifts.

CHAIR PRZEPIORKA: Dr. Blayney, would you like to address the questions?

DR. BLAYNEY: Has accrual to an on-going trial been satisfactory for timely study completion? I think so but the field really in lung cancer has been pointed out that it's moved. Most people treat if they use a platinum agent with carboplatin not because really of nephrotoxicity but because of the neurotoxicity and some of the other toxicities. That again makes trying to complete this trial more difficult.

We're likely to see other agents and we have seen other agents in the last few years that have substituted for either of the platinums. That is going to make complete even more difficult for them.

Other strategies that they might consider where I mentioned the testis cancer thing that would require a complete trial rethinking of the trial design. Perhaps that's not practical but these patients are likely to live a long time if they do develop toxicity. Testis cancer patients will live for a long time with that toxicity. So if they can be

protected, that may be a useful thing.

Perhaps also including the other solid tumor versus platinum which has been used and you've alluded to it earlier is ovary cancer. If the trial can be opened up to include ovary cancer, it might be a reasonable strategy and also cisplatin combination of choice as an inclusion criteria. Perhaps you've already thought about that.

Thirdly, has the approval impeded the ability to conduct a planned trial? I don't think so. It's more approval of other agents rather than the approval of Amifostine. I've already alluded to other alternative designs which might be contemplated.

CHAIR PRZEPIORKA: Other comments from the committee? Dr. Redman.

DR. REDMAN: Do you have data that suggests that those patients that were on the control group actually got a total cumulative doses of platinum?

DR. PLUDA: Total cumulative doses of platinum?

DR. REDMAN: Yes.

DR. PLUDA: What we did have was the data

that demonstrated that the time to the cumulative dose of platinum before the onset of nephroprotection which is where you would begin to start to dose reduce this platinum. There was a significant difference in the cumulative dose as well as the dose of platinum that it would take before the nephroprotection actually began. As you can see when you got up to 360 mg/M^2 there that there was a significant difference in the amount of toxicity. That would presumably relate to patients being able to get more cisplatin than patients who did not have nephrotoxicity and required dose reductions.

DR. REDMAN: I'd just offer another hypothesis to Dr. Fleming's that maybe the survival difference is due to the fact that the control group got less cisplatin.

CHAIR PRZEPIORKA: Dr. Cheson.

DR. CHESON: Could you give me some idea of the magnitude of the nephrotoxicity in both of the arms? How reversal was it? In other words, is it just that you get a 25 percent decrease in your clearance or is it something that's significantly worse than that?

DR. PLUDA: We also did an exploratory

analysis looking at 40 percent decrease in creatinine clearance as well. In that analysis, there was a still a significant difference between the Amifostine and the control arms as you see here. So even if we looked at a much higher standard for prevention of nephrotoxicity, we still were able to maintain a significant difference between the arms. You can see the cumulative dose in nephrotoxicity was significantly different again between the two arms. That was to 40 percent, not just 25 percent reduction.

DR. PAZDUR: But was some of this reversible? I think that what Bruce is getting at. You may have a P-value there but is it clinically meaningful however you want to term that?

DR. REDMAN: That is true. When you administer cisplatin if you do serial creatinines on them in the middle of the cycle, most people will bump their creatinine up to two and then come back down to their baseline.

DR. PAZDUR: You may have a P-value there but how does this correlate into clinical benefit and how would you envision this? I don't really mean to

revisit the whole approval of this drug at this time.

DR. PLUDA: Thank you.

DR. FLEMING: Just to add to that question, are there data in this study on differences in occurrences of fatal renal toxicities or is there a difference in dialysis or end stage renal disease or anything more extreme like that?

DR. PLUDA: I don't believe there was a difference.

DR. PAZDUR: Obviously looking at dialysis is an extreme situation and the medication would be stopped. In dose delays specifically because of nephrotoxicity are dose reductions. Then one would have to make the assumption that more is better.

CHAIR PRZEPIORKA: But why is that important if in fact they actually lived longer if they didn't get the stuff? To me you still come down to that ultimate point that whatever little nuisances that you might have had to change or not change, hey if anything I've lived longer if you didn't touch me.

DR. PAZDUR: Here again that's the issue of clinical benefit of the nephrotoxicity that I'm trying

to eke out here.

CHAIR PRZEPIORKA: Dr. Kelsen.

DR. KELSEN: Following up on other patient populations, I would be a little nervous about studying an agent that might be a tumor protective in patients such as testicular cancer patients who are curable. I would think you might want to focus on a palliative population.

CHAIR PRZEPIORKA: Does anyone from the agency or the sponsor have any other questions for the committee?

DR. PLUDA: I don't have any questions. I just want to thank the agency and the committee to allow us this opportunity to get your guidance on these issues.

CHAIR PRZEPIORKA: Thank you and let's close the program for today and we will reconvene tomorrow at 8:00 a.m. Off the record.

(Whereupon, at 3:46 p.m., the above-entitled matter concluded.)