FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

SIXTY-FOURTH MEETING

OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE

9:04 a.m.

Monday, December 13, 1999

Versailles Ballrooms
Holiday Inn
8120 Wisconsin Avenue
Bethesda, Maryland

ATTENDEES

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ATTENDEES (Continued)

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ATTENDEES (Continued)

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PATIENT REPRESENTATIVES:

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ATTENDEES (Continued)

FOOD AND DRUG ADMINISTRATION STAFF:

JULIE BEITZ, M.D. (for Taxotere)
DONNA GRIEBEL, M.D. (for Taxotere)
JOHN JOHNSON, M.D. (for Targretin)
ROBERT JUSTICE, M.D.
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RICHARD PAZDUR, M.D.
ROBERT TEMPLE, M.D.

ON BEHALF OF LIGAND PHARMACEUTICALS, INC.:

MADELEINE DUVIC, M.D.
FRANCINE M. FOSS, M.D.
HOWARD T. HOLDEN, PH.D.
KENNETH HYMES, M.D.
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STEVEN D. REICH, M.D.
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RICHARD C. YOCUM, M.D.

ON BEHALF OF THE RHONE-POULENC RORER PHARMACEUTICALS, INC.:

JEAN-PIERRE BIZZARI, M.D.
PHILIP CHAIKIN, PHARM.D., M.D.
SYLVAIN DURRLEMAN, M.D., PH.D.
FRANCES FOSSELLA, M.D.
RICHARD GRALLA, M.D.
MARK GREEN, M.D.
LUZ HAMMERSHAIMB, M.D.
GARY KOCH, PH.D.
FRANCES SHEPHERD, M.D.

ATTENDEES (Continued)

ALSO PRESENT:

NANCY W. BORCHERDING (for Targretin)
JOHN H. CARTER (for Targretin)
GAETANO GIORNO (for Taxotere)
GAETANA GROBLUSKI (for Targretin)
JUDY JONES (for Targretin)
BARRY KUPSCH (for Targretin)
SCOTT RIVERS (for Taxotere)

C O N T E N T S - MORNING SESSION

NDA 21-055, TARGRETIN (bexarotene) CAPSULES
LIGAND PHARMACEUTICALS, INC.

C O N T E N T S - AFTERNOON SESSION

NDA 20-449/S-011
TAXOTERE (docetaxel) for Injection Concentrate
RHONE-POULENC RORER PHARMACEUTICALS, INC.

P R O C E E D I N G S

(9:04 a.m.)

DR. SCHILSKY: Good morning, everyone. I'd like to ask everyone to please be seated. Welcome to the 64th meeting of the Oncologic Drugs Advisory Committee.

I'd like to begin with an introduction of the committee members. Maybe we can just go around the table. Perhaps we could begin with Dr. Simon.

DR. SIMON: Richard Simon, biostatistician from the National Cancer Institute.

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

DR. ROOK: Alain Rook. I'm in the Dermatology Department at University of Pennsylvania.

MS. KRIVACIC: Susan Krivacic, Patient Representative.

DR. LIPPMAN: Scott Lippman, medical oncology and cancer prevention, M.D. Anderson.

DR. PELUSI: Jody Pelusi, oncology nurse practitioner in Arizona, Consumer Rep.

DR. KELSEN: David Kelsen, medical oncology,

Memorial Sloan-Kettering.

DR. ALBAIN: Kathy Albain, medical oncology, Loyola University, Chicago.

DR. DAVID JOHNSON: David Johnson, medical oncologist, Vanderbilt University.

DR. SLEDGE: George Sledge, medical oncologist, Indiana University.

DR. SCHILSKY: Richard Schilsky, medical oncologist, University of Chicago.

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

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

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

DR. ZACKHEIM: Herschel Zackheim, dermatology, University of California, San Francisco.

DR. RAGHAVAN: Derek Raghavan, medical oncology, University of Southern California.

DR. JOHN JOHNSON: John Johnson, Clinical Team Leader, FDA.

DR. PAZDUR: Richard Pazdur, Division Director, FDA.

DR. SCHILSKY: Thank you.

Dr. Somers has a conflict of interest statement.

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

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

In accordance with 18 U.S.C. 208, full waivers have been granted to Dr. Derek Raghavan, Dr. Douglas Blayney, Dr. David Kelsen, Dr. Victor Santana, Dr. Scott Lippman, and Dr. Kim Margolin. A copy of these waiver statements may be obtained by submitting a

written request to the agency's Freedom of Information Office, room 12-A30 of the Parklawn Building.

In addition, we would like to disclose that Dr. Albain, Dr. Raghavan, Dr. Schilsky, and Dr. Sledge's employers have interests which do not constitute a financial interest in the particular matter within the meaning of 18 U.S.C. 208 which may create the appearance of a conflict. The agency has determined, notwithstanding these involvements, that it is in the best interest of the government to have these individuals participate fully in all matters concerning Targretin.

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

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

Thank you.

DR. SCHILSKY: Thank you.

We now have time for an open public hearing. We have a number of people who have requested an opportunity to speak to the committee. I'm just going to call on people in the order that they're listed on our agenda.

I'd like to ask each person, first, to come to the podium; second, to identify yourself and whether you received any financial support to be here; and to try to make your statement as concisely as possible in the interest of time.

So, let's begin with Barry Kupsch. Is Mr. Kupsch here? Please come to the microphone. Please let us know if you've received any support for being at the meeting today. Mr. Kupsch, as I requested, before you begin your statement, would you please let us know if you've received any support for being here?

MR. KUPSCH: No, I have received nothing.

DR. SCHILSKY: Thank you.

MR. KUPSCH: Good morning. I am Barry Kupsch, a sufferer of CTCL. I'm voluntarily appearing

this morning to share my experience with Targretin capsules. Ligand is not paying me to speak but are reimbursing for necessary expenses.

Several years ago, I was afflicted with an unusual skin disorder and was seen by several dermatologists. Not one of them could come up with the diagnosis, just a guess. My body was covered with a very raised, red, itchy rash, accompanied by the enlargement of the lymph nodes in my neck and groin. The itchiness progressively worsened and I started getting large cracks in my hands, heels, and soles of my feet. Walking was an experience in pain every day with every step I took. The only way I could walk was to use crazy glue and glue the cracks together, hoping none would end up in the crevices. When I did walk, I would shuffle along at the same speed as an elderly person.

During the following months, I was started on PUVA treatments in Edmonton. This was a trip twice a week and a drive of 2 hours one way. At first there seemed to be some improvement, then suddenly I reacted to it. My skin became very reddened as if I was severely sunburnt. After this, I was unable to tolerate

the sun at all. The only way I could be outside was to cover my body with sunscreen and wear sun protective clothing.

Shortly thereafter, I was admitted to the hospital twice with generalized swelling due to fluid retention. My skin started weeping fluid, especially from my legs and ears. At this time I was sloughing skin and my face looked like it was dipped in water, then oatmeal. The pain was very severe.

Some of the medications which I was on were methotrexate and soralen which made my skin even more sun sensitive. The itchiness worsened, which was one of the side effects of this drug, and the pain remained constant.

In March of 1996, I was started on interferon injections and a positive diagnosis of CTCL was made. I did start having some improvement in my hands and feet, but the itchiness remained. I took the interferon for a year and a half. The major side effects for me were depression, irritability, and constant flu-like symptoms. My arms and thighs were sore from all the needles.

My condition was not improving and the itch was so bad I took a wire brush to my hands, desperate for some relief from the itch. Instead of sleeping at night, I would scratch till the early morning hours, and our bed sheets would be constantly covered with blood.

Since my occupation is farming, I spend many hours outside. While doing my field work, I thought I was protected from the sun by the tractor cab. Much to my surprise, the sun rays were magnified by the glass, burning me even more severity. Thus, I was unable to do my farm work outside in the daytime. So, when other people were sleeping, I was out working. My condition was to the point of being unable to work, so I hired people to help me farm.

There were many times I hated being around people, and people did not like being around me because I was constantly scratching. My sleep habits were messed up and my family was having a hard time coping with the miserable person I became. Since I could not see any light at the end of my tunnel, suicide did cross my mind just to end the constant itch and pain.

In September of 1997, I was given the

opportunity to partake in this Targretin study which was the only thing left for me to do. I found the Targretin easy to take and I noticed a change in my skin within a few days. I started shedding layer after layer of skin. The cracks all healed and my skin slowly started to look normal. After being on the Targretin for a year and a half, the itchiness had finally subsided. My skin is now a normal texture and color. My lymph nodes have decreased dramatically in size.

The only side effects I have had are higher levels of cholesterol and triglycerides. I have been taking Lipidor to counteract this. I finally can live a normal life, work, and have fun outdoors, and feel there is a future for me and my family.

In October, I decided to come off the Targretin temporarily just to give my body a rest from all the drugs, but plan to resume the treatment should any problems arise.

Thank you.

DR. SCHILSKY: Thank you very much.

Next is Gaetana Grobluski.

MS. GROBLUSKI: Good morning. My name is

Gaetana Grobluski. I'm here to speak voluntarily regarding my use of Targretin capsules as treatment for my CTCL. I am not receiving any payment for being here except for expenses directly related to my travel.

About two and a half years ago, I developed symptoms on my body which were red, very itchy, skin pealing. My hands were like claws. I couldn't open them. Fissures were deep. And doctors didn't know what was happening at first. I was being treated for eczema. I was being treated for psoriasis. They gave me prednisone. Prednisone just made my body swell up and did nothing.

After being introduced to the doctors at NYU Medical, they put me on something called cyclosporine. Cyclosporine didn't seem to help to do anything.

I was introduced to my current doctor who, after substantial treatments -- or I should say, after trying to find out what was wrong with me, he put me on something called interferon A. Interferon A did nothing for me except make like a zombie. I was lethargic. I had no interest in life. I didn't want to get out of bed. It was a major decision whether to have a cup of

soup to eat or a plate of spaghetti. I describe it as a zombie like feeling.

After approximately three months of being on interferon A, they tried methotrexate. Methotrexate had a reaction to me which made me like a crazy lady. I'd be scratching and pulling at my body. I'd go through chills and completely uncomfortable.

After methotrexate, we tried what they call PUVA treatments. PUVA treatments I felt did nothing for me except give me a very lovely tan. I got lots of compliments on what a beautiful looking tan I had, and that was about it.

After discussing with my doctor, we decided to try this Targretin. I've been on it for a little over two years now. Targretin I feel has given me back my life. The fissures are gone. The scaling has gone. I used to get up in the morning and my skin used to just peal off. I felt like a snake shedding its skin. Today my skin is smooth again. I have a life.

I do experience some side effects with Targretin, but nothing I can't overcome and control. I take some Tricor and Lipidor and Synthroid. In

addition, I have such experience as losing hair and some weight gain. Those I feel I can overcome.

But my experience with Targretin has been lifesaving as far as I'm concerned, and I'm happy to be in the program and hope to continue using it.

And I thank you for listening to me.

DR. SCHILSKY: Thank you very much.

Next will be Nancy Borcherding.

MS. BORCHERDING: My name is Nancy Borcherding, and I'm excited that I have the opportunity to talk to you today. I came here voluntarily to tell you my story. Before I begin, I want to make it clear that Ligand has not paid me to speak here today, but they have only reimbursed me for my expenses so that I could be here.

I was diagnosed about 18 years ago with CTCL. Since then, I have tried many treatments, the same that have been told to you by others today, Accutane, methotrexate, prednisone, PUVA, UVB, UVA. All of these treatments did help me for some time, but they eventually became intolerable and also ineffective, producing itching and sometimes added skin lesions.

Two and a half years ago, I thought my only option was interferon. Again, the two people who spoke to you today had mentioned that. I was terribly frightened by that drug. I had had a friend who was on it. I do lead and have always led a very active life. I work full-time and I work out every day. I knew that on this drug none of that would be possible and that my life would change.

Fortunately for me, my doctor who had been treating me, who was a man of great compassion and a person who had kept in very close contact with all kinds of studies and things that were going on with this disease, suggested that I enter this study of Targretin. I began by using the topical Targretin, which at the beginning again gave me relief, but again only temporarily, and after a year Dr. Deborah Brenneman suggested that I go on the Targretin capsules.

This drug has improved my condition dramatically. The skin lesions have faded. The itching has stopped, and everything almost has virtually disappeared. How could anybody ask for more than that?

I do have some side effects. I do have

raised triglycerides, lower thyroid, and my white blood count also is lowered. But all of these have been able to be treated with medication. The side effects certainly can't compare to how wonderful the treatment has been on the Targretin capsules. I feel that I am a very, very fortunate person.

I have been on the capsules for two and a half years, and I continue to take them as I speak to you today. My CTCL is 95 percent cleared, and the side effects are all under control.

I guess more importantly the fact that I'm here today, that I'm happy and alive and have a wonderful quality of life is more than I can say. I can't complain about just popping a pill to get me to that level. I hope that through my appearance today that I will be able to help other people who have the same disease as I do, and I just thank you for the opportunity of being here.

DR. SCHILSKY: Thank you very much.

Next is John Carter.

MR. CARTER: My name is John Carter. I'm 75 years of age and I'm a retired surgeon, having retired

the 4th of July of this year. I was a clinical professor of surgery at the Albany Medical College prior to my retirement.

I come here voluntarily. I have nothing whatsoever to do with Ligand Corporation. They've paid my way down and they're paying for the hotel expenses.

In the winter of 1997, I began to have a terrible itch. I went to see several dermatologists, all of whom told me I had dry skin, and they gave me all kinds of salves to work and try with. None of them seemed to work.

As time went on, my dry skin and itching worsened. I began to develop generalized adenopathy. I had many biopsies, and finally a positive biopsy was obtained in the summer of 1998. At that time, I was referred down to Yale, and at Yale they started me on PUVA, supplemented by photopheresis. Both of them tended to make things worse. I developed edema, large lymph nodes throughout my body. I had so much edema in my left leg that I thought that I had a deep phlebitis, and I had an ultrasound done, proving that my veins were clear. At that time I also had biopsies done which

showed only a chronic inflammation.

At that time I was asked if I would be willing to go on the Targretin study, and I said, sure, and I went on it in August of 1998. I've been on it since that time, 8 capsules per day. No problem taking the capsules.

Within a short period of time, my itching disappeared. I might say that the itching didn't bother me particularly in the operating room, but it had a terrible effect upon me at night. I was unable to sleep, and the lack of sleep began to show in my work. Anyway, when I went on the Targretin, the itching soon disappeared and everything became fine again.

I've had no bad side effects from the Targretin. My triglycerides went up a little bit, but they're down to normal with Lipidor, 10 milligrams a.m. and p.m. Although I had no clinical symptoms of hypothyroidism, my thyroid function test deteriorated a bit, and I'm on 0.05 milligrams of Synthroid per day to control that problem. I have had no problems with the disease.

I think Targretin is a fine drug, and I hope

that you people will approve it for the rest of the people in this country who might be suffering from T-cell cutaneous lymphoma.

Thank you for listening.

DR. SCHILSKY: Thank you very much.

Next will be Judy Jones.

MS. JONES: My name is Judy Jones, and I'm President of the Mycosis Fungoides Foundation, a nonprofit patient advocacy group dedicated to helping patients with mycosis fungoides, Sezary syndrome, and other forms of cutaneous T-cell lymphomas, CTCL.

I have not received any compensation for attendance at this meeting.

This foundation came about as a result of an on-line support group I started because I felt so isolated with my disease that nobody had ever heard about. As I listened to people talk about the problems they were having getting treatment, which what you heard this morning is what I listen to every day or I read on my computer, three things stood out for me.

In some cases the treatment was worse than the disease symptoms. The therapies being used had not

changed since the disease was identified. There was no money available for research for this orphan disease.

There are over 16,000 people with mycosis fungoides in the United States for whom there has been little interest and insufficient research to address the devastating impact of this rare form of non-Hodgkin's lymphoma. 450 of these people belong to my support list.

As a long-term MF patient and a member of this list, I would like to speak for all of us to ask for support, increase awareness, and promote research and funding for treating this orphan cancer. There is significant unmet clinical need for new, effective, and safe therapies to treat CTCL. There has been a lot of money spent on other types of cancer, but Ontak was the only new therapy approved by the FDA in the past decade for CTCL. Ten years is a long time.

The most widely used current therapies include nitrogen mustard, PUVA which is soralen, which makes you queasy, with ultraviolet light, and electron beam radiation. Each of these therapies is accompanied by significant complications or side effects, especially

for some of the more frail and elderly MF sufferers.

Nitrogen mustard is a topical treatment. Applying it all over one's body is a very complicated, time-intensive project for most people. Tonight when you go home, see if you can reach every spot on your back.

The PUVA protocol starts with treatment three times a week for two or three months and is slowly tapered down, sometimes extending for several years. Many MF patients are not fully mobile or able to travel the sometimes great distances to be treated with PUVA that require multiple visits to a doctor. There are very few jobs that will allow for that much flexibility, creating financial hardships for many families. When you use PUVA, you also have to wear a plastic goggles, sunglasses for 24 hours afterwards, which also is a constant reminder that you have this, and people are constantly asking, how come you're wearing those glasses inside?

Electron beam radiation means the loss of hair and nails. The patient must deal with swelling, loss of the ability to sweat, and possible burns. PUVA

and electron beam therapies are embarrassing and undignified. Both of those you strip down to nothing while people are watching.

Another side effect of all of these therapies is that they increase the likelihood of other skin cancers. Not only do we have to learn to live with the cancer that we have, we always have to be aware of the possibility of getting another type of cancer.

The idea of being able to have an oral therapy that can be taken at home and does not increase the likelihood of getting a different type of cancer is of tremendous interest to us. New drugs will hopefully have improved safety and effectiveness with increased convenience.

One of the goals of the Mycosis Fungoides Foundation is to support research for new treatments for our disease. For this reason, we are here to encourage the Oncologic Drugs Advisory Committee to thoroughly consider this new treatment, Targretin capsules. I'm not a physician and do not have firsthand experience with Targretin, but I have heard from several physicians who have worked with it in clinical trials and have

reported good results.

Thank you.

DR. SCHILSKY: Thank you very much.

There are a number of letters that have also been submitted, and Karen has a statement regarding the letters.

DR. TEMPLETON-SOMERS: In the interest of time, I'm going to summarize the three letters I received about Targretin rather than read them. All three of the writers wrote at the suggestion of the sponsor, but did not receive a financial incentive to write.

Mr. Cruse, Ms. Russotto, and Mr. McVoy all participated in the clinical trials for Targretin, had very positive experiences with the drug, and urge for its approval.

The letters will be included as part of the meeting record and are available for reading by the public in the notebook at the meeting registration desk. And for committee members, they're also included in your blue folders at the table.

Thank you.

DR. SCHILSKY: Thank you.

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

(No response.)

DR. SCHILSKY: If not, we'll move on to the sponsor's presentation. Dr. Holden?

DR. HOLDEN: Thank you very much, Dr. Schilsky, and good morning. I'm Howard Holden, Vice President of Regulatory Affairs and Compliance from Ligand Pharmaceuticals. We're pleased to be here today to discuss our NDA for Targretin capsules.

Targretin capsules have been developed to treat patients with cutaneous T-cell lymphoma. The proposed indication is for the treatment of cutaneous manifestations in patients with all stages of CTCL, stages IA to IVB, in the following categories: patients with early stage CTCL who have not tolerated other therapies, patients with refractory or persistent early stage CTCL, and patients with refractory advanced stage CTCL.

After I've provided some background information on the drug, Dr. Francine Foss, who is

Associate Professor of Medicine in the Division of Hematology and Co-director of the Skin Oncology Program at New England Medical Center, will provide an overview of the disease.

Next, Dr. Richard Yocum, who was the project the physician for the Targretin program at Ligand, will present the efficacy data from the clinical trials.

Then Dr. Steven Reich, Senior Vice President of Clinical Research, will review the safety findings from the patients who received Targretin.

Following this presentation, two of our clinical investigators, Dr. Kenneth Hymes, who is Associate Professor of Medicine in the Division of Hematology at the New York University, and Dr. Madeleine Duvic, who is Professor of Medicine and Dermatology and Chief of the Section of Dermatology, as well as Director of the Multi-disciplinary CTCL Clinic at the M.D. Anderson Cancer Center, will provide their perspectives of the response of patients with CTCL to Targretin.

I'll then return to summarize the findings and address questions.

Here's the regulatory history of Targretin

capsules. I'd like to point out that Targretin received orphan drug designation in June of this year, and the NDA was granted priority review by the FDA in August of this year.

This is the structure of bexarotene. It's a lipophilic solid with one crystalline form. The final clinical formulation is a 75 milligram soft gels in capsule, which is filled with a suspension of micronized crystalline bexarotene and a polyethylene glycol vehicle.

Bexarotene is a novel synthetic retinoid analog that selectively binds to and activates the retinoid X sub-family of RXR intracellular receptors. At high doses, some degree of activation of the RAR receptors could be expected. Although classified as a retinoid due to its biological activity, it is structurally distinct from the vitamin A derived retinoids such as tretinoin, alitretinoin, and isotretinoin.

Once activated, RXR receptors function as transcription factors that regulate processes such as cellular differentiation and proliferation, apoptosis,

and insulin sensitization.

Bexarotene has been studied in the treatment of various advanced cancers, actinic keratosis, non-insulin dependent diabetes, as well as psoriasis.

Before proceeding further, I'd like to note that Ligand has made available to the committee copies of our presentation. These slides are numbered for easy reference during the question and answer period.

Now I'd like to introduce Dr. Francine Foss who will provide an overview of cutaneous T-cell lymphoma.

DR. FOSS: Thank you very much. It's a pleasure to be here today to provide an overview of CTCL, a disease that I've been treating as a clinician for about 15 years now.

The cutaneous lymphomas, albeit uncommon, are highly symptomatic malignancies of mature CD4 expressing T-lymphocytes that share many features in common with low-grade B-cell lymphomas. Most patients are symptomatic even at the earliest stage of disease with itching and susceptibility to recurrent skin infections, and the majority suffer cosmetic disfigurement.

Despite the fact that the disease may be clinically localized to the skin, molecular studies document that it is disseminated even at the outset since clonal populations of tumor cells can be detected in the peripheral blood using PCR even in early stage patients.

Like low grade B-cell lymphomas, CTCL by and large is incurable except in a subset of very early stage patients who may sustain durable remissions using a variety of topical therapies.

Most patients with CTCL undergo a series of therapies as the disease symptoms persist and progress over the course of years. Since the most commonly used therapies are skin directed, cumulative overlapping toxicities limit the duration and intensity of therapy over time.

Unlike other cancers, palliative benefit from the variety of therapies used in this disease is especially important for these patients, even without a definitive survival benefit, and a recent phase III trial with Ontak, which employed a quality of life tool, documented this.

Because of the compromising skin integument, the major morbidity in these patients is infection, both cellulitis and sepsis, and in fact, this is the major cause of death. The relatively short response durations using current available therapies point to the need for novel therapies which are non-immunosuppressive.

The term CTCL has been used to define a spectrum of diseases, including mycosis fungoides and the Sezary syndrome and peripheral T-cell lymphomas, which are all manifest by infiltration of the skin by malignant T-cells. Mycosis fungoides defines a syndrome with skin involvement in the form of patch, plaque, or erythroderma, with or without detectable lymph nodes, whereas the Sezary syndrome defines a triad of generalized erythroderma, lymphadenopathy, and circulating Sezary cells. In most instances, the term CTCL is used synonymous with mycosis fungoides and Sezary syndrome, and that's how I'll use it here.

There are about 1,000 new cases of CTCL per year in the United States and the prevalence of the disease is estimated at 16,000 to 20,000. CTCL comprises 2.2 percent of all non-Hodgkin's lymphomas,

and the incidence is increasing concomitant with an overall increase in non-Hodgkin's lymphoma. The disease is more common in men and blacks and the median age at diagnosis is 45 to 65.

The staging system for CTCL is unique from other non-Hodgkin's lymphomas in that it is primarily based on the skin manifestations in the form of limited patch or plaque, diffuse patch or plaque, cutaneous tumors, and erythroderma. In some instances where lymph node biopsy is available, histopathologic involvement is included in the staging system, as is visceral disease.

This slide shows an example of the skin manifestations of this disease. This is a patient with limited patch stage disease which can look very much like eczema.

This is patient with diffuse patch or plaque stage disease involving greater than 10 percent of the body surface area.

This is a patient with a cutaneous tumor. Oftentimes these can become ulcerated.

And this is a patient with diffuse erythroderma or diffuse redness involving the entire

skin surface area.

A recent retrospective study of over 400 CTCL patients published by Dr. Zackheim demonstrated that although patients with plaque-only disease are considered early stage, their survival in fact is impacted by their disease when compared to age and race-matched controls. As shown here, patients with plaque stage disease involving greater than 10 percent of the body surface area have a 10-year relative survival of 67 percent.

This points to the systemic nature of the disease even at its earliest stages and justifies the practice that most CTCL physicians have undertaken to complement skin-directed therapies with biologic or systemic therapies early on in the course of disease.

The current treatments for CTCL are either skin-directed, as in topical chemotherapy, PUVA, or skin irradiation, or systemic.

In the early stages of disease, skin-directed therapies are implemented first. The toxicity of these therapies include premature skin aging, secondary skin cancers, and hypersensitivity reactions.

As the disease becomes more advanced or refractory, systemic therapies are used. The first systemic therapy for most patients is interferon alpha which is associated with constitutional symptoms and which must be administered for a median of 4 months before a response is observed. Other systemic therapies include oral methotrexate, alkylating agents, Ontak, multi-agent systemic chemotherapy, and other investigational therapies, including cytokines and other novel agents. Most of the systemic therapies, particularly the cytotoxic therapies, are further immunosuppressive in this group of patients who suffers from a primary defect in T-cell mediated immunity.

Most of these therapies I've talked about have not been formally studied in CTCL, and with the exception of Ontak, none of them are approved for this indication. Most of these studies have been small, and there's only one randomized controlled study in the literature which took 7 years to complete.

There are no standardized response criteria in this disease and the observed response rates are variable depending on prior therapies. By and large,

response durations are short, ranging from 4 to 13 months, and there has been no demonstrated survival benefit with any therapy.

The assessment of response in these trials has been difficult and suffers from the lack of standardized response criteria. In some instances, as shown here, a lesion may shrink considerably, leaving an area of hyperpigmentation which on biopsy may or may not contain residual malignant cells. Likewise, in the erythrodermic patient, the intensity of erythema may vary at different times, even during the day, due to conditions of heat or application of moisturizers. And it's often very difficult to quantitate improvement in these patients just using skin photographs. In fact, many of these patients who tend to be intensely pruritic will often report improvement in their pruritus before objective skin response can be documented.

The goals for management of advanced and refractory CTCL include: first and foremost, palliation of symptoms, including pruritus and skin infections; second, to attempt to slow or prevent further progression of the disease. The therapeutic strategy

involves the use of combination approaches directed at the skin, as well as systemic therapies, with the goal being to attempt to avoid further immunosuppression related to the therapy.

In summary, CTCL is a highly symptomatic disfiguring disease which is life-threatening in the advanced stages and there are no spontaneous remissions. The disease is incurable except at its very earliest stages. And given the limitations of our present therapeutic armamentarium, there's a desperate need for novel therapies which are easy to administer and which are non-immunosuppressive.

I'd now like to introduce Dr. Richard Yocum, who's the project physician and senior medical director at Ligand, who will present the phase II/III clinical studies efficacy data.

DR. YOCUM: Good morning. I will be presenting the phase II clinical study data for Targretin capsules in CTCL beginning with an overview of the design and scope of these studies. Next I will review the eligibility criteria in the patient population enrolled and then discuss the efficacy

endpoints, results, and conclusions from these studies.

Beginning then with the design and scope of these trials, a total of 690 patients were treated with Targretin capsules in 16 clinical studies. Of these 690 patients, 200 patients with CTCL were treated, and of these 200 CTCL patients, 152 were enrolled prior to the cutoff date for inclusion in the NDA per agreement with the FDA. And of these 152 patients, 84 began treatment at the 300 milligram per meter squared per day dose level, which was determined to be the optimal starting dose based on the risk/benefit assessment of the drug.

The decision to proceed to pivotal clinical trials was based on four factors. First, non-RXR-selective retinoids were known to have activity in this disease. Second, the phase I/II program had shown Targretin capsules to be generally well tolerated in a variety of cancers. Third, 2 of 9 patients with CTCL had experienced clinical improvement in a phase I trial of Targretin capsules. And fourth, responses were observed in CTCL lesions being treated with topically applied Targretin gel in an ongoing phase I/II program.

The two pivotal trials were similar in many

aspects. They were both open-label and historically controlled, about which I will say more in a moment. They were conducted multi-nationally at 32 enrolling study centers in the U.S., Canada, Europe, and Australia. Both studies contained explicit criteria for prior CTCL therapy specific to each protocol. The early stage protocol, comprising stages IA through IIA, employed a treatment program that allocated patients to low and high dose therapy. The advanced stage protocol, comprising stages IIB through IVB, used only the high dose therapy. The separation of the CTCL patient population into early and advanced disease, according to TNM staging and divided at the IIA/IIB point, was an arbitrary one for the purpose of protocol design.

The historical control of these studies was based on the absence of spontaneous remissions in this disease, especially in the refractory, persistent patient population as defined in the protocols.

There were two statistical targets for a successful study. First, a point estimate response rate of at least 20 percent, and second, the lower bound of the 95 percent confidence intervals around that point

estimate, excluding 5 percent as a conservative estimate of the spontaneous response rate.

The study objectives were to evaluate the safety, tolerability, and antitumor efficacy of Targretin capsules in patients with CTCL who had been previously treated and failed prior therapies according to the protocol criteria. In addition, the high and low dose therapies were to be evaluated in the early stage study.

The dose regimen utilized in the early stage study was as follows.

The low dose of 6.5 milligrams per meter squared per day was chosen to approximate the dose at which responses were seen in two CTCL patients in the phase I study.

The high dose was based on the maximum tolerated doses determined in two initial phase I/II studies, namely 300 milligrams and 600 milligrams per meter squared per day. The high dose in the initial versions of the protocol, namely 650 milligrams, was reduced by successive protocol amendments to 500 and then finally to 300 because of a relatively high

incidence of dose-limiting toxicities in the earliest patients enrolled.

Patients were to be randomized 1 to 1 to low dose or high dose. The lose dose was not intended to act as the control for the high dose arm. Instead, the controlled nature of the study was based on a comparison of the response rates in each dose group individually and with the lower bounds excluding the conservative estimate of 5 percent, rather than hypothesis testing of response rates in the low versus high dose groups.

In addition, the early stage study permitted patients to cross over from low to high dose in the event of disease progression by week 8 or with the absence of any response by week 16.

Only the high dose therapy was utilized in the advanced stage study. The relative high incidence of hypertriglyceridemia and to a lesser extent leukopenia in the earliest enrolled patients at 650 led to protocol amendments reducing the starting dose to 300. The protocols contained specific dose reductions in the event of toxicity, and for those patients who initiated therapy at 300, these dose reduction levels

were 200 and 100.

Finally, for the purpose of analysis, patients were grouped according to their initial dose level, namely 6.5, 300, and greater than 300.

Turning now to the eligibility criteria, the main criteria, which were common to both studies, included a clinical diagnosis of CTCL confirmed to be at least histologically consistent with CTCL by two independent dermatopathologists, failure of prior CTCL therapy meeting the specifics of each protocol, and adequate washout from all prior CTCL therapies. In addition, patients were to have a Karnofsky score of at least 60, 18 years of age, acceptable organ function, the absence of pregnancy, along with provisions for effective contraception.

For the early stage study, the entry criteria for prior CTCL therapy were as follows. Patients must have been refractory to, intolerant to, or have reached a response plateau for at least 6 months on two prior therapies from this list, including the phototherapies of PUVA and UVB, electron beam therapy, photopheresis, interferon, systemic chemotherapy, or the topical

chemotherapies of nitrogen mustard or BCNU. At least one of these prior therapies must have been a phototherapy or a topical chemotherapy, and in particular topical steroids and systemic retinoids could not be used to qualify patients.

For the advanced stage study, patients had to be refractory to one or more systemic anticancer therapies for CTCL.

The protocols contained a specific definition for refractory, defined as the lack of at least 50 percent improvement or progression of disease while still on therapy after an initial response.

In addition, the early stage protocol, which permitted enrollment of patients on the basis of intolerance, defined intolerant as discontinuation of therapy due to side effects or toxicity.

The application of the eligibility criteria led to the enrollment of the following patient population. Shown in this table is enrollment by TNM stage of disease at baseline. The horizontal dotted line separates early from advanced stage disease according to the protocol design.

The 300 milligram initial dose group is highlighted because this was determined to be the optimal starting dose level and will be the focus of many of my comments. At this dose level of 300, the most common TNM stages were IIB, IB, and stage III, but patients were enrolled at this dose level in each of the seven TNM stages.

The distribution of patients at the 6.5 dose group in the early stage reflects the fact that this dose level was utilized only in the early stage study, and there was little substantial difference between the 300 and greater than 300 dose groups with regard to TNM staging.

In response to the FDA's question number 3 to the committee regarding characterization of prior therapies, patients in both of these studies generally had been heavily treated in the past for CTCL. This figure shows for the early stage study the percent of patients as a function of number of prior therapies. Patients are shown according to initial dose group with the 6.5 dose group in red, 300 in yellow, and greater than 300 in green. The median number of therapies was 3

and 4 and ranged up to 12. And as the graph shows, there was little substantial difference in the number of therapies between initial dose groups with regard to prior therapy.

This figure shows the number of prior CTCL therapies for the advanced stage study, again with the 300 dose group in yellow and the greater than 300 in green. The median number of therapies in this study were 4 and 6, respectively. Again, the two initial dose groups did not differ substantially by the number of prior therapies.

To elaborate further on the FDA's question number 3, this slide takes a look at the most common prior therapies previously experienced by at least 10 percent of patients in either study. The most common therapy in the early stage study was topical mustard at 93 percent, followed by PUVA, electron beam therapy, interferon, and then a number of other therapies. For the advanced stage study, these same therapies were commonly employed, but as one might expect, there was a higher prevalence of use of combination chemotherapy, methotrexate, and other systemic therapies. In

particular, this table shows that the CTCL therapies to which these study patients had been exposed were the conventional, mainstream treatments utilized for treating CTCL.

The FDA's question number 3 to the committee also addresses the characterization of responses to prior therapy. For those prior CTCL therapies that were specifically used to qualify patients for this study, 100 percent of patients met these criteria in the early stage study, and in fact 96 percent of patients were refractory to at least one and 78 percent refractory to at least two prior therapies. Besides refractoriness, the other categories that might have qualified the patients, namely intolerance and response plateau, were relied on relatively infrequently in only 21 and 3 percent of patients, respectively.

In the advanced stage study, 96 percent of patients were refractory to at least one, and 62 percent of patients refractory to at least two prior systemic therapies. The median number of prior systemic therapies to which they were refractory are two, ranging up to six.

In summary, the majority of patients exceeded the protocol requirements for the minimum number of prior qualifying therapies.

Both studies defined the same primary efficacy endpoints. There are no standardized or widely accepted response criteria in this disease, a disease that presents substantial challenges to devising a comprehensive system of evaluating responses to treatment. For this reason, Ligand introduced two primary efficacy endpoints: a physician's global assessment abbreviated PGA, and a composite assessment abbreviated CA. In addition, the primary endpoint classification for the studies, abbreviated PEC, was based on the PGA and the CA. I will now describe each of these endpoints individually.

The PGA was a 7-point grading scale for the investigator's assessment of the degree of improvement or worsening as compared to baseline. Similar grading scales have been used in numerous published clinical trials, especially in disorders with visually apparent disease manifestations, such as psoriasis and also CTCL. Our response classification required confirmation over

at least two assessments, separated in time by at least 4 study weeks. A complete clinical response, or a CCR, required a grading of 0, indicating complete clearing, the absence of disease, and grades 1, 2, and 3 constituted partial response, indicating improvement of at least 50 percent, but less than 100 percent improvement.

The CA endpoint was similar to composite systems published and in standard use such as the ACTG criteria for Kaposi's sarcoma and the Pazzi score for psoriasis. This endpoint concentrates on detailed, sequential measurements of index lesions to allow for consistent and precise disease assessments. Up to 5 index lesions designated 1X through 5X were selected on the basis of being representative of the patient's cutaneous disease. For each of these index lesions, five clinical signs, namely erythema, scaling, plaque elevation, pigmentation change, and surface area, were graded at each visit. A straight summation of scores for each of these clinical signs for each index lesion was performed for each post-baseline visit and then divided by the corresponding summation at baseline to

calculate the CA ratio.

As with the PGA, classification of response according to CA required confirmation of at least two assessments separated in time by at least 4 study weeks. If the CA ratio dropped to 0, indicating a complete absence of any index lesion disease, the patient would be a CCR, provided there was no other evidence of disease elsewhere. If the CA ratio dropped to at least .5, indicating at least 50 percent improvement, the patient would have been classified as a PR, provided that there was no new disease and no disease progression elsewhere.

It's important to realize that new or progressive disease elsewhere would override any degree of improvement according to the CA ratio no matter how substantial, and also that improvement or resolution in adenopathy, cutaneous tumors, or other disease manifestations could never constitute a response per se. In this regard, the CA endpoint was a conservative and more stringent assessment of response.

Both the PGA and the CA endpoints provided valuable measures of clinical benefit in these studies.

In particular, the PGA allowed clinicians with expertise in treating CTCL and assessing disease to evaluate all of the varied disease manifestations that were important to patients. Also, the improvement or resolution in lymph nodes, cutaneous tumors, and pruritus could contribute to the classification of response.

It's also noteworthy that the PGA assessment was made by the investigator independent of knowledge of the classification of response according to CA since CA responses were determined by programmed algorithm.

Finally, both protocols defined that a patient meeting response criteria by either PGA or CA would be classified a responder for the study, and this endpoint was abbreviated PEC. The only exception is that if a patient progressed by one endpoint prior to the confirmation of response by the other, then this patient would be classified as progressive disease for the duration of the study.

The focus of my presentation of efficacy findings will be on the PEC response at the 300 milligram initial dose group.

In addition to the primary endpoints, both studies included a number of secondary efficacy endpoints as shown on this table. Photographs do not appear on this list of protocol-defined endpoints because photographs were not a study endpoint, rather they were included only as supporting data. However, because of the emphasis that FDA appears to be placing on photographs, I am compelled to make some comments about the prospective intended role of the photos.

The concept of using photographs to validate one or both of the primary endpoints was introduced by the FDA only after the NDA submission and was never the intent of the study designs. In fact, Ligand did review the photographs and found the appearance of lesions to be generally consistent with response classifications in the studies.

In addition to close-up index lesion photographs, this protocol specified global photographs that were to be half-body, front and back. After the protocols were written, but prior to the initiation of either study at any center, Ligand rethought the half-body technique and for a number of reasons determined

that a regional index technique, capturing about 8 by 10 inches of skin surface area would be more useful. It was the regional index technique that was introduced at the outset provided to all centers in detailed written instructions.

Unfortunately, Ligand was remiss in not issuing an administrative amendment to the protocol, but did notify the FDA of this change in technique at the December 1998 pre-NDA meeting.

The reasons for instituting regional index photographs rather than half-body were as follows. The faint and subtle nature of lesions in this disease become indiscernible at greater focal distance as does the assessment of height, and the areas that may be commonly affected by CTCL would have been missed in the half-body photos.

Both the PGA and the CA endpoints were based on all cutaneous and extracutaneous disease manifestations. Photographs did not capture the entire body surface area and could not be expected to show extracutaneous disease, and in fact, even the half-body photographs would not have captured 100 percent of the

body surface area. Due to these and other limitations, photographs remain inferior to the direct, hands-on evaluation by the investigator.

Compliance with photographs was extremely high at study centers at about 95 percent, and Ligand submitted 6,142 photographs with this NDA. Although the photographs do generally support the response assessments, response and in particular patient clinical benefit cannot be reliably determined in these studies from photographs alone.

Before presenting the findings of these endpoints that were prospectively defined in the protocols, I want to acknowledge and thank the FDA for their input and contributions to the study design, particularly with regard to review of the primary efficacy endpoints during the time of protocol development. The identification of suitable and acceptable primary endpoints was very important, given the absence of standardized response assessments in this disease. The knowledge that the Division of Oncology had reviewed Ligand's proposed endpoints and could not identify more relevant oncology criteria and that the

open-label study design, combined with compelling results would, in fact, support an NDA allowed Ligand to proceed to protocol initiation with confidence.

All of the efficacy results that I will be showing are based on the intent-to-treat data set of all patients enrolled. In addition, the protocols did define an evaluable patient data set, and although time constraints prevent me from showing the evaluable patient data set, I am prepared to discuss, if requested, the reasons for exclusion, as well as the resultant response rates that still met the protocol-defined statistical targets.

This figure shows the primary endpoint results for the early stage study by dose group along the x axis for each of the endpoints, with the PGA in gray, the CA in lavender, and the PEC in yellow. The percent of patients responding, along with 95 percent confidence intervals, is plotted against the y axis.

Focusing on the 300 milligram dose group, both statistical targets for a successful trial were met whether considering the PGA, CA, or PEC, namely the point estimate response rates exceeded a 20 percent

target and the lower bounds of the 95 percent confidence intervals, shown at the lower whiskers, comfortably exceeded the 5 percent conservative estimate. In particular, the response rate according to PEC at 300 milligrams was 54 percent. Similarly, both statistical targets were met and exceeded at the greater than 300 milligram dose group.

In contrast, for the 6.5 dose group, the 20 percent point estimate was met but not exceeded according to CA and PEC, but not for the PGA, and in particular, the lower bound of the confidence intervals was unable to distinguish this dose as being superior to no treatment at all.

Finally, a dose-response relationship according to initial dose groups is evident.

This figure shows the analogous display for the advanced stage study, again by initial dose group. As seen with the early stage study, both statistical targets were met and exceeded at the 300 milligram dose group and also for the greater than 300 milligram dose group, for each the PGA, CA, and PEC. In particular, according to the PEC at 300, the response rate was 45

percent.

This slide shows the response rates for both studies combined in the integrated data set. A dose-response relationship is evident across the three initial dose groups, with the PEC response rate at 300 for both studies combined of 48 percent.

This figure shows response rates for the integrated data set by initial dose group using shading to represent the degree of response where the darkest shade, shown here, represents 100 percent improvement, indicating a CCR. These data show a dose-response relation for CCR which was 4 percent at the 300 milligram dose group and rose to 17 percent at the greater than 300 milligram dose group.

This is a Kaplan-Meier analysis of the time to response for the integrated data set showing the response rate on the y axis plotted against the number of days, time to response, on the right, with each of the initial dose groups color coded, the 6.5 patients in red, the 300 milligram patients in yellow, and the greater than 300 milligram patients in green. A dose-response is apparent not only for the rate of response,

but also for the projected time to response. Too few patients responded at 6.5 to be able to project a median time to response, but for the 300 milligram dose group, the projected median time to response was 16 weeks, 16.3, somewhat longer than the 12.3 weeks required for the greater than 300 milligram dose group.

This Kaplan-Meier figure shows the time to relapse for the early stage responders in the 300 dose group according to PEC. When these patients were followed for nearly 300 days, the relapse rate was 13 percent, that is, 2 of 15 patients, a rate too low in order to permit a projection of the median time to relapse.

In the analogous Kaplan-Meier figure for the advanced stage study for those responders according to PEC at 300, when these patients were followed for nearly 300 days, the relapse rate was 36 percent and the projected median time to relapse was 43 weeks, indicating that responses to Targretin capsules are durable.

As shown previously, patients were accrued in these studies at each of the TNM stages of disease, and

this figure, showing the response rate as a function of TNM stage, shows that responses were observed in each of the TNM stages. Note that even in the more typically difficult to treat stage III and stage IV patients, response rates for cutaneous manifestations of disease were in the range of 32 to 44 percent.

The early stage study permitted crossover of patients from low dose to high dose therapy, as shown in this table, and of the 15 patients who initiated therapy at 6.5, 11 were crossed over to either 300 or greater than 300. Prior to crossover, the response rate at the 6.5 dose group was 18 percent and climbed after crossover, at which time there was a resetting of the baseline to 73 percent.

Also, the rate of progression was 64 percent, according to the PEC endpoint, prior to crossover, and after crossover, again with the resetting in the baseline, progressive disease dropped from 64 percent to 18 percent, demonstrating the ability of high dose therapy to rapidly reverse disease progression that was observed on low dose therapy.

In addition to the correlation observed for

the primary endpoints, these responses were reinforced by positive findings of secondary efficacy endpoints, including a dose-response relationship by various measures, as well as additional measures of clinical benefit, including body surface area involvement, the individual index lesion clinical signs, pruritus, and questions on the CTCL specific questionnaire. Because of time constraints, I will only briefly show a small amount of data on these secondary efficacy endpoints.

This Kaplan-Meier analysis shows the time to progressive disease for all patients in the integrated data set in both studies, again color-coded by initial dose group. Not only was the rate of progressive disease inversely correlated with the initial dose level, but the time to progression also showed an inverse dose relationship where the projected time to progression for the 6.5 dose group was 13.6 weeks, climbing to 21 weeks for the 300 milligram dose group and then more than doubling to 59 weeks for the greater than 300 milligram dose group.

Note that with any Kaplan-Meier analysis, as the number of patients at risk drops to very small

numbers at the right side of the curve, the curve can take on an unreliable and spurious appearance. The dose-response relationship seen for response rates and time to progression is, therefore, mirrored by an inverse dose-response relationship for the rate of progression and also for time to progression.

Cutaneous tumors were present in 24 of the patients in the 300 milligram and greater than 300 milligram dose group at baseline. A response classification that would be based solely on cutaneous tumors showed that 38 percent of patients would be classified as responders and would include 17 percent of these patients having had complete resolution of all of their tumors present at baseline. In fact, only 4 patients had progression of those tumors that were present at baseline.

This figure shows the change in the aggregate area of the index lesions plotted in square centimeters along the left axis and also the assessed percent total body surface area of involvement plotted against the right axis. The index lesion area is shown in yellow and the percent body surface area shown in green.

Patients experienced improvement by both of these measures, in particular indicating that the aggregate area of the index lesions was, in fact, an accurate representation of the total body surface area involvement.

I would like to emphasize that these data are based on not only those patients who met primary endpoint response criteria, but also include the patients who failed to meet the response criteria.

As a secondary and independent endpoint, separate from and not included in the CA endpoint, pruritus was graded on a scale of 0 to 8, with 8 being the most severe. For the 300 milligram dose group, this figure shows the change in pruritus for these patients in yellow diamonds and also the two subsets of patients for the 41 patients who took no antipruritic agent at any time during the study shown in green, and for the 43 patients who took at least one antipruritic agent at some time during the study shown in blue. At baseline, 85 percent of these patients had pruritus with a mean grade of 3.6.

The improvement that was noted, regardless of

concurrent antipruritic use, indicated that this improvement could not be attributed to antipruritic use during the study. The far right data points are skewed by just 1 or 2 patients' contributing data at that point. As with the previous figures, these data include not just the primary endpoint responders, but also the patients who failed to meet criteria by the primary endpoint.

Finally, this figure shows the patients' self-assessments on the last two questions of the CTCL-specific questionnaire for the 300 dose group and, again, includes the primary endpoint responders as well as the nonresponders. Question 8 inquired about the patients' assessed change in CTCL, and this is plotted in yellow. Question 9, plotted on the right side of the curve, asked the patient to describe their level of satisfaction or dissatisfaction with study drug treatment. The horizontal line represents a neutral or no change in assessment, such that points above the line indicate a positive improvement and points below the line a negative change.

Because these assessments were strictly a

change from baseline assessment, the first assessment was at week 4 when this questionnaire was first administered. These patients self-assessed an immediate and sustained at least moderate degree of improvement in their change in CTCL and also an immediate and sustained, if not increasing, at least moderate level of satisfaction with study drug, once again including both the responders and nonresponders according to the primary endpoint.

The consistent efficacy findings in these two pivotal studies led to the following conclusions.

Both prospective statistical targets for a successful study were exceeded by each of the endpoints, whether considering the PGA, CA, or PEC, in each of the two studies independently.

The drug was observed to be efficacious in the cutaneous manifestations in all TNM stages of disease.

And the dose-response relationship observed for rate of response, CCR, and time to response was mirrored by the inverse dose-response relationship for rate of progression and time to progression and further

reinforced by the reversal of disease progression upon crossover of patients from low to high dose therapy.

The 300 milligram per meter squared per day starting dose was determined to be the optimal dose when the dose-related safety profile was also considered.

The primary endpoint results were reinforced by positive findings in secondary efficacy measures, further documenting clinical benefit, and even those patients not meeting the primary endpoint criteria were commonly observed to derive benefit according to the various secondary efficacy response measures.

And finally, the prompt and durable responses were remarkable in this heavily pretreated patient population with few, if any, remaining treatment options.

I will now introduce Dr. Steven Reich who will present the safety findings from these studies.

DR. REICH: Thank you, Dr. Yocum.

Good morning. I will be reviewing the safety profile of Targretin capsules.

Ligand has studied Targretin capsules at dose levels of less than 10 through 1,000 milligrams per

meter squared per day in 690 patients from 16 studies.

651 of these patients are presented in the NDA for safety.

152 patients with CTCL have been treated with Targretin capsules in the phase II/III studies. A mean exposure of 166 days and a maximum duration of treatment of 97 weeks was reported in the NDA.

84 of these patients have been treated at the initial dose of 300 milligrams per meter squared per day, the dose intended for marketing.

The maximally tolerated dose, MTD, in one phase I study of advanced cancer patients was determined to be 300 milligrams per meter squared per day, in another study to be 650 milligrams per meter squared per day. Ligand elected to use the higher dose when designing the phase II/III CTCL studies, but this dose was decreased to an initial starting dose of 300 milligrams per meter squared per day.

The two studies of patients with CTCL started with doses of 650 milligrams per meter squared, but because of difficulty in controlling asymptomatic serum triglyceride levels and leukopenia without infection,

the starting dose was progressively decreased through protocol amendments to 300 milligrams per meter squared.

For the purpose of this presentation, we will focus primarily on the 300 milligrams per meter squared and greater than 300 milligrams per meter squared initial dose groups and not discuss the 6.5 milligrams per meter squared dose group.

The most common adverse events seen in the two phase II/III studies are listed by COSTART Dictionary terms. The coding of several COSTART terms deserves comment.

Hyperlipemia is primarily hypertriglyceridemia. Asthenia is the dictionary term that includes fatigue and generalized weakness. Erythema, skin reddening, and scaling code to rash, while flaking and pealing code to exfoliative dermatitis.

We have drawn a line that separates those events with an incidence of at least 20 percent in the 300 milligram per meter squared group.

The most common adverse events in patients

with CTCL receiving 300 milligrams per meter squared were hyperlipemia in 79 percent of patients. Hypercholesterolemia occurred in 32 percent of patients, with headache, hyperthyroidism, pruritus, and asthenia occurring in 30 to 20 percent of patients.

This table does not distinguish between drug-related and unrelated events. That means that the expected manifestations of disease, in particular, pruritus, where the incidence decreases with increasing dose are included. For the other listed adverse events, there appears to be a dose-response relationship that supports the dose reduction to the current recommended dosing schedule.

Most of the common adverse events at 300 milligrams per meter squared were mild or moderate. It should be noted that the severity associated with the terms, hyperlipemia, hypercholesterolemia, and hypothyroidism, reflect the investigators' grading and are not necessarily tied to specific laboratory test result ranges.

The most common laboratory abnormalities reflected the major adverse events as reported by the

investigators. At the initial dose of 300 milligrams per meter squared per day, serum lipid abnormalities, thyroid axis alteration, and leukopenia were frequent enough to deserve special mention. While not as common as the other abnormalities, elevated liver function tests are listed because of their potential clinical importance.

The following slides present data for the 300 milligrams per meter squared initial dose group in the CTCL studies.

79 percent of patients had at least 1 event of hyperlipemia. Investigators categorized 26 percent of patients as having moderately severe or severe hyperlipemia. This was reflected in the laboratory results database with 28 percent of the patients having a grade 3 or 4 abnormality in triglycerides. These elevations appeared to be dose-related in terms of incidence, time to maximum value, and maximum value. They were reversible, even in those patients with grade 4 values, usually within 1 to 2 months of onset.

43 percent of patients had to have doses adjusted at least once for increased triglycerides or

cholesterol. Concurrent anti-lipid therapy was given in 60 percent of cases. Only 1 patient had to be withdrawn for the primary reason of lack of control of lipids and another for pancreatitis. There were 4 patients with CTCL who developed pancreatitis, and all 4 recovered.

With the increased serum lipids, there is no evidence of increased cardiovascular events. A search of adverse events associated with ischemic heart disease revealed a 5 percent incidence in the CTCL population, which is generally an elderly group of patients, with a median age of 64 years in our studies, and a 1 percent incidence in patients who do not have CTCL.

There were 4 patients who were hospitalized for pancreatitis in the CTCL patient population. All 4 of the patients had one or more prestudy risk factors, so care should be taken to identify such factors in patients treated with Targretin capsules.

With the advent of protocol amendments that limited the initial dose to 300 milligrams per meter squared per day and incorporated strict monitoring guidelines and dose adjustments, including suspension or termination of dosing of Targretin capsules, no further

cases of pancreatitis have developed in the CTCL nor the non-CTCL patient population.

59 percent of patients had TSH and 45 percent had T4 levels less than 75 percent of normal. With patients still ongoing, most patients had normalization of T4, although many were on replacement therapy. TSH would not be expected to resolve unless the patient was taken off of Targretin capsules therapy, in which case normalization was prompt.

Only 2 patients had Targretin doses adjusted because of thyroid related events. No patients were withdrawn for any Targretin capsules studies for hyperthyroidism. At the 300 milligram per meter squared dose level, 37 percent of CTCL patients started thyroid hormone replacement therapy. Symptoms of hyperthyroidism are ameliorated by hormone replacement. Once Targretin dosing is terminated, the laboratory values promptly return to pretreatment levels. Overall this side effect is easily managed with thyroid hormone replacement therapy and monitoring of serum T4 levels.

Most of the observed leukopenia is explained by neutropenia. Only 3 patients had neutropenia less

than 500 cells per millimeter cubed, and 3 patients required dose adjustments. None of the patients withdrew for the primary reason of leukopenia.

At the time of database closure, the leukopenia and neutropenia experienced during Targretin capsule therapy resolved within a month in most patients.

No drug-related events of neutropenic fever or sepsis were observed in the integrated CTCL or non-CTCL patient database.

Of importance, leukopenia and neutropenia were reversible, rarely were associated with infection or serious adverse events, and infrequently required concomitant growth factor therapy such as filgrastim.

The overall incidence of liver function abnormalities is low and the severity rarely exceeds moderate. There were no dose-limiting liver toxicities and only 1 patient withdrew for a primary reason related to liver dysfunction.

The only possibly drug-related death reported in the CTCL program as a patient who died with liver dysfunction, termed "liver failure" by the investigator.

However, independent review by an expert of this complicated case does not confirm a relationship to drug and is more likely related to the patient's underlying lymphoma.

Slit-lamp eye examinations were introduced by protocol amendment into ongoing clinical trials after dose-related posterior subcapsular lens opacities were observed to develop in rats and dogs administered bexarotene. In the CTCL studies, age-corrected prevalence of lens opacities did not appear to differ from the general population.

For the 393 patients with at least one slit-lamp examination, there were no unexpected changes in visual acuity, nor any pattern or consistency in the reports of new or changes in lens opacities.

According to our experts, the pattern seen is consistent with the expected sequence of events in an untreated population. Furthermore, most of the opacities described were not in the posterior subcapsular area of the lens. Based on two years of intensive surveillance, there is no evidence that Targretin capsule therapy is associated with lens

opacity in the clinical situation.

At the closure of the database for this submission, 38 percent of the patients with CTCL at an initial dose of 300 milligrams per meter squared per day were still on study. Another 30 percent withdrew with progressive disease, with 5 percent of patients withdrawing because of stable or controlled disease. 24 percent of patients withdrew for an adverse event not necessarily related to Targretin capsule treatment or withdrew consent.

For the 300 milligram per meter squared per day initial dose group in the CTCL studies, there were 11 adverse events cited as the primary reason for withdrawal. There were a variety of events with different organ systems involved such that there is no evidence for any consistent organ-damaging effect.

Among the patients with CTCL, there was only one death judged by the investigator as at least possibly related to Targretin capsules. As mentioned, this patient had lymphoma in his liver and died of hemorrhage from multiple metastatic sites.

The four cases of pancreatitis in the

patients with CTCL were considered serious adverse events because each patient required hospitalization prior to recovery.

There was one case each of the serious adverse events listed.

Overall, drug-related serious adverse events were uncommon.

The pharmacokinetics of bexarotene were determined from studies of patients with and without CTCL. There were no apparent differences according to underlying disease. At the recommended initial daily dose of bexarotene of 300 milligrams per meter squared, single and multiple dose pharmacokinetics were similar. Half-life values were generally 1 to 3 hours when evaluated over a 6-hour period following dosing. There was minimal accumulation with repeat daily dosing.

Bexarotene is metabolized through oxidation by cytochrome P450 3A4 and through glucuronidation.

Based on limited clinical data, no interaction between bexarotene and P450 3A4 inhibitors was observed.

Concomitant administration of gemfibrozil was

associated with increased bexarotene concentrations and is therefore now recommended with Targretin capsule therapy.

With respect to safety, Ligand has the following conclusions.

Targretin capsule therapy is generally well tolerated based on patient observations over a mean of 166 days, or approximately 24 weeks.

There were no deaths confirmed to be drug-related, and serious drug-related adverse events were uncommon. With extended duration of treatment, there were no new adverse events. This finding is supported by the additional data contained in the 4-month safety update.

Abnormalities of lipids, thyroid hormone, and white blood cells at times required pharmacologic intervention. However, these abnormalities were controllable with appropriate therapy or by Targretin dose modification, rarely had sequelae, and were reversible.

Our clinical experience has led to a recommended dose regimen. While there was a dose-

response in terms of efficacy, there was also a dose-response in terms of adverse effects. So, as with many other anticancer drugs, Targretin capsules should be dose adjusted on an individual patient basis, down for safety, and in selected patients, up for efficacy. Because dose reductions below 300 milligrams per meter squared per day were sometimes accompanied by loss of efficacy, the dose at 300 milligrams per meter squared per day confers the best risk-to-benefit ratio.

The dose regimen proposed for labeling includes adjustments for safety reasons. Ligand also recommends for those patients not responding at 300 milligrams per meter squared per day and who are tolerating the drug without symptomatic or clinically significant laboratory abnormalities a dose increase. Because of the dose-response, patients without safety issues who are not responding might benefit from increased doses.

There's only limited experience with dose escalations for patients who start at 300 milligrams per meter squared per day. However, there is considerable experience with patients who start at higher doses.

In conclusion, the clinical data from Targretin capsules' development program supports the safety and efficacy of the drug in patients with previously treated CTCL at the dose regimen recommended within the package insert.

I would now like to introduce Dr. Kenneth Hymes. Dr. Hymes is an oncologist at the New York Medical Center. He participated as an investigator on the advanced stage protocol. He will describe his experiences using Targretin capsules in the treatment of CTCL.

DR. HYMES: Good morning. Thank you, Dr. Reich.

I'd like to present 2 patients who were enrolled on the Targretin study in my institution not only from the perspective of an investigator, but also from the perspective of a physician who cares for a larger number of patients with cutaneous T-cell lymphoma. I have over 200 patients in my practice who I'm actively following with cutaneous T-cell lymphoma and see 1 to 2 new patients per week.

The first patient I'd like to present is a

67-year-old woman with a history of stage IIB cutaneous T-cell lymphoma with a 10 and one-half year history of disease duration. There was 70 percent body surface area involvement with plaques, patches, and tumors, as well as three large cutaneous tumors, which the photographs will reflect.

She's been refractory to previous treatments, including topical nitrogen mustard, as well as refractory to treatment with systemic interferon alpha 2B at doses of 7 and a half to 10 million units 3 times per week.

This is the appearance of a large tumor on her right forearm at baseline. Following 12 weeks of therapy, there was significant flattening of the tumor. The bi-dimensional measurements of this area have not changed, but of course, there's actually a significant reduction in the total volume. At week 28, the skin had returned to normal texture with only some residual hypopigmentation. I would like to point out that based upon the very conservative composite assessment lesions, there would still be a tumor score despite the apparent major clinical response because of residual

hypopigmentation.

This is a lesion on the top of her scalp. If you notice, it's actually two large necrotic tumors which are communicating underneath a bridge of normal skin. This lesion is referred to in the letter which this patient submitted in the open public hearing. She described this tumor as being quite odoriferous to the extent that her grandchildren would not want to ride in the same automobile with her.

I'd also like point out that because of the location, this would not be immediately apparent in hemi-body photographs. Nonetheless, the localized photographs show that at week 12 there was significant healing with a replacement of the tumor with granulation tissue. At week 41, the scar is barely visible under normal regrowth of her hair.

If we're to look at the assessments based upon protocol endpoints, she achieved a 50 percent improvement, the definition for response based on physician's global assessment, and the composite assessment ratio determined independently at week 8.

In summary, she had a 75 percent response, 75

percent improvement of her skin, with a duration of greater than 2 years. The body surface area involvement reduced from 70 percent to 12 percent. The three cutaneous tumors present at baseline all completely resolved.

Interestingly, because dose reduction and concomitant medications were required to control hypertriglyceridemia, there was the appearance of a new tumor measuring 1.1 centimeters with dose reduction. This was in an area previously uninvolved with a cutaneous tumor. With dose increase, the tumor again resolved.

The second patient I'd like to present is a 58-year-old woman with stage III cutaneous T-cell lymphoma. There was a 2-year duration of disease. She was erythrodermic with 100 percent body surface area involvement. There were two clinically abnormal lymph nodes, and her previous treatment included refractoriness to interferon, as well as refractoriness to high dose methotrexate with leucovorin rescue.

Photographs of her arm showed thickening and erythema of the skin at baseline. By week 12, there was

a reduction erythema. By week 36, the texture of the skin and the color of the skin had returned to normal. This improvement is not a photographic artifact. This was reflected in my personal clinical assessment of this patient.

Similar improvement was noted on her back with the hypertrophic erythematous skin becoming paler and assuming more color and texture by week 36.

There was good correlation between the composite assessment ratio and the physician's global assessment ratio, with the patient achieving a 50 percent improvement in both by week 16, and it being sustained and consistent improvement by up to 52 weeks on this slide. In fact, the patient has a 65 to 75 percent response based on the PGA and the CA over 2.2 years, and the patient continues on medication.

Her complaints of pruritus, alopecia, and nail changes fully cleared.

There were two nodes at baseline which completely resolved, as well as toxicity defined as elevated triglycerides requiring dose reduction and administration of medication.

Since cutaneous T-cell lymphoma is a chronic, symptomatic, incurable, and relapsing disease, patients with this disease will require a sequence of multiple different therapies. Targretin is impressive because it has a very high single agent response rate in patients refractory to drugs which are ordinarily our only agents useful in this disease.

The safety profile is qualitatively different from other treatments for cutaneous T-cell lymphoma, providing an advantage in avoiding cumulative and overlapping toxicities.

The common toxicities, hypertriglyceridemia and hypothyroidism, can be easily controlled with medications that most physicians are familiar with using.

The ease of oral administration eliminates the need for travel to centers for PUVA, electron beam therapy, or photopheresis.

And the long duration of response is particularly impressive in this heavily pretreated group of patients.

I'd now like to introduce Dr. Madeleine Duvic

from the M.D. Anderson Cancer Center who will discuss her experiences with Targretin.

DR. SCHILSKY: I'd just like to remind the sponsor that you've already exceeded your allotted time. So, I'd ask that you either abbreviate this presentation or move directly to your conclusions. Thank you.

DR. DUVIC: Thank you. My name is Madeleine Duvic, and I've been involved with the care of CTCL patients at M.D. Anderson since 1985. We actively treat over 600 patients and evaluate 100 new patients per year, and 41 percent of my patients have been treated in the Targretin trial.

I would like to share with you the dramatic and long-lasting improvement seen in four elderly patients.

First was a 71-year-old man with stage IIA mycosis fungoides for 13 years who had failed 9 previous therapies, including several combinations of chemotherapy and pentostatin. He had 59 percent patch and plaque involvement. The patches are not shown well in the global photograph. But at 9 months, you can see

he has a complete remission.

However, there's an index lesion here that did not resolve and is shown in the next slide and remains to this day.

Again, the CA in yellow and the PGA in green are back to back and show a response of 50 percent as early as week 4.

This patient had a 98 percent response, disappearance of all cutaneous lesions, resolution of adenopathy and normalization of Sezary cell counts to 0 by week 12. He has had only triglyceridemia as a side effect, and he's been in almost complete remission for over 17 months.

Secondly, an 81-year-old man with 7 years of CTCL and 7 previous therapies presented with 48 percent thick plaques on the body and adenopathy. He resolved with only residual hyperpigmentation on the trunk and on the extremities.

His skin biopsy at baseline has shown resolution of the dermal infiltrate by week 8 and normalization of the epidermal changes.

Again, the CA and PGA were similar confirming

PR at 4 weeks and CR at 12 weeks.

To summarize, this patient had a complete response confirmed by biopsy, resolution of nodes and Sezary cells which is ongoing at 17 months. Only mild side effects were present.

The third case is a 63-year-old male with a 5-year history of CTCL who submitted a letter. He developed a large tumor with large cell transformation that relapsed on both CMED and ESHAP chemotherapies. This tumor resolved by week 4, leaving only an ulceration, and healing with normal skin that remains to this day.

He also had clearance of 39 percent of his body involved with patch/plaque disease. Again, a biopsy comparing week 8 to week 0 shows resolution of the dermal infiltrate, resolution of the ulceration, and normalization.

Again, his response was rapid, as shown by both the CA and the PGA, and he continues in almost complete remission ongoing at 2 years.

Finally, we saw patients with exfoliative erythroderma such as this 71-year-old man with Sezary

syndrome who had at baseline 100 percent body surface area and lichenified skin. He had failed interferon, photopheresis, nitrogen mustard.

This patient was actually classified as a progressive disease in the study because lymphadenopathy noted prestudy was not appreciated at baseline and reappeared at week 4 evaluation. Since he had no index lesions, his assessment can only be determined by PGA, and it reached 50 percent by week 24 with sustained improvement shown at week 40 on the next slide.

This man has skin like an alligator. It was thick, scaly, with lichenification of all his extremities, and over the course of therapy, his skin completely normalized, returning to normal color which remained after study.

In summary, excellent clinical responses are seen for oral Targretin at all stages of this disease. As shown, the composite assessment was overly conservative and underestimated the clinical responses seen in some patients.

Targretin has important advantages over other available agents. As an oral capsule, it does not

require venous access or catheters. Patients do not get infections resulting from lines or from treatment.

Targretin is not immunosuppressive.

The responses to Targretin are rapid, dose-related, and durable. Side effects are reversible and can be prevented, treated, and monitored. From my experience, Targretin is an important new therapy for CTCL. Targretin would be helpful and a welcome addition for treating CTCL at all stages of the disease. Many of the patients I treat have run out of available or non-immunosuppressive options.

And now I'd like to turn the podium back over to Dr. Holden.

DR. HOLDEN: Thank you very much.

I think in the interest of time, I'll just inform the committee members that there are summaries of the efficacy and safety slides in the booklet and in a tabular form at the end of the presentation that we handed out.

Thank you very much. Ligand thanks you very much for your attention, and we'd be willing to address questions at this time.

DR. SCHILSKY: Thank you very much.

We'll take questions from the committee. Perhaps I could just start by asking one question about a little bit about the underlying biology here. Can you tell us something about whether the RXR receptors are present on the malignant T-cells in this disease and whether you consider the target tissue for this therapy to be the T-cells or the skin epithelium?

DR. HOLDEN: I'll ask Dr. Yocum to come to the podium.

DR. YOCUM: If it's okay, I'll start with the second question first, and that is, do we consider the target of the disease to be the epithelium versus the tumor involvement?

I hope that by showing the positive findings on the study, that the committee would be convinced that it is, in fact, the drug effect on the tumor cells and not just a retinoid effect on the epithelium itself. The documentation of cutaneous tumor involvement, that is, the skin tumors melting away with therapy and the improvement in pruritus, the improvement in generalized erythroderma, and other tumor-related changes I think

indicate that the effects of the retinoid, this RXR-selective retinoid, do in fact go well beyond what might be some anticipated effects on the epithelium itself.

With regard to your first question, which was are the receptors --

DR. SCHILSKY: The RXR receptors on the malignant T-cells.

DR. YOCUM: Right. I personally can't speak to that but, Dr. Duvic, would you have any information that might shed any light on that question?

DR. DUVIC: By in situ hybridization, we see up-regulation of RAR and RXR receptors in the epidermis with treatment and in the lymphocytes.

DR. SCHILSKY: I'm sorry. I didn't hear your last statement. And in the what?

DR. DUVIC: And in some of the lymphocytes that remain after treatment.

DR. SCHILSKY: In patients prior to exposure to this therapy, do we know that their lymphocytes have receptors?

DR. DUVIC: T-cells have the RAR alpha receptor.

DR. SCHILSKY: But that's not a target for this particular retinoid.

DR. DUVIC: We don't know.

DR. SCHILSKY: Questions from the committee? Dr. Zackheim?

DR. ZACKHEIM: Yes. First I wanted to raise a question about listening to anecdotal reports from patients. No doubt we're very gratified these four patients told us how well they've done with the treatment. But nevertheless, we're hearing only from patients who did well, and in my opinion just hearing from patients who did well creates a bias in favor of the drug, which may or may not be justified.

Let's assume a hypothesis of a study involving 104 patients in which 4 patients did well, and they presented their beneficial result, but 100 patients did poorly, but none of them cared to testify. So, I think if we're going to hear anecdotal reports from patients who have done well, it's only fair to hear patients who have not done well.

Now, I have a question regarding the sponsor. According to the protocol, post-treatment biopsies are

supposed to have been done in all patients who had a CCR, complete clinical response. However, I could find no documentation anyplace indicating that these post-treatment biopsies were done. In fact, the only idea I could get was from the fact that no CRs, no complete responses, were obtained. In other words, a complete response has got to have evidence that histologically there was no evidence of disease after treatment. So, I'd like to know where is this documentation about post-treatment biopsies.

Now, one reason why I raise this question is because there have been two previous reports of treatment of CTCL with retinoids. One was by Kessler published in the Archives of Dermatology in 1987 in which they make the statement that 3 CCRs were noted with total disappearance of all visible skin lesions. However, random skin biopsy specimens of previously involved skin revealed residual atypical lymphocytes in the epidermis.

In another report published in the British Journal of Dermatology in 1983 by Cloudy, et al., again with a similar finding. The exact words are: "Despite

the good clinical response, complete histologic clearing was never obtained."

So, I would like to know were post-treatment biopsies obtained, and if so, why isn't this documented in the report?

DR. YOCUM: In fact, the protocols, I'm quite sure, did not require post-baseline biopsy, but suggested that they might be done on lesions which had undergone a complete or the appearance of a complete remission. And the informed consent included that provision as well, but they were not specified as a protocol procedure.

We did collect the data that was available to us on post-baseline biopsies, and in these studies as of the database closure, there were a total of 21 patients who had at least one post-baseline biopsy. 9 of those included at least one biopsy that was shown as not consistent with CTCL. The others were recorded as either consistent or diagnostic. The 9 patients that had biopsies that were not consistent were, in fact, responding patients according to the PEC. We feel that there was at least some degree of correlation between

histologic clearing and disease, but as you well know, there is a lot of inter- and intra-observer variability in terms of biopsies and also the issue of sampling error.

But the most important answer to your question I think is that they were not required by the protocols.

DR. SCHILSKY: Dr. Margolin?

DR. MARGOLIN: I have a question about the mechanism of the endocrine abnormality. The etiology of the hypothyroidism is said to be on a central basis with suppression of TSH as well as T4. So, I'm curious about mechanism, but also more curious about whether any other manifestations of pituitary dysfunction were looked for and were seen and what management was required.

DR. YOCUM: Thank you.

These other pituitary changes were not observed as part of the data collection in this study. There is a purported mechanism of action for the effect on the thyroid axis, and that in fact involves the anterior pituitary gland-specific RXR gamma 1 receptor subtype and a TSH beta promoter. The RXR agonists,

either alone or in combination with thyroid hormone, do suppress the TSH secretion. I think given that we have, I think, a fairly good hypothesis for what is causing this thyroid axis alteration, there's no reason that we would suspect effects on the rest of the pituitary system, and those were not observed.

DR. SCHILSKY: Dr. Rook.

DR. ROOK: A question about protocol design. There is a big jump between 6 milligrams per meter squared and 300 milligrams per meter squared. Can you explain some of the rationale for making that jump and why there wasn't a dosing level in between?

DR. YOCUM: Yes. The low dose 6.5 was, as you point out, two orders of magnitude less than the high does that was in the initial studies. The 2 out of 9 CTCL patients that were observed to improve in the initial phase I dose escalation study had responses in the range of about 6.5 milligrams per meter squared. In addition to that, we had MTD determinations from the two dose escalation phase II studies that were 650 and 300 milligrams per meter squared.

We anticipated that there would be a dose-

response relationship with study drug in this disease and were interested in designing the protocols with a starting dose at the MTD but, at the same time, wanted to at least cover the possibility that we might see responses at the very low dose. And so, it was to include the approximation of the low dose at which the 2 patients in the phase I/II study had responded and also using the MTD determinations that evolved into the study design in the early stage disease.

DR. SCHILSKY: Dr. Nerenstone.

DR. NERENSTONE: I'm just a little concerned about the long-term toxicity which I'm not sure was discussed much at length. It's not clear to me or it wasn't brought out in this presentation exactly when patients stopped taking the drug. We have people who are out over a year, 2 years, some of them are still on it, some of them are off of it. I guess in the patient description, they talk about some patients who have to be dose-reduced because of side effects, but you don't really discuss that much.

What are your recommendations going to be about long-term usage? When are patients supposed to

stop this? What are physicians supposed to do? And what kind of doses are patients down to when they are out 1 year and 2 years? Can somebody describe that a little bit more?

DR. YOCUM: Yes. That's a mouthful. I think I can put up a slide that I think would characterize what we're seeing in terms of the dose levels that patients ended up at maybe to cover the last part of your question first. Let me see if I can call up a slide for that.

While we're bringing up that slide, the duration of therapy, as we showed you, in the NDA database I think was a mean of 166 days and up to 97 days maximum treatment. In the 4-month safety report, the mean duration of treatment had risen to 206 days and the maximum duration of exposure in the 4-month safety update was 2.3 years. As you heard from one or two of the patients presenting today, the duration for some of those patients was on the order of 2 and a half years.

This shows for the patients in the phase II/III studies the last dose at which the patient was on, as of the database closure, where the 300 milligram

patients are shown in yellow, the greater than 300 in green, and with the approximated actual dose shown along the axis here. Actually most of the treatment that was administered to the patients in the 300 milligram dose group, about two-thirds of those actually remained at the 300 milligram dose group levels, 21 percent at the 200, 8 percent at 100. As you can see, the patients that started at 650 and 500 spent a greater deal of their treatment in a range of lower doses.

And then I think the first thing you asked was the recommended duration of treatment that we're proposing in the labeling. I don't know whether anyone else has been able to pull that up for me, but I'll see if I can.

The protocols, in fact, specified an initial treatment period of 16 weeks but with the provision that treatment could be continued in the event the investigator deemed that treatment might be of potential benefit to the patient and also if there was no unacceptable toxicity that was ongoing.

The dosing guidelines in terms of duration of therapy are that Targretin capsules should be continued

as long as the patient is deriving benefit.

DR. SCHILSKY: Dr. Blayney.

DR. BLAYNEY: I have two questions. The first relates to the pharmacology of your agent, and the second relates to the staging issue.

I too, as many I think of the committee did, struggled with how to define response, and perhaps Dr. Foss or Dr. Duvic could have the expertise to answer the second question.

But the first question. The pharmacology seems to be different when you ingest the capsules with a fatty meal. The AUC varied by 30 percent according to your documents. Is this going to impact your labeling?

And could you also talk about the topical preparation? I don't know if that's your drug or not, but you did mention this topical Targretin in your presentation.

DR. YOCUM: We do have ongoing studies of the topical gel. That is under our sponsorship. Perhaps I'm going to ask Dr. Loewen, our pharmacokineticist, to respond to your first question, and then after his response, I can come back and answer questions you might

have or I'll try to answer questions about the topical studies.

DR. LOEWEN: Thank you, Dr. Yocum. I'm Gordon Loewen, clinical pharmacokineticist at Ligand Pharmaceuticals.

As you indicated, we did note that administration of a fatty meal enhanced the absorption of bexarotene. This was not surprising to us as it has been shown for many of the retinoids previously, and in fact, we designed the clinical studies such that patients were instructed to take the food with the evening meal to enhance the absorption. For that reason, our package labeling suggests that the patients do take the food with a meal.

DR. BLAYNEY: Thank you.

DR. YOCUM: And your questions regarding the topical study were?

DR. BLAYNEY: There is a topical preparation. Perhaps that's not germane to this.

DR. YOCUM: There is a topical preparation which has been in parallel clinical development.

DR. BLAYNEY: And the second question. The

staging and the endpoint determination I had trouble with during my reading of the documentation. Could one of your clinicians maybe talk about -- it seems to be a ginned-up response criteria -- how this relates to psoriasis and KS?

DR. DUVIC: This disease is just like psoriasis clinically in most cases. Patients have discrete plaques or patches. Sometimes they're completely red. So, what we look at as a clinician is the body surface area, feel nodes, look at the lymph nodes. And that's reflected in the physician's global assessment that quantitates body surface involvement, which we actually measure percentage-wise and calculate for patches, plaques, and tumors each visit.

The composite assessment is looking at five individual lesions, whose diameters and heights are actually measured, and combining that with other manifestations of the disease.

So, they're parallel, but one looks at the whole patient and the other looks at the index lesions.

This is not dissimilar from what's done in other skin diseases where the physician's global

assessment looks at the extent of disease on the patient compared to baseline over the course of treatment.

Does that answer your question?

DR. BLAYNEY: Yes. I think most of us are familiar with the pleomorphic manifestations. I needed your input that this is an acceptable response.

DR. DUVIC: (Inaudible.)

DR. FOSS: I had one other point with respect to the staging. There have been a number of studies which have shown in mycosis fungoides that most of the patients, in fact, present with skin manifestations without significant visceral disease with or without palpable adenopathy. And on biopsy in many instances, those lymph nodes are not involved. So, looking at the skin staging really is an important prognosticator with respect to the disease, and clinically that's what we follow as a clinician when patients are on therapy. Very few patients actually have visceral involvement, and there's very good correlation between the degree of skin involvement and prognosis.

DR. SCHILSKY: I wonder if I could just ask the sponsor to tell us a little bit more about the

reproducibility of the response criteria?

You basically have introduced new response criteria for purposes of these studies in a disease that has very heterogeneous clinical manifestations and a variable course in the setting of an unblinded study where the physicians might have some biases with respect to expectations. And you also have, as far as I can tell, 32 centers that enrolled patients on the study and only 150 some patients that are actually presented to us. So, no center would have had a great deal of experience in applying these response criteria.

That's a long preamble, but I'm wondering if you can tell us something about whether you have any way of assessing inter- and intra-observer variability with respect to application of the response criteria.

DR. YOCUM: I may not have an answer that's directly on point to your question, but I think I can show you some data that I think reflect on your issues at least.

One thing that I was impressed with was, as you heard from the definition, the description of these endpoints, the PGA and the CA, really come about the

disease assessment at very different angles. But what was striking in a number of patients, a few of whom I've selected here, is a very impressive correlation between the two endpoints from the initial assessment and then throughout the course of their time on study. These are 4 patients from the early stage study, and similarly these are 4 patients from the advanced stage study.

Another point that I've tried to make in my presentation is that there was a reinforcing of the primary endpoint findings based upon a number of the secondary efficacy endpoint measures and this was true for some of the individual index lesion clinical signs and symptoms and also was also seen with regard to the quality of life questionnaire.

To give you an example of that, I'm going to put up a plot from one of the quality of life questionnaire questions, along with the assessment that was being made of the index lesion clinical signs and symptoms. This regards the lesion redness, scaling, and plaque elevation which are three of the index lesions clinical signs that were monitored.

What I've done here is I've combined the mean

score for the index lesions graded, 0 to 8, plotted those against the left axis here. Those are the green, yellow, and blue curves, and the corresponding CTCL-specific question number 3 that asked the patient to grade their change in redness, scaling, or plaque elevation. And you see a parallel degree of improvement both in the quality of life and the assessments for the composite assessment ratio.

So, the more one looks at the data, the more one sees that there is a cohesiveness between these various measures and the secondary efficacy endpoint measures.

DR. SCHILSKY: Dr. Albain and then Dr. Kelsen.

DR. ALBAIN: Thank you.

I'm still not clear on what happens when the patient achieves their maximum response. You just said earlier they can stop the drug when they've achieved the maximal benefit. I believe those were your words. I'd like to ask the two clinicians that presented to respond. Once you reach your maximum response, is the drug stopped? Is it continued, going back to the

earlier question?

DR. YOCUM: Dr. Duvic and then Dr. Hymes?

DR. DUVIC: This is a disease that's like the Ever Ready battery: It keeps going and going and going. When you stop therapy, with the exception of some therapies like total body skin electron beam, the disease comes back. So, patients who achieved a maximal clinical response were continued at the lowest dose that would keep them in remission that was satisfactory for them.

DR. HYMES: I would agree with Dr. Duvic's comments that this is a chronic disease, that any treatment, whether it be a topical therapy or systemic chemotherapy is not curative. The disease always comes back, and for the patients who were continued on this drug, doses were lowered to maintain their responses. However, it's important to note that there was a relapse of the disease when the drug was lowered past a certain level.

Interestingly and I think quite uniquely among drugs that treat lymphomas, upon reinstitution of the drug or elevation of the dose, there were again

responses. We don't see this with cytotoxic chemotherapy. We often don't see it with other of the light-based therapy or biological response modifiers available for this disease.

DR. ALBAIN: So, what type of guidelines will be given to the treating clinician on how to lower the dose? In what increments?

DR. HYMES: There is a dose adjustment recommendation within the labeling.

DR. ALBAIN: For toxicity.

DR. HYMES: For toxicity. I don't believe that there's really any firm evidence or plan as far as how the dose should be reduced.

DR. SCHILSKY: Dr. Kelsen, then Dr. Margolin.

DR. KELSEN: Following up on Dr. Schilsky's question about RXR expression in malignant T-lymphocytes, if it's not known whether or not the malignant lymphocyte expresses RXR, what's the advantage of this retinoid over the other retinoids that you mention in your manual that did have some activity? Is it less toxic? Is it more efficacious?

DR. YOCUM: There are no comparative data

that I can cite. There haven't been any studies comparing this RXR-selective retinoid with the currently available retinoids. I can ask if one of our investigators might have some experience with other retinoids and might have some anecdotal experience that she could share in terms of answering your question. I see Dr. Duvic rising.

DR. DUVIC: Well, I entered 41 patients on this trial, and about 10 of them had seen previous available retinoids and had failed.

I think this drug acts on both the epidermis and on the T-lymphocytes. This is a disease where the cytokines in the skin probably allow an environment where the lymphocytes can proliferate, and I think it probably, as a hypothesis, has activity in both areas.

DR. SCHILSKY: Dr. Margolin?

DR. MARGOLIN: My question is related somewhat to Kathy Albain's questions which has to do with the recommended dose. The comparisons that were made between the greater than 300 and the 300 groups are really not valid because they do not come from prospective randomized assignment to those groups. So,

it's nice to see that there's a difference in response rate, but I don't know that it's meaningful in the same way that it would be if they were randomized and they were pre-stratified for various other prognostic factors.

I think it's pretty clear there's some relationship between doses and toxicity. If we're looking at treating very early stage patients with this therapy, we could be looking at years and years of therapy with the associated need for lipid lowering agents and other changes that may occur and risk factors for other diseases.

So, the questions I had are there seems to be a very big gap in areas of starting dose where we really don't know what could happen, 200 milligrams, 150, for example.

Furthermore, there's a lot of patients who didn't complete the 16 weeks of therapy in these papers that we were given.

So, it's kind of a vague question, but I'd like to know that at least in animals there was a steep dose response or there are some other more convincing

data suggesting that the starting dose, being higher than what most patients tolerate long term, really makes medical sense.

DR. YOCUM: Maybe not getting to the exact heart of your question, I showed you a dose-response versus initial dose of therapy. This is a plot that shows the response versus the last administered dose of therapy for the primary endpoints and for the 300 milligram dose group. Whether assessing response by either the PGA or the composite endpoint assessment of response, the majority of the cluster responses occurred with the last administered dose in the 250 to 350 milligram dose range.

With regard to any animal findings or preclinical findings of dose responsiveness, I would have to defer to Dr. Loewen or Dr. Ulm, if you have any information that you could possibly use to discuss the question.

DR. ULM: I'm Ed Ulm. I'm Director of the Drug Safety and Disposition Group at Ligand.

In all of the preclinical toxicology studies, there is a clear dose-response relationship. Be it with

our teratology findings, liver weight findings, they all follow a dose-response. So, I think that that dose-response relationship is quite clear, particularly in the dose range used for the clinical studies.

DR. SCHILSKY: We're going to hear from Dr. -- I'm sorry. Kim, do you have a follow-up?

DR. MARGOLIN: I just want to comment on the answer. I think that that's a very valid answer. I don't think Dr. Yocum's answer is valid because responders do better and are able to continue higher doses of things, and we know that in general in clinical trials.

DR. SCHILSKY: Maybe we could hear from Dr. Sledge and then Dr. Simon and then Ms. Pelusi.

DR. SLEDGE: Could you comment on what seems like a relatively high rate of protocol deviations, both in terms of inclusion and exclusion criteria, but also I guess potentially more importantly what has been coded by the FDA as having received prohibited drug or therapy?

DR. YOCUM: I'd like to preface my answer by saying that the sponsor is still not privy to the

medical reviewer's evaluation. So, I have no idea what's in that except for the questions that we received on Friday and from some issues that were transmitted to us through a teleconference. So, just for the committee's information, I don't know what's in the medical evaluator's report.

Your question was about protocol deviations in particular. I believe it was the prohibited medications.

There were a sizeable number of protocol deviations in the study, but what I want to emphasize is that most of the deviations were in categories of deviation that had little clinical meaningful importance.

In particular for the question you raise about -- well, let me put up one slide I think that might illustrate the nature of the evaluations.

The most common area of deviation in the study was the actual timing of the skin biopsy, not that the skin biopsy did not provide a confirmation of CTCL according to the protocol, but the protocols required that the skin biopsy be within the 30-day period

immediately prior to entry in the study. In fact, 36 percent of patients had that biopsy outside the timing of that window.

But as of the database closure, or especially following the database closure, I think what's really important is that 99 percent of the patients had at least two independent dermatopathologists' confirmation of the CTCL.

Less than 24-weeks treatment was not a protocol eligibility criteria but that was the criteria for the evaluable patient data set.

The second most common deviation was an abbreviated duration of time for a washout from prior CTCL therapy. And in almost every one of these cases, the investigator was calling Ligand saying I've got a patient who is on therapy X or has been off therapy X for 2 weeks and is rapidly progressive, and I really don't think the patient can wait another X number of weeks before they can enter this study. Can you, for compassionate reasons, provide a waiver for the patient to begin study at an abbreviated duration of time?

So, in each of these cases in the discussion

with the investigator, we've documented that disease was either progressing or not responding to therapy such that there would be no reasonable confounding of the attribution of response if the patient started to respond after exposure to study drug.

In particular, you asked about the category of deviation which was the prohibited medications. If I can have slide 14 from that set.

Those drugs that were administered during the protocols that were protocol described as prohibited were primarily topically applied drugs and primarily antibiotics and antifungals. These drugs would have no known direct anti-CTCL activity. They were applied in general for indications other than CTCL, applied to limited body surface areas and areas remote from the index lesions and usually for a limited period of time such that in general the vast majority of these therapies were not reasonably expected to affect the response classifications in the study.

DR. SLEDGE: Thank you.

DR. SCHILSKY: Dr. Simon.

DR. SIMON: You showed a graph of time to

relapse, but you didn't indicate time from when. Was this from entry on study, or was this from declaration of a response or what?

DR. YOCUM: The time to relapse graphs that I showed were from day 1, the first day of treatment.

DR. SIMON: Well, that's then not very interpretable because many of these patients didn't have a response until many, many months.

That was the other uncertainty I had. You also showed a graph -- I think it was on page 31 -- of time to response which I found to be a very misleading and invalid graph because it suggests that the response rate goes up 70 percent and higher. It's invalid because it sort of looks -- I don't know if I'm giving the right page here. This was page 31, the top graph on the top plot there.

What I want to know is if you just said by 3 months or by 4 months what percentage of your patients entered on study have a response, what would that response rate be?

DR. YOCUM: Dr. Simon, is this the graph that you're referring to?

DR. SIMON: Yes. That looks like some kind of a Kaplan-Meier curve in which it drops off --

DR. YOCUM: Correct.

DR. SIMON: -- people who progress.

So, that's not a valid way of estimating a response rate, and it's not really a valid way of showing how long it took to respond of those who did respond.

For example, if you were going to say if we had a time window of 3 months to try the therapy, what percentage of the patients would show what you're calling a response by 3 months?

DR. YOCUM: I don't have those data tabulated to show you.

DR. SIMON: Well, then I don't know how we can conclude that what you're claiming that you have a 20 percent response rate -- your response rate has a lower confidence interval that -- you know you're claiming some of the order of a 40 percent response rate. I don't know what the response rate actually is because you're permitting a response for patients to be on study for 9 months, and then the first time that they

get something that suggests that they had a 50 percent decrease relative to their baseline, if that happens once, separated by 4 weeks, then you're calling it a response. So, for a chronic disease, that's a problematic definition of response.

So, I would like to know of the patients who 3 months or 4 months you selected, you had a 3-month trial or a 4-month trial, what percentage of patients have a response within that time period.

DR. YOCUM: The response rates that I showed not in the Kaplan-Meier plots but in the vertical bar graphs, that is, the 45 percent response rate for early stage disease and the 54 response rate for advanced stage disease, were not based on a Kaplan-Meier analysis. They're based on number of patients responding over the intent-to-treat denominator of patients in that dose group.

DR. SIMON: Right, but those responses may have occurred 9 months out.

DR. YOCUM: Right. Your criticism is well taken. I can't provide you at a given, specified time interval the response rate. I can provide some insight

into your question by showing what the time on study was for those response rates.

So, the best answer I can provide you at this point in time is the response rates that I showed you for the 300 milligram dose group, 45 and 54 percent, or for a median of 17 weeks on study. So, this would be in the 4 and a quarter month period of time, those are the response rates that are being realized. I can't provide you an interpolation back to 3 months and tell you what it is, but these were the response rates over a median duration of treatment of just over 4 months.

DR. SIMON: Sorry. I don't understand. The median? What does the 17.3 represent there?

DR. YOCUM: Shown here is the time on study as of the database closure for the NDA versus the initial assigned dose group. So, the response rates that I was focusing on were for the 300 milligram initial dose group, the second row in the table. And for that n of 84 patients at this dose group, these are the descriptive statistics of the amount of time that those patients were on study.

DR. SIMON: I had one other question. You

showed a graph. You showed very little data. As far as I can tell, the only evidence for symptomatic benefit were the case studies that were presented. You did apparently quality of life evaluation, but all you showed us about it was, in your presentation at least, on page 36 of your handout, one graph that shows two quality of life questions jumping up at week 4. And that's for the 300 milligram dose group. You don't show us anything about whether that was also true for the greater than 300 milligrams and you don't show us whether that -- you made some kind of comment that about whether that was restricted to the responders or not. But I don't think I heard it correctly.

DR. YOCUM: The point I was trying to make in the presentation, when I showed the change over time in the body surface area, index lesion area, the change over time in pruritus, and the change over time on the scoring of those two quality of life questionnaire questions, that the data I was presenting was for all of the patients in that initial dose group, that included both those patients who met the primary endpoint response criteria and those who didn't meet the primary

endpoint criteria. So, by lumping both the protocol defined responders and nonresponders together, we could still show a trending to improvement by those measures.

DR. SIMON: What if you showed them separately? What does it show?

DR. YOCUM: In general, it shows a greater degree of improvement for the responder group than you might expect for the nonresponder group. But by many of those measures, actually most, there is still a trending of improvement for the nonresponders.

DR. SIMON: Well, I mean, it's a double-edged sword. It just may indicate that your response assessment isn't really meaningful. In other words, if you're getting some nonstatistically significant difference at 4 weeks, if the main difference is what's happening at 4 weeks and there's no major difference between what's happening for the responders as for the nonresponders, it may indicate that your response assessment isn't really picking up anything really of symptomatic importance.

DR. DUVIC: No.

DR. SIMON: I don't know. All I wanted you

to do is to -- whether you have any additional information that from all of the quality of life assessment did, that indicates, other than your case studies, that there's symptomatic benefit.

DR. DUVIC: It means that the people who are getting drug who don't make it to the cutoff for response are also deriving benefit from the drug.

DR. SIMON: Well, we don't know what it means because you don't have the control group.

DR. DUVIC: Well, I can tell you because I took care of the patients.

DR. SIMON: Well, you didn't have a control group, so you don't really know what it means.

DR. SCHILSKY: We're running pretty late. We're going to take questions from Drs. Pelusi, Santana, Lippman, and Raghavan, and I think that will close out the questions. So, Dr. Pelusi.

DR. PELUSI: Mine is just a comment. When I looked at the primary reasons for withdrawal from the phase II and III studies on your slide 88, my concern was that 13 percent had adverse reactions and so they were not in the study. 10 percent withdrew from their

own consent, and 2 were non-adherence. When you add up those numbers, that's a fourth of patients.

Many of us will be faced with when these people go off study and there were no quality of life issues or what was found in terms of was their quality of life worse on study. Or what were the reasons they went off? We need to be able to have some guidance in terms of where do we go with these patients. So, I would hope that that information is available on those one-fourth of patients who actually went off. But when I reviewed, I did not see those patients had quality of life or any other type of follow-up for us to find.

I also hope that that doesn't set a precedent in terms of when we do quality of life studies, that if you don't stay in the study, we don't follow it anymore. I think that's very valuable information we need to see long term.

DR. SCHILSKY: Dr. Santana.

DR. SANTANA: I understand that this is a rare disease and it's a disease that's chronic in its disease manifestations and its possibility of responding. Can you help me put this medication in the

context of what's out there? I know that there haven't been any controlled, if any, well-designed trials with this drug or with any other medications used in this disease.

Maybe the clinicians can answer this. So, how does this drug fit in the armamentarium in terms of what's expected in terms of responses, what's expected in terms of the benefit to the patient versus the side effects that we've seen here in comparison to other agents?

And as a corollary to that, have there been any data on long-term follow-up of these patients both in terms of resolution of toxicities, but their subsequent responses to other medications?

DR. YOCUM: To take your last question first and then I think your first question would be best addressed by our investigators with the greatest experience in treating the disease.

The protocol specified a follow-up visit that was to occur approximately 4 or more weeks after discontinuation of study drug. Actually the data that I've shown is for both on treatment and post treatment,

but I don't have data to show in general more than 4 weeks after discontinuation of drug.

Dr. Foss?

DR. FOSS: Yes. I'd like to address the issue with respect to how this fits into the therapeutic armamentarium. After patients are refractory to topical therapies, which occurs in most patients in this disease, we start implementing systemic therapies. Usually we're looking at interferon, oral methotrexate, or other oral alkylating agents. At that point in time, patients are making a long-term commitment to these agents.

There's very little data in the literature looking at response rates to oral methotrexate, and we all have our anecdotal reports of patients who have done well. But by and large, that therapy doesn't hold patients for very long.

Interferon is difficult, as you've heard from some of the patients who've had it. It's very difficult to take interferon for a long-term period, and many of these patients, as I said, take 4 to 6 months to respond. When you come off interferon, you relapse.

It's a chronic, long-term therapy. It's subQ and it's expensive.

Beyond that, we're looking at systemic therapies like chemotherapy, and given that these patients are immunocompromised to begin with and they get recurrent skin infections whether we treat them or not, we as clinicians don't like to further immunosuppress them. When they get chemotherapy, particularly multi-agent chemotherapy, they have a very high incidence of line infection and sepsis. Most patients come into the treatment saying that they want to try to maintain their normal lifestyle to whatever degree they can.

Now, Ontak is available and is FDA approved, but Ontak requires 5 days of intravenous infusion in a chemotherapy clinic every 3 weeks, and there are toxicities associated with Ontak.

I think that this agent fits in very well for patients who are beyond the initial topical therapies and are starting to look at these systemic options. Many of these patients are working full-time, have families, want to maintain a normal lifestyle, but are

highly symptomatic from their disease, and come in desperate asking for some therapy that's going to be effective and not interfere with their life to a significant degree.

As you've heard from the patients that have testified, patients are willing to put up with some toxicities from these agents because their disease is so bad. I think most patients know that there's no miracle cure for this problem, and they're willing to put up with some minor inconvenience from this medication for the long-term benefit.

I can also tell you that I've had some of those patients who have not met the criteria for a partial response or a complete response, but nevertheless, those patients have attained benefit from this agent in terms of overall decrease in their itching and overall improvement in their quality of life. Some of those patients wanted to remain on the medication just because it was so convenient even though they hadn't really attained what I would consider to be an optimal response.

DR. SCHILSKY: Thank you very much.

Dr. Lippman.

DR. LIPPMAN: I had a question really in follow-up to Dr. Kelsen's comments and potential cross resistance to other retinoids. The comment, which we all know, is that this is a very uncommon disease and most studies are small. The comments were about 15 patients.

In this particular series, there are about 25 patients that have been treated with the same retinoid in the past, isotretinoin, in the failed prior therapy. So, I was wondering if you had the Targretin response in that group of 25 or so patients, and also if you do have the data, whether there was a correlation of prior response to isotretinoin with subsequent response to Targretin.

DR. YOCUM: We have not done that subset analysis. I don't have the answer for you.

DR. SCHILSKY: Dr. Raghavan.

DR. RAGHAVAN: I'm sympathetic to the investigators and the company because I think this is a difficult disease to treat, and it is heterogeneous and it's hard to quantify. So, it sort of makes the quality

of life information maybe a little more important. This is an illness that does cause a lot of symptoms and patients are clearly happy if the symptoms go away. So, it's kind of puzzling to me that the quality of life data aren't a stronger part of the presentation.

I wondered if you could talk a little more about numbers. There seems to have been a dramatic drop-off in quanta of information as you follow the patients along over a relatively short period. So, I wondered, is this subsetted information? Do the quality of life questionnaires come from everywhere? Is it just one or two hospitals that pushed them and lost interest? What happen there?

And my second question, which is a much easier one, is, is the information derived from this study published anywhere or submitted for publication at the present time?

DR. YOCUM: If I forget all your questions, please remind me.

With regard to the quality of life questionnaires, there were two questionnaires. There was what we call the CTCL-specific questionnaire which

was designed for this study and intended to draw out the patients' self-evaluations on study.

We also utilized a published 6-item general status questionnaire, the Spitzer questionnaire. One of the difficulties with the application of this questionnaire to this population of patients is this instrument was designed as a quality of life measure for survivors in settings such as palliative care and hospice services. By nature of the protocol design, Karnofsky 60 percent or above and by nature of the general higher functional status of the patients in these studies, the initial scores on the Spitzer questionnaire were generally in the 80 percent-plus range, such that it was very difficult to demonstrate an improvement from that high range.

There were some measures on the Spitzer questionnaire which did show improvement, and in general, those degrees of improvement were more apparent looking at the subset of patients who responded according to the primary efficacy endpoint results.

There was some suggestion or at least a visual degree of correlation between the two

questionnaires as well, and I can show you at least one example of that in this slide which shows the results from the two questionnaires regarding the patient's level of activity during the study where the line in red is the first question on the Spitzer questionnaire, which asked the patient about their assessment of activity. And then the lines in yellow, green, and blue plotted the patient's self-assessment of their limitation in activities with regard to physical, social, and work activities.

Your point about diminishing number of patients is highlighted here by the numbers of patients who were answering the questionnaire at each time point, color-coded to match the line plots.

The questionnaires were administered with a very high rate of compliance at all of the study centers, and I'm not aware of any centers which had a noticeably low level of compliance.

Did I miss any of your questions?

DR. RAGHAVAN: Publication.

DR. YOCUM: Publication. Thank you. Aside from some abstracts that were presented a week or so ago

at the ASH meeting, there have been no published data of these studies right now. There are manuscripts in preparation.

DR. SCHILSKY: Thank you very much.

We're going to take a break. I'd like to shorten the break and ask that we reconvene promptly at 11:45.

(Recess.)

DR. SCHILSKY: If everyone will please be seated, we'll now proceed with the FDA presentation.

DR. ODUJINRIN: Good morning. Mr. Chairman, members of the committee, my name is Wole Odujinrin. I will be presenting the FDA assessment of this submission.

The other members of the review team are listed in this slide, and they're sitting very eagerly on that side of the hall. I will not attempt to mention their names, but it's on this slide.

The general information concerning this submission has already been well discussed, and I will not dwell too heavily on it.

But I just wish to point out that the

indication was modified about 2 weeks ago after a meeting between the sponsor and the FDA. The modification reflects the indication to be only for the cutaneous manifestations of CTCL and not for any other aspect of this disease.

There were two pivotal trials in this study, and the titles are as indicated in the slide. They have been gone over in great detail.

The three determinants of efficacy in this submission were primary, secondary, and supportive. The primary efficacy assessments were the physician's global assessment, composite assessment of index lesions, and primary endpoint classification of response. Dr. Yocum has gone over these already, and all I will say is that the PGA is determined by the physician.

The secondary efficacy assessment is listed on this slide. Again, Dr. Yocum has gone over this as well. I will only add that Ligand, not the investigators, determined the response category of each patient in terms of complete response, clinical complete response, partial response, stable disease, and progressive disease.

The issue of photographs came up and I will address it. This was a third efficacy measure and it's supportive. It attempts to complement the first two measures. This is the principal measure that is truly available to the FDA for independent verification of PGA and CA responses claimed by the applicant. Because of the importance of this issue, I shall read the portion of the protocol as it is on the slide.

Five designated index lesions will be serially photographed at baseline and every 4 weeks thereafter for the duration of treatment. At the follow-up visit, these five index lesions must be photographed. Global photographs, half-body fields, and anterior and posterior, of each patient's CTCL disease will be obtained on day 1, every 4 weeks during treatment, and again at the patient's follow-up visit. All index lesions and global areas which are photographed at baseline must be photographed every 4 weeks, even if the lesions have cleared, until the patient completes the follow-up study visit.

I shall indicate later why the lack of full-body photographs is a very important issue with the FDA

and in the evaluation of this submission.

I shall now present the FDA's assessment of the results of the studies conducted by the applicant.

This slide shows baseline characteristics in patients in the early disease study. I wish to make three points with regards to the baseline characteristics.

This was initially a randomized study between a low dose group of 6.5 milligrams per meter squared per day and a higher dose group of 650 milligrams per meter squared per day. Subsequently the high dose had to be reduced to 300 milligrams per meter squared per day because of toxicity.

There were 15 patients in the low dose and 43 patients in the high dose group. 11 of 15 of the patients in the low dose group were subsequently switched to the higher dose upon progression. Most of the patients, 88 percent, had stage I disease. That is truly early disease.

And the third point I wish to make is the median duration of first manifestation of disease prior to entry on the protocol was 161 months, or 13 years.

One patient had a manifestation of this disease for 59 years, 706 months, and another for 52 years prior to entry on this study. Dr. Johnson likes to say that these were before the medical officer was born, and I'm no spring chicken.

(Laughter.)

DR. ODUJINRIN: This implies that we're dealing with a population of patients with very indolent long-term illness. The design of a study that will show a treatment effect in this population of patients is, therefore, of critical importance.

This is a slide of patients in the advanced group category. The points regarding the baseline characteristics here are similar as well. This was not a randomized study. Initially the dose was 650 milligrams per meter squared per day, but had to be decreased in subsequent patients to 300 milligrams per meter squared per day because of toxicity.

There were 56 patients in the 300 milligram dose group and 38 patients in the high dose group. Most of the patients, 73 percent, had stage II or III disease. That is not very extensive disease for an

advanced disease category.

The third item is that the median duration of first manifestation of disease prior to entry on the protocol was 113 months, or 9 years. One patient had a manifestation of this disease for 31 years, 372 months, prior to entry on this study. This again implies that even in this category of patients, we're dealing with a population still with indolent, long-term illness. The design considerations previously mentioned apply here as well.

This slide shows the two more response results in the early disease study.

The applicant did not comply with protocol-specified requirements for full-body photographs.

VOICE: Excuse me. I think you want the previous slide.

DR. ODUJINRIN: I'm sorry. Right.

The FDA, therefore, was unable to assess the sponsor's claimed responses on the PGA. Only the CA results will, therefore, be presented.

Some of the photographs of index lesions and information from case report forms do not confirm all

the claimed responses on CA. Generally, the FDA was able to confirm most of the applicant's claimed CA responses.

In the 6.5 milligrams per meter squared group, there were 0 complete responders, 1 out of 15 clinical complete responders, and 3 out of 15 CCR plus PR.

In the 300 milligrams per meter squared group, both 300 and greater than 300, again there were no CR responses; 3 of 43 CCR responses, which is pretty similar to the CCR response in the low dose group; and 15 of 43 CCR plus PR, for a 35 percent response.

This slide shows the tumor response results in the advanced disease study. Again, for reasons previously mentioned, the FDA was unable to assess the sponsor's claimed responses of the PGA. Only the CA results will again be presented. The FDA findings generally agree with Ligand's.

In the entire group of 94 patients, again there were no complete responders. 6 of 94 patients had clinical complete response and this generally agrees with Ligand's assessment, and 27 of 94, or 29 percent,

had CCR plus PR.

In terms of the secondary efficacy results, the FDA findings are generally similar to those of the sponsor in terms of duration of response and time to disease progression. These results should be interpreted with these considerations however. The lack of a control group creates difficulty establishing true treatment effect. Treatment duration was short with many patients censored for time to events. Reliable time to event estimates are difficult to make, and there's a potential for a large margin of error. The Kaplan-Meier curves are exploratory.

I think these issues have been reflected in the questions by Dr. Simon, and they seem to have captured our dilemma in reviewing these results.

In terms of secondary efficacy assessment, the total body surface area involved, this showed a reduction in area of skin involvement of greater than 50 percent in 37 percent of patients with early disease and 33 percent of patients in advanced disease.

In terms of the quality of life assessment, Dr. Yocum has described the criteria in the assessments.

There were two quality of life instruments that were used: a standard QOL questionnaire by Spitzer and a CTCL-specific QOL questionnaire designed by Ligand for this study. There was unexplained discrepancy between results of the Ligand developed CTCL-specific global quality of life and the Spitzer global quality of life questionnaires. It seemed to show worsening on the Spitzer global quality of life, but good improvement on the CTCL-specific global quality of life assessment. Overall, no clear beneficial effect on quality of life could be seen.

And Dr. Simon's and Dr. Raghavan's questions appear appropriate on this issue.

In terms of all the secondary efficacy criteria, the pigmentation and pruritus are major concerns for patients with this disease.

In terms of pigmentation, there were very few patients that had baseline pigmentary abnormalities in both studies and, hence, no meaningful information can be made with regards to pigmentation.

With regards to pruritus, there was no clinically significant change from baseline among

patients taking antipruritics and those not taking antipruritics in both studies.

In terms of clinically abnormal lymph nodes, there were 8 of 58 patients in the early disease study that had clinically abnormal nodes, and we saw no meaningful change with treatment. In the advanced disease group, there were 38 of 94 patients with clinically abnormal nodes. 3 patients had a complete or greater than 50 percent reduction in the number of aggregate areas of positive nodes.

There were 33 of 94 patients, or 35 percent, all of them advanced disease patients, that had CTCL tumors, and we felt 1 had a complete resolution of the tumor.

I shall now turn to safety results. The FDA generally agrees with Ligand's findings of the safety profile in both studies. At least one adverse event was seen in 97 percent of patients in early disease and 99 percent of patients in advanced disease. There were numerous laboratory abnormalities in all the adverse events. Dr. Reich has described these adverse events in detail, and I will not dwell very much over them.

We'll talk about serum triglycerides. Some patients had serum triglycerides in excess of 3,000 milligrams per deciliter. For patients with levels greater than 800 milligrams, there were 55 percent of patients in the early disease and 56 percent in the advanced disease in this category. The increase occurred rather rapidly, in 2 to 4 weeks of initiating treatment. 78 percent of patients with advanced disease and 62 percent overall required anti-lipemic therapy.

There were associated clinical complications, mostly of pancreatitis, and 4 patients that required hospitalization.

There were other patients with gastrointestinal complaints in whom serum amylase was not obtained.

All the adverse events whose relationship to Targretin I would regard as unknown.

With regard to cardiac disease, a cause-effect relationship of the cardiac adverse events to drug therapy cannot be made because cardiac disease is a common problem in patients in this age group. All these patients, however, had markedly elevated triglycerides,

and the investigators implied an association of drug therapy with the adverse event.

In terms of cataracts, 47 patients had baseline and serial slit-lamp examination. Visual problems, including cataracts, are common in this age group of patients. 21 percent, 10 of these 47 patients, had new or worsening cataracts. While the number does not appear very high, it remains a concern to us in this age group. Furthermore, it was a common problem in preclinical studies conducted in different species of animals, as had been previously mentioned by Dr. Yocum.

There was one death from hepatic hemorrhage in a treatment-induced coagulopathy patient. This patient also had elevated triglycerides and abnormal thyroid function. The investigator believed the event was treatment related.

Other issues that related to safety. The patients required numerous medications to counter multiple AEs, and this is in addition to at least 7 daily tablets of Targretin, and usual patient medicines that they have to take for other health problems. This creates a high risk for drug-drug interaction problems.

Preclinical studies reveal decreased clearance of Targretin and gemfibrozil with prolonged elevation of Targretin levels, and this had been previously mentioned. Given the effect of Targretin on CYP 3A4 and hepatic microsomes, drug-drug interaction potential with other drugs is a real concern.

In terms of symptoms from hypothyroidism, it was not easy to determine from the study if the abnormal thyroid function tests correlate with symptoms. Dr. Duvic's report, or the report from M.D. Anderson, on this subject I found useful. There was a publication using information from the early disease protocol. It noted dose-dependent declining TSH levels to below normal and a prior decline in thyroxine in 26 of 27 patients, or 96 percent, who had both pre-study and post-baseline thyroid studied. Symptoms consistent with hypothyroidism were observed in 19 of 26, or 73 percent, of the patients with the biochemical abnormalities. 17 of these patients were treated with supplemental thyroxine and 15 had symptomatic improvement. So, it suggests that the symptoms are reversible with anti-thyroid medication.

In terms of pruritus, this is a major concern for patients with this illness. The need for antipruritics continued in spite of Targretin treatment.

The issues of data quality have been touched upon in the different questions by members of the committee, and I will just summarize our information on that.

There were numerous amendments to the original protocol. There were eight in the advanced disease protocol alone. There was a higher patient withdrawal due to AEs. I place this as 30 percent in the early disease study and 35 percent in the advanced disease category.

Dr. Nerenstone has very appropriately pointed out the information provided in slide number 88 by Ligand, which essentially showed patient withdrawal due to AE and withdrew consent as separate. My review of the case report forms suggested to me very strongly the that patients who withdrew consent withdrew because of inability to continue treatment.

There were numerous protocol violations, and Dr. Sledge has a question about this. 75 percent and 90

percent, respectively, had at least one protocol violation. Dr. Yocum in his presentation indicated that one of the violations was a washout problem and the other violation regards the inclusion criteria. So, the primary causes of violation were inclusion criteria to this protocol.

Some patients were not eligible regarding the refractory, reached a plateau, or had progressive disease on prior therapy aspect of the protocol requirement.

Some patients were still within the washout period of their prior therapy at enrollment on study, and Dr. Yocum has attempted to give the reason for that.

I will now turn to issues of photographs. As mentioned at the beginning of the presentation, full-body photographs were required by the protocol as a supportive efficacy requirement. It was the only opportunity available to the FDA to independently verify the PGA and CA claims of the applicant. The applicant did not comply with protocol-specified requirements for full-body photographs and no protocol amendment was made to reflect the change. The FDA, therefore, cannot

assess the sponsor's claimed responses on the PGA. Some of the photographs of index lesions do not confirm the claimed responses on CA and raise questions on the claimed responses on PGA.

I shall now show some sample photographs.

This is an example of a successful treatment. It has been shown at least twice by previous speakers. This patient had a response to therapy that began from week 4 and continued through week 44, according to the pictures and CRFs available to us.

The following 3 patients, however, illustrate the need for full-body photographs. This slide shows serial photographs of an index lesion that's been circled by the applicant. This is supposedly the response. It goes on like that.

This is the same patient with a wider view. The areas surrounding the index lesions appear to be worsening. The patient was coded as a partial response on the PGA. This shows the need for full-body photographs to confirm claimed PGA responses.

This is another patient with close-up pictures of an index lesion. With a wider view of the

arm, however, a new tumor is rapidly developing near the index lesions. These are actually serial follow-up visits. The index lesion is over here.

This is yet another patient. This patient was called a responder by PGA and stable disease by CA. A huge ulcer is developing. I don't even need to show a pointer for this. Unfortunately, we have no follow-up pictures on this patient beyond the second visit, and we had asked Ligand for them. Again, this illustrates the need for full-body photographs to confirm the claimed PGA responses.

I will now go to the risk-benefit issues. What has been shown to be the benefit of Targretin therapy in this study?

The body surface area reduction of greater than 50 percent appears credible in 37 percent and 33 percent of patients in both studies, respectively, as demonstrable improvement in index skin lesions in 29 percent and 35 percent of patients with early disease and moderately advanced disease. Data on duration of improvement are, however, limited.

If approved, this will be another available

oral medication to patients with CTCL. The sponsor claims this is an alternative to methotrexate. There are, however, many other FDA approved drugs for CTCL, including other oral drugs, as the next slide demonstrates.

This shows both oral and injectable FDA approved drugs and they're available in the PDR.

These are topical treatments available for CTCL, and these have been mentioned in the course of the discussion. I just wish to point out that good complete response rates are achievable in this disease, and that's the point of this slide.

This slide provides a summary of literature reports on useful single agents in this disease. I wish to draw attention to the last slide, which is Bunn's summary of useful single agents in the disease. Again, complete responses of up to 33 percent and overall responses of 62 percent are tenable, and duration of response of 3 to 22 months.

Molin articles on other retinoic agents also show that complete responses are feasible in this group of patients.

Well, I don't expect you to be able to read this. This is a summary of combination chemotherapy agents that are available to patients with CTCL, and this is an article by Bunn in the Annals of Internal Medicine. Again, it shows the complete response rate of 29 percent and a combined response rate of 81 percent, with a duration of response of 9 months.

In conclusion, I will say the following about this submission. In the context of the study design, Targretin does have activity in this disease in approximately a third of patients. The activity, however, is exclusively cutaneous. Without the protocol-stipulated full-body photographs, the FDA is unable to confirm the claimed PGA tumor responses.

Data on duration of the activity are limited.

In the absence of a comparator, it is difficult to determine the true effect size of Targretin vis-a-vis other existing therapies.

The disabling symptom of pruritus was not affected by therapy.

There were not many patients to assess pigmentary changes.

There were many flaws in the execution of these studies.

The study represents a heterogeneous population regarding refractoriness to prior therapies and for whom alternative therapies exist.

Patients enrolled in both studies mostly represent groups with less extensive disease, with 88 percent in stage I, early disease, and 73 percent stage II or III in the advanced disease study.

There are safety issues with the use of Targretin capsule therapy.

Thank you very much for your attention. I will be happy to entertain any questions.

DR. SCHILSKY: Thank you very much.

Time for questions from the committee. Dr. Raghavan.

DR. RAGHAVAN: You showed a couple of slides that are a bit disturbing in the sense that you've suggested that claimed partial responders have progressive lesions concurrently. I wondered, is that evidence available to you only from the large body photographs that you showed or if you played the role of

detective? Is there evidence written down in the CRFs to suggest the appearance of new lesions, or is there any other evidence, apart from these large photographs, that would let you have that information available to you?

DR. ODUJINRIN: The CRF does document when new lesions occur and indicating progressive disease. The investigator does have diagrams that are filled in. But the photographs we find very useful in following the patients.

DR. RAGHAVAN: No. I understand that, but a big part of your submission is the absence of the large photographs is a deal-breaker.

DR. ODUJINRIN: Yes.

DR. RAGHAVAN: And my question is, allowing for the fact that those photographs are not there, if you as the FDA investigator go through the CRFs, are you in a position, without photographs, to identify concurrently emerging lesions?

DR. ODUJINRIN: No.

DR. RAGHAVAN: You're not.

DR. ODUJINRIN: I would say no.

DR. SCHILSKY: Dr. Rook.

DR. ROOK: In your estimate, how often was there a discrepancy between the submitted photographs that you had and the conclusion that there was a response?

DR. ODUJINRIN: I will be guessing and I really don't want to guess. But we used the photographs when we had some concerns about what was seen in terms of the claimed responses.

DR. ROOK: You said 10 responses?

DR. ODUJINRIN: No. I said claimed responses.

DR. ROOK: Was this a small number? Was it less than 10 percent of cases? Was it less than 5 percent of cases? Can you give us an estimate?

DR. TEMPLE: For the index lesions, there were relatively few discrepancies, and the photographs tended to confirm the observation. Right?

DR. ODUJINRIN: Yes.

DR. TEMPLE: But you've made the point that for the whole body response, we don't have any independent way of looking, so we don't know.

DR. ODUJINRIN: These were measures of index lesions, and it's possible -- in fact, it's not possible. We do have information in that regard. The index lesion can improve while the other lesions are increasing or unchanged. Am I answering your question? And this happened quite often, quite frankly.

DR. SCHILSKY: Dr. Nerenstone.

DR. NERENSTONE: There's sort of a basic difference in your evaluation of the patient population and perhaps the sponsor's. 15 percent of the protocol violations were due, according to the sponsor, because the disease was rapidly progressive and so they could not wait for the washout period. Your evaluation, though, implies that this is an indolent disease patient population.

So, I wonder, was there any information presented by the sponsor to you on those 15 percent of patients underscoring that they really were rapidly progressive? And if that data was available, would that change your relative weight about the response rate if, indeed, those patients responded to the treatment?

DR. ODUJINRIN: For me personally, I think it

does affect my perception of the claimed responses because some of the drugs that the patients were taking, like interferon, for example, have long durations before you see an effect. So, when a patient goes on Targretin therapy, less than 30 days of interferon or PUVA, and you see a PGA response of 50 percent on the first visit, as a physician it raises a red flag in my head.

DR. SCHILSKY: Dr. Kelsen.

DR. KELSEN: I know this is an uncommon disease in incidence. It sounds like there's about 16,000 patients, however, in prevalence in the country. I'm wondering when you're approached about a disease that's relatively uncommon like this, in which there are at least some approved oral medications, when you recommend that a comparative study be done, because I feel my job would have been a lot easier today if this had been a random assignment trial. I understand you might not be able to do a placebo-controlled trial. Maybe that was felt to be unethical. But there were other therapies that are at least oral from your presentation.

When you talk to a company, when do you say,

gee, the best way -- it's hard to evaluate this disease. It's hard to get a handle on it. We suggest that you do a study which compares an approved indication, oral methotrexate or whatever, versus your new treatment. I'm just sort of asking for how you approach that problem.

DR. ODUJINRIN: Well, the FDA can only make suggestions. We cannot compel the company to do anything.

DR. KELSEN: Did we make such a suggestion?

DR. SCHILSKY: Can I suggest that we hold that question till we get into the more general discussion? Because I think some of the questions that are being asked of us pertain to the question that you're just raising. So, let's for right now just keep the questions focused on the FDA presentation.

Kathy, did you have a question? Dr. Albain.

DR. ALBAIN: Going back to a question Dr. Lippman asked earlier, in your review of the patient case reports, for those patients who had had previous retinoids, did you get a sense for what the response to this was? And if so, what was the previous response to

retinoids? And I say this because in the second booklet that we were given from the sponsor, there are case reports where they outline in great detail. Earlier, when asked, the sponsor was not able to answer that question.

DR. ODUJINRIN: Quite frankly, I don't think I can answer the question either in terms of effect of retinoids or prior treatment.

DR. SCHILSKY: Dr. Santana?

DR. SANTANA: I want to get back to this issue of the pruritus and whether there's benefit from this medication regarding that symptom. The sponsor showed just one slide where actually it was a mean score of pruritus, and then you made a comment that in your assessment overall there was no less use of antihistaminics in patients across the study. So, was this coded in the database that you could look at it that way, or is this a general comment on your part, looking at the whole data?

DR. ODUJINRIN: Yes. Actually I think Dr. Yocum can expand more on that. The pruritus data were presented in terms of patients who were continuing on

antipruritics and patients who were not taking antipruritics. And that's how the data were presented to us.

DR. SANTANA: But for those that were on antihistaminics, what data did you have to validate your point that there was no less use over time in those patients? Was this coded?

DR. ODUJINRIN: It's a table that Ligand presented, and they probably have that table here. Maybe Dr. Yocum can address that issue some more.

DR. SCHILSKY: Dr. Lippman.

DR. LIPPMAN: Regarding your slide on the quality of study data, can you elaborate on the point that some patients were not eligible regarding the refractory criteria, which is really the central eligibility criteria of the study?

DR. ODUJINRIN: Well, that's really what I was referring to in terms of the time period that 6 months is supposed to elapse that a patient is supposed to have been refractory, intolerant, or persistent on therapy. And many patients did not fulfill that inclusion criterion for entry.

DR. SCHILSKY: Could I just follow up on that? Because the sponsor in one of their slides showed us a slide that said that 96 percent of the patients were refractory to one or more therapies and 78 percent were refractory to two or more therapies. You obviously don't agree with that.

I guess my question is, what data were available to you to make a determination as to whether a patient was, in fact, refractory? Was there a protocol-specified definition of refractory that had to be met? And what documentation was submitted to FDA with respect to whether patients met some criterion for being refractory?

DR. ODUJINRIN: Yes. There was a protocol-defined criterion for refractoriness, and that's what I just mentioned, that a patient has to be refractory, intolerant, or have persistent --

DR. SCHILSKY: But what does refractory mean? That's what I'm asking. When you say the protocol says the patient had to be refractory. So, all these patients are being treated by lots of doctors all over the place. They come into a doctor. They're enrolled

in this study. They have to be determined to be refractory. So, what does refractory mean?

DR. ODUJINRIN: Well, my interpretation of that is that they no longer respond to that drug.

DR. SCHILSKY: And so, if that's your interpretation, then what you're telling is that you believe that many of the patients were, in fact, not refractory.

DR. ODUJINRIN: If we have to use the 6-month criterion that's in the protocol, yes, that's what I'm saying.

DR. REICH: Mr. Chairman, point of clarification in terms of order.

DR. SCHILSKY: Yes.

DR. REICH: There are some erroneous statements being made by the agency we believe, and we are not sure whether we'll have a chance to correct any of these issues.

DR. SCHILSKY: Let me ask you, Dr. Reich, if you could answer my question, which is what was the definition of refractory that patients had to meet in order to be eligible for the protocol, and how was that

definition documented for purposes of protocol entry?

DR. REICH: Dr. Yocum will answer that question.

DR. SCHILSKY: Please.

DR. YOCUM: The definitions of refractory, and in general all the definitions that were specified in the protocol for defining the degree of refractory or persistent disease, were developed in conjunction with the FDA, close consultation with the Division of Oncology, during the period of protocol development. And that's documented in the communications back and forth between the agency.

The protocols did contain a very specific definition of refractory. I put that up and that was a lack of 50 percent improvement to the prior therapy or if the patient relapsed, but only if they relapsed while they were still administering the therapy, not the definition that was given by Dr. Odujinrin, which was response sometime after the therapy, which I would consider to be a relapse, not refractory.

In addition, the case report forms were redesigned with close attention to each one of the

specifications that was provided to us in a telecommunication from the division and collected specific information not only on the nature of the therapy, but the best response to prior therapy; if there was intolerance, what that specific intolerance was; if there was a relapse, what the date of that relapse was, if that therapy was used to qualify the patient for the study. And for those therapies that were specifically used to qualify the patients for the study, we had stop and start dates of therapy and dates of relapse or progressive disease.

The protocols did not require that the patient be refractory for 6 months. The 6-month requirement pertained only to the response plateau criterion as one of the three for the early stage disease: in the early stage, if patients were refractory, if they were intolerant, or if they had the response plateau for 6 months. And there was certainly no 6-month provision at all in the advanced stage disease protocol.

DR. SCHILSKY: Thank you.

So, having heard that, I presume that FDA had

an opportunity to review the same documentation with respect to refractoriness that the sponsor did. So, do you still believe that there was a large number of patients who were not actually refractory upon entry into the study? I just think this is an important issue for us to get clarification on.

DR. ODUJINRIN: This is a Ligand slide, and it shows protocol violations in early disease. I assume the violations are listed in order. 53 percent in greater than 300, 32 percent and 40 percent, had deviation from inclusion criteria. And in the advanced disease, again we have 55 percent and 35.7 percent deviation from inclusion criteria.

DR. SCHILSKY: That doesn't tell us much about what inclusion criteria they've deviated from, though.

DR. ODUJINRIN: The two main inclusion criteria were the protocol entry prior to the 6 months required for refractoriness, and Dr. Yocum has tried to address that. The patients were within a 30-day washout period of prior therapy. Again, Dr. Yocum has tried to give a reason for that.

DR. SCHILSKY: Do we have other questions from the committee?

DR. YOCUM: Just a point of clarification. I hope it's clear to the committee that the FDA has applied a criterion for entry that wasn't in the protocols in their analysis.

DR. SCHILSKY: I think you made that point clearly. Thank you.

Dr. Margolin.

DR. MARGOLIN: Well, I think it's going to be very, very difficult when we come down to trying to answer the FDA's questions, how we're going to answer them because there's quite a bit of disagreement between the reviewer and the sponsor. I don't know how that's going to get sorted out.

So, just to get to a more practical question -- and I guess it's okay to ask the sponsor now because the sponsor didn't have a chance to look at the FDA's review before they spoke this morning, nor did we know that -- I'm very bothered by the pictures that Wole showed of tumors that were growing or further ulcerating. I don't really understand why they had

pictures but didn't consider those patients progressors. But I guess we oncologists would call those responses mixed responses, if you believe in that sort of a category. Also, as an oncologist in clinical trials, we know that most mixed responses are just the first version of a progressive disease.

But the real question related to that is how many of those troublesome responses -- I think somebody else asked you that earlier -- but also a practical question from the sponsor is, what do you do with such a patient? Do you continue that patient on the retinoid? Do you consider adding another drug that has activity against the more tumor or visceral disease while they're on the retinoid, in which case then you have to worry about interactions?

DR. SCHILSKY: Do you want to address that question to the sponsor?

DR. MARGOLIN: Yes, if that's okay.

DR. DUVIC: First of all, I don't believe that lesions that were occurring like that would have been graded as anything other than progressive disease.

Secondly, what we do in practice is either

switch to another therapy or add another therapy.

And patients who had new lesions on this protocol were graded as progressive disease and were removed from the protocol.

DR. SCHILSKY: Apparently the illustration that was given to us, though, was scored as a partial response. So, whatever you think might have been the appropriate grading, that apparently was not the grading in that particular case.

Dr. Blayney.

DR. BLAYNEY: Dr. Odujinrin, I agree with you that it looks like, from what I've read, that this drug does have activity in patients, but clearly there were flaws in execution of these studies. I think many of the questions get to that.

This PGA seems to be an important endpoint. There were approximately 137 patients treated, and we heard in the comment earlier that 41 of these patients were at one center. Do you have an idea of the distribution? This gets to the experience of the treating physicians performing and the reproducibility of this physician's global assessment. What's the

distribution of other centers that were involved?

DR. ODUJINRIN: Well, I think the company can give a better response to that. But you are correct in that one center had most of the patients.

DR. REICH: We could show a slide, if you wish, but in general the distribution, according to center, was in fact pretty consistent across the board.

DR. SCHILSKY: Perhaps if you have that on a slide, it would be useful to see it.

DR. ODUJINRIN: My count of the patients showed most of them from M.D. Anderson.

DR. YOCUM: This slide is restricted to the 84 patients that initiated therapy at 300. The top of the bar is the number of patients who were enrolled by study center at this dose group, and then the bar is divided into red, which represents patients who met the PEC response criteria and yellow for patients who did not meet response criteria.

DR. ODUJINRIN: If I can just use this slide. This is M.D. Anderson.

DR. YOCUM: That's correct. Site 14 is M.D.

Anderson and Dr. Duvic is here to respond to questions about that center.

DR. SCHILSKY: Dr. Lippman.

DR. LIPPMAN: A lot of this comes back to the issue of refractoriness. I'd like to ask the FDA when they list the table of single agent activity slide, I'm assuming that these were -- were these refractory patients or a mixture? Because I think the sponsor has gone through at least a tremendous amount of work to attempt to get a fairly refractory population, and the response rates are substantial. That would really make it differ I think from this table. Any comment about prior therapies?

DR. ODUJINRIN: Yes. I cannot comment on the conduct of the studies that were reported in the literature because we did not have a chance to review the information before they were published.

DR. LIPPMAN: But in the papers, did they comment about prior therapies? Were these heavily pretreated patients in general?

DR. ODUJINRIN: In the Bunn article, yes, and also the one of combination chemotherapy agents by Bunn.

DR. REICH: The Bunn article is a review and it covers a whole variety of drugs and a whole variety of studies, not all of which have characterized the pretreatment the way we have, nor have they used the same endpoints that we have. So one, I believe, cannot use literature to compare.

Furthermore, the side effects of combination chemotherapy are a little bit different than the side effects that we're reporting today. So, without the risk-benefit assessment that we're required to do, I think it's a little unfair to show those kinds of numbers.

DR. SCHILSKY: Thank you.

I have another question for you about some discussion we had earlier today with respect to whether there are dose-response and dose-toxicity relationships because apparently there's some proposal in the labeling that the dosage might be adjusted upward in some circumstances. I'm wondering, based on your assessments, since there are roughly equal numbers of patients who got treated at 300 and then got treated at more than 300, would it be your assessment that there is

either a dose-response or a dose-toxicity relationship?

DR. ODUJINRIN: I think it would have been possible to answer that question if the randomized study in the early phase disease had been completed. In the absence of that, it's difficult to answer that question.

DR. SCHILSKY: I guess what I'm driving at is from looking at the information, I'm not persuaded that doses higher than 300 confer additional benefit. I am concerned, however, that doses higher than 300 result in additional toxicity. So, if the drug were actually to be approved, I would wonder about whether it actually is appropriate to include any recommendation for dose increase in the labeling. That seems to me a bit of a stretch to suggest that there should be an increase in dosage even under carefully monitored circumstances. I don't know if you would agree with that or not.

DR. ODUJINRIN: The observation is right, that the patients in the higher dose groups, especially the 500 milligrams and 650 milligram per meter squared, had more toxicities, and that was the basis for the various amendments to the protocol.

DR. SCHILSKY: Dr. Temple.

DR. TEMPLE: I thought the question was raised about the global response and its distribution among clinics. The slide that was shown was the PEC which represents response either on the indicator lesion, which of course was verifiable by photograph, or the global. Do you actually have the same slide for just the global?

DR. REICH: We do not, Dr. Temple.

DR. SCHILSKY: Dr. Margolin.

DR. MARGOLIN: I have a question that maybe Dr. Temple or somebody from FDA needs to answer having to do with sort of the policy and how we can deal with the difficult data. Usually when accelerated approval is requested, it has to do with the fact that the clinical benefit endpoint was not necessarily reached, but some surrogate for it is looking good, and then some restrictions are placed on the sponsor for post-marketing studies.

This, I guess, is an orphan indication. I don't know whether that would, therefore, be not qualified for accelerated approval or whether the problems that we're looking at are not the kind that are

addressed by granting an accelerated approval with a requirement for post-marketing.

DR. TEMPLE: Well, orphan indications are certainly eligible for accelerated approval.

The trouble here is that it isn't clear that we've identified a situation that's suitable for accelerated approval, which means a serious -- this is certainly serious -- or life-threatening disease with no alternative therapy or where this represents an advantage over alternative therapy. I suppose one could make the case that toxicity is different.

But in the present case, I think the company would argue that the endpoint is not a surrogate, that it's a real benefit to have your lesions fixed. So, that really in some sense doesn't come up.

DR. SCHILSKY: Ms. Krivacic?

MS. KRIVACIC: On your quality of study data slide, you mentioned a number of protocol violations there. Does this refer back to the background information we were given from Ligand on the errors at the study centers, or are there some more protocol violations above and beyond this? Or are these errors

at the study centers something different?

DR. ODUJINRIN: Well, I don't look at them necessarily as errors. They are events that occurred. I showed the table that was provided to us by Ligand and the same is provided to you as well.

MS. KRIVACIC: I guess what I'm wondering is, is it referring back to that background information that they supplied us with, what you have presented here, or are there some more protocol violations that have not been addressed in this background information that you know about?

DR. ODUJINRIN: No, not that I know of.

DR. SCHILSKY: Dr. Margolin?

DR. MARGOLIN: Just a comment or question that might clarify maybe what you're getting at. There are always going to be protocol violations whenever you review protocols.

But I don't think you threw any patients out as having met sufficiently major eligibility violations that they were considered ineligible, and those are the patients one always throws out from analysis. Is that correct?

DR. ODUJINRIN: We threw no patient out due to protocol violations. As I showed and as the slide from Ligand showed, 97 percent of the patients had at least one violation, and a significant number had violations that were not minor. If we had to throw out patients for violations, there wouldn't be too many patients left in this study.

DR. SCHILSKY: Wole, I wonder if you could answer a question that Dr. Simon asked earlier that the sponsor was not able to answer having to do with what was the percentage of responding patients at approximately 3 to 4 months into the study. Do you have any sense about that?

DR. ODUJINRIN: 3 months would be about 12 weeks.

DR. SCHILSKY: So, within 12 to 16 weeks or so.

DR. ODUJINRIN: From this slide that Dr. Yocum showed, in the early disease category, the median response was 16 point something weeks, and my sense would be about that as well.

DR. SCHILSKY: Any other questions for the

FDA?

(No response.)

DR. SCHILSKY: All right. If not, thank you very much.

So, we can have some general discussion, if the committee likes, or we can go directly to the questions. It seems to me -- and perhaps we could discuss this for a little bit -- at least in my mind, the crux of the matter here really is whether patients who received this therapy benefit from it. I think there's a general sense among all the parties involved that this agent has biological activity in this disease. The issue then is, does that biological activity result in benefit for the patients who are receiving the therapy? I wonder if any of the committee members would like to discuss that issue. Dr. Simon?

DR. SIMON: I just want to say I think it's clear that some patients have benefitted. I think what's difficult is to know what proportion of the patients have benefitted.

DR. SCHILSKY: Dr. Zackheim.

DR. ZACKHEIM: Well, to me a disturbing thing

was the high rate of withdrawal from the study for various causes, over 30 percent, which to me indicates something is going wrong. It's hard for me to believe that there's a significant benefit-risk ratio that can be documented or established with such a high withdrawal rate.

DR. SCHILSKY: Other comments? Dr. Margolin?

DR. MARGOLIN: I think that the high withdrawal rate may have to do with the fact that the doses weren't exactly picked well, but I think with all the flaws and all the issues, this is a malignancy, it's indolent for some, not so indolent for others. This is a relatively well-tolerated therapy and there's certainly a fraction of patients who benefit. That fraction is hard to quantitate but certainly looks like it's well within the range, if not higher than what we ordinarily give much worse therapy to for perhaps even less impressive responses.

DR. SCHILSKY: Dr. Nerenstone.

DR. NERENSTONE: I agree with Dr. Margolin, but I have some concerns and wonder, getting back to the question for the FDA, what kind of post-marketing

requirements we could potentially add on if this is approved. I am still very concerned about the very high rate of secondary medications needed to control high lipids and what that means for people who are going to be on these medications for 2 or 3 years. I think this is compounded by the fact that we really don't have a good idea of the response rate. Is it 5 percent? Is it 10 percent? Is it 20 percent? And what kind of long-term side effects are we going to give people who may not really have much benefit, especially in the stable disease population? But we don't really have a lot of long-term follow-up for the patients who are on this long-term medication.

So, my question is, can we put some monitoring and analysis of those patients post-approval or is this an all-or-nothing deal?

DR. SCHILSKY: Dr. Temple?

DR. TEMPLE: Companies can agree to carry out post-marketing studies. Nowadays because of changes in the Food, Drug and Cosmetic Act, their compliance with those promises will be public knowledge, so we're hoping the embarrassment factor will contribute to their

performance. But most people carry out the studies they've agreed to.

We've asked people to conduct registries. If you're interested in long-term effects, one way to do that is to register patients. Or you could recommend comparative trials or add-on studies where this is added to other kinds of therapy. The world is your oyster. Make suggestions.

DR. SCHILSKY: Dr. Raghavan.

DR. RAGHAVAN: Just one of the things that as a perspective that I've been sort of thinking about is the fact that these are not virgin patients from the point of view of treatment, and time and again at this committee we've worried about compliance. I think the discontinuation rate for people who have already been through several lines of treatment is actually not that high. I think we shouldn't forget the fact that these are people who have had chronicity of disease, potentially, as I understand the data that have been presented, failure of treatment on at least one or two occasions. Thus, their expectation will have been modified in terms of previous experience. So, I'm

actually not impressed that the discontinuation rate is that high.

It may be that we're creating a self-fulfilling prophecy; that is, patients who don't feel they're improving will have a more rapid lack of interest in continuing a medication and those who are getting benefit will continue it. The numbers, when you add them up, are difficult, but I don't think it's all that egregiously high a discontinuation rate, just to keep a perspective.

DR. SCHILSKY: Dr. Rook?

DR. ROOK: I agree with that last statement. As an individual who treats hundreds of patients with cutaneous T-cell lymphoma, I am, first of all, going to tell Dr. Temple that at many stages of this disease, it is a life-threatening disease, particularly when you have multiple tumors and Sezary syndrome. Indeed, it is an indolent disease, but it is a disease from stage IB on that carries with it a tremendous impact on these patients' lifestyles.

In that regard, I'm not going to question the veracity of the data at this juncture. But in that

regard, I'm very impressed with the responses that were characterized by some of the presenters, and a 40 percent response rate for patients who've been refractory in my opinion is a quite substantial one.

DR. SCHILSKY: Dr. Lippman.

DR. LIPPMAN: Addressing fundamentally the issue that you raise right off of the benefit, well, I think there are issues of toxicity and activity. I think clearly experience with this agent in many settings compared to the RAR-specific or non-specific retinoids is that this is better tolerated by patients. So, I think from a toxicity perspective, this is probably a better tolerated drug.

The activity seems to be as active or more than even sort of historical comparisons and may even be more active because it's a carefully selected group, maybe not perfectly selected, to be refractory.

So, I think based on both of those issues, there's a benefit.

DR. SCHILSKY: Dr. Temple.

DR. TEMPLE: I certainly never meant to suggest it wasn't serious or life-threatening. I didn't

think I said that, but I didn't mean to if I sounded like I did.

I have a question. Like many skin diseases, this one was evaluated where the principal endpoint used sentinel lesions, one particular part, and the reservations expressed by the reviewer really don't relate so much to the sentinel lesions, which we could confirm photographically, but to the possibility that even though the sentinel lesion improves, the rest of the body isn't doing very well.

Now, I would be interested in hearing the committee comment on how worried about that we should be. The whole idea of the sentinel lesion is that that's taken as a random piece of the body and that effectiveness can be studied there because you can look at it very closely and it's easier to measure than the whole body. But are we being reasonable there, or is that only sensible when you have a control group? Or is it overwhelmingly plausible that how the sentinel lesion responds is, on the average at least, a good reflection of the disease state? Because that really is the major reservation about effect that I think we've expressed.

DR. SCHILSKY: Dr. Raghavan, how worried are we?

DR. RAGHAVAN: Well, I think it depends on how you view the investigators who are participating. I have no reason to doubt the ingenuousness of the investigators concerned. We've heard three people, who are well respected in the field, who have said that they think this is a good drug, that they'd to have their patients on it, and it's helpful.

Now, having spent more time looking after melanoma than I have this disease, I can tell you that in the trials that I've participated in, if I have an index lesion that's regressing and the patient who's regressing with it, I don't conclude that I'm winning. So, I think if you have a T-cell lymphoma where one spot is regressing and the patient is dwindling, losing weight, has multiple other lesions, I think a well-intentioned investigator won't make that mistake. So, I'm not personally particularly concerned.

I think it's quite on the cards with this disease that you could have, as was identified, some cases where maybe someone made a mistake. I personally

have real difficulty in the sort of centers that have participated, as I gather in this study. I have trouble imagining that that's a systematic error.

DR. TEMPLE: Even without photographic documentation.

DR. RAGHAVAN: I'm sorry.

DR. TEMPLE: You're not worried even without the photographic documentation.

DR. RAGHAVAN: That is correct. I mean, I think it was astute of the medical officer to identify that, and I don't doubt that he's caught them. I just don't think it's a generic phenomenon because I think if it were, the patients would have done worse and the investigators who testified today wouldn't have testified. I have real trouble imagining that it's a generic problem.

DR. SCHILSKY: I think we do also take some comfort in the fact that at least for the index lesions, that FDA was able to corroborate a very high proportion of the responses. So, presumably if you had the whole body photographs, you might have been able to corroborate a similar high proportion of responses.

DR. TEMPLE: Well, probably not now but sometime we should probably discuss whether index lesion responses should be modified specifically in the protocol by some measure of overall deterioration. I don't know but we don't have to do that now.

DR. SCHILSKY: Perhaps as a lead-in to the first question, maybe we could just have a little bit of discussion about whether the committee members believe that the response criteria employed in the study are sort of acceptable response criteria because they were response criteria that were developed specifically for this study, as far as I can tell. Dr. Blayney?

DR. BLAYNEY: I think I tried to ask that question of the two or three investigators, and they seemed to say yes. We heard an independent investigator say yes. So, I would say yes, that they are valid.

Also, I'm a little bit troubled. I think, again, this is an active agent. This is a rare disease, and I would hate to see us try and micro-manage the practices of physicians by imposing further study requirements on the sponsor in order to get approval.

DR. SCHILSKY: Dr. Simon?

DR. SIMON: For me personally, I have to go by what everyone else says. From what I know about follicular lymphoma, for example, I think these would not be adequate response criteria because if you have a disease which is waxing and waning and you have patients staying on study a long time, you're going to have a substantial response rate. When you have an open-ended period of time under which the patient can respond, you will tend to get a response rate that may be higher than reflects meaningful clinical --

DR. SCHILSKY: It does seem, though, that the great majority of the responses occurred within the first 3 to 4 months, as best as we can tell.

Dr. Lippman?

DR. LIPPMAN: Yes. In addition to this being a very uncommon disease and debilitating disease, it's further compromised by the difficulty in measuring and determining responses. There's just no question it's very different than follicular lymphoma or any other tumor in that regard. I think that these studies really attempted to do, I think, the best possible job to really define rigorous criteria that may have missed

some cases, but the response rates are high and one or two cases I don't think are going to affect that much.

DR. ROOK: I just want to say a spontaneous response of 50 percent or better, which characterized the partial response, is unusual to occur without therapy. It's also unusual for it to be maintained in a spontaneous way for more than 4 weeks. These are standard evaluation criteria for this disease, the PGA and CA.

DR. SCHILSKY: Dr. Temple?

DR. TEMPLE: Well, I'm not in any way disagreeing with the comments on the unlikelihood of these responses spontaneously. But there are ways of dealing with situations where the response is hard to evaluate and where you're not sure of whether there is spontaneous improvement. It's called having a control group and using blinding, either of which could have been done in this trial. If the responses are seen within 4 months, you're really only asking the untreated group to stay untreated for 4 more months. In a chronic disease, it doesn't seem impossible to have asked those questions. So, without in any way addressing the

question of what your conclusions should be, I think it's worth pointing out that there are ways of doing this, almost always.

DR. SCHILSKY: So, we have to deal with the way that it was done, and then we can talk about the way it might have been done.

Dr. Raghavan?

DR. RAGHAVAN: Then that opens up the question of statistical significance in a randomized trial, and this is a disease that's uncommon. You then start to get into the problem of heterogeneity of pretreatment. The figure of 16,000 was thrown out there as a prevalence figure, but that gets to be pretty distributed and pretty heterogeneous. I don't disagree with the principle, but with an uncommon disease, it becomes more complicated.

DR. TEMPLE: But, Derek, they're saying -- and people are agreeing with them -- that the effects here are so obvious you don't even need a control group to determine them. That means that a control group, had there been one, would have had essentially no responses, unless we've been misled, and significance would be not

so hard to detect if the effect is as dramatically different from spontaneous improvement as we think.

DR. SCHILSKY: Dr. Johnson.

DR. DAVID JOHNSON: I'd like to comment on Dr. Temple's point that he's making. He has made it many times before to this particular committee. I actually agree with him. Let's say this were a perfect world and we had a controlled study and we had a nice response rate and the placebo group, whatever that might have been, did not do particularly well, or not even a placebo group. Let's say it had been an accepted oral therapy or even a non-oral therapy. It couldn't have been blinded or maybe you could have blinded it. It would have been difficult to do it.

I'm sympathetic to the issue that this is a rare disease. It's not too rare, though, because we've heard at least several investigators tell us how many hundreds of patients that they treat with this disease, and the sponsor managed to get 600 patients into 16 trials. It would have been nice if they had done them all in one trial and done a randomized trial.

DR. SCHILSKY: I'm not sure all of those were

CTCL trials.

DR. DAVID JOHNSON: They, nevertheless, got a lot of patients into these trials. As I said, several of the investigators have told us how many hundreds of patients they treat.

Having said all that and dealing with a disease that's considerably more common than CTCL and having difficulty getting randomized trials sometimes done in that more common illness, like lung cancer, I'm sympathetic.

What it does mean to me, though, is that if you do a phase II trial and you want to come to the FDA with those data, then it should be done scrupulously, with great care, with adherence to the protocol, with careful attention to detail, with assistance to the investigators to ensure that the endpoints of importance are, in fact, evaluated in a very precise manner.

What we heard today -- and actually Dr. Margolin made the comment that clinical trials are difficult. Errors are made because we can't cage humans like we do rats and feed them all human Purina Chow, or whatever it is, and make them the same. The fact of the

matter is one can do studies well.

This study, it seems to me, was done okay. I wouldn't say it was done particularly well. Maybe individual investigators did well, but the overall study itself doesn't seem to me to be terribly helpful. That's why we're all sitting around here struggling.

My grandfather used to have a comment for most things, and one of his favorite comments was if you see a turtle on a fencepost, it didn't get there by accident.

(Laughter.)

DR. DAVID JOHNSON: And I don't think these results are accidental. But just like how that turtle got there, we don't know how we got to this point, and that's what we're struggling with. We're trying to figure out how did we get to these data and what do these data actually mean. For those individuals who treat this disease around the table, they're feeling very positive about these data and are assuring us that they are meaningful.

Again, the only precautionary note I would put forward is that I recall when a regimen, popularly

used in this country, called carboplatin and taxol was proposed for lung cancer in a phase II trial that was hailed as just about the answer for cancer. Over a year median survival in advanced disease, all these wonderful end results. Now in three randomized, controlled trials, it shows results that are inferior to other so-called lesser regimens.

So, I don't know what these data actually mean other than the fact that it appears that a few patients who Ligand has brought forward to us to hear from today benefitted. I have no doubt that those patients benefitted. I have none whatsoever. But we haven't heard from the other 80-some patients on this trial at that dose. So, I agree with the earlier comment made that what we're hearing is anecdotal data that's very persuasive, and the question is does the committee use that data to go forward and approve this product for the indication.

DR. SCHILSKY: Well, let's find out.

(Laughter.)

DR. SCHILSKY: So, why don't we go to the questions. I'll direct the committee members to the

questions that were in your blue folder. The first two pages are the summary of information we've heard, including the tumor response data from the early disease and advanced disease trials. I think that has been adequately summarized for us in the presentations. So, perhaps we can go right to the questions.

So, question number 1 is, does the committee believe that a clinically meaningful tumor response rate using acceptable tumor response criteria has been adequately demonstrated? Does anyone wish to discuss that?

(No response.)

DR. SCHILSKY: Should we go directly to a vote? So, no one wants to discuss it.

So, all those who would answer that question yes, please raise your hand.

(A show of hands.)

DR. SCHILSKY: 11 yes.

And no?

(A show of hands.)

DR. SCHILSKY: 5 no.

Abstentions?

(A show of hands.)

DR. SCHILSKY: 1 abstention. Okay, 11 yes, 5 no, 1 abstention.

Question 2. Has clinical benefit other than tumor response been adequately demonstrated?

All right. We need to take a recount on the first question. The total number of voters is 16. So, I must have miscounted.

DR. DAVID JOHNSON: I voted twice.

DR. SCHILSKY: It wouldn't surprise me.

(Laughter.)

DR. DAVID JOHNSON: We do it in government elections all the time. Chicago does it that way.

DR. SCHILSKY: We're familiar with that technique.

Can we just revote question 1? All who would vote yes for question 1?

(A show of hands.)

DR. SCHILSKY: I get 11 yes.

All who would vote no?

(A show of hands.)

DR. SCHILSKY: 4 no.

And abstentions?

(A show of hands.)

DR. SCHILSKY: 1 abstention.

On to question 2. Has clinical benefit other than tumor response been adequately demonstrated?

Dr. Margolin?

DR. MARGOLIN: Could I just make a comment or ask a question on that one before we vote? I don't think in this disease and in these manifestations, the way the wording is indicated, that you can separate those two. I think this is a situation where the tumor response, tumor being used as their burden of skin disease as opposed to the specifics, and the itching and the disfigurement and the flaking and what it looks like and what it feels like, is all tied in together.

DR. SCHILSKY: Does anyone want to discuss that?

I'm not sure I would entirely agree with that myself. It seems to me that, again depending upon the response criteria, you might find a few lesions that improve and everything else is the same or worse and the itching is no better. So, I don't know that response

according to some fairly stringent criteria actually means that overall the patient is having a benefit. It gets back again a little bit to the issue of how response is defined.

Why don't we vote on this one then? So, let me just restate the question. Has clinical benefit other than tumor response been adequately demonstrated?

All who would vote yes?

(No response.)

DR. SCHILSKY: No yes.

All who would vote no?

(A show of hands.)

DR. SCHILSKY: 13 no.

Abstentions?

(A show of hands.)

DR. SCHILSKY: 2 abstentions. So, am I missing one again? Sorry.

All who would vote no? There must be 14 noes.

(A show of hands.)

DR. SCHILSKY: 14 no. Sorry. All right, 14 no, 2 abstentions.

On to question 3. Are the patient populations in the early disease study and the advanced disease study adequately characterized in terms of, first, prior therapy?

Does anyone want to discuss that?

(No response.)

DR. SCHILSKY: All who would vote yes with respect to adequately characterized for prior therapy? I assume that means what prior therapies they received.

DR. DAVID JOHNSON: Yes. That was my question.

DR. SCHILSKY: All right. So, let's be clear on that.

DR. DAVID JOHNSON: Is this just a listing of their prior therapies?

DR. SCHILSKY: Because of what part b asks, which is about response to prior therapy, I'm assuming that part a is, are they adequately characterized as to what prior therapies they received?

All who would vote yes?

(A show of hands.)

DR. SCHILSKY: Any no?

(A show of hands.)

DR. SCHILSKY: 1 no.

Any abstentions?

(No response.)

DR. SCHILSKY: It's easier to subtract. 15 yes, 1 no.

Are they adequately characterized with respect to their response to prior therapies?

All who wold vote yes?

(A show of hands.)

DR. SCHILSKY: 1 yes.

All who would vote no?

(A show of hands.)

DR. SCHILSKY: 14 no, and I'm going to abstain because I actually can't tell.

Are they adequately characterized with respect to the reason for discontinuing or not repeating prior therapies?

All who would vote yes?

(A show of hands.)

DR. SCHILSKY: 1 yes.

All who would vote no?

(A show of hands.)

DR. SCHILSKY: 13 no.

Abstentions?

(A show of hands.)

DR. SCHILSKY: 2 abstentions.

Question 4. Given the availability of other systemic chemotherapy agents active in this disease, should Targretin capsules be compared to another systemic therapy in a randomized, controlled clinical trial? And then part a is for early disease and part b is for advanced disease.

DR. NERENSTONE: A question please.

DR. SCHILSKY: Go ahead.

DR. NERENSTONE: Rich, could you comment on the statistics of such a trial? Given the implication that there's a 0 response rate to a placebo, what kind of numbers would you need to have for a statistically valid phase III to indicate a reasonable 20 percent response rate in this patient population?

DR. SIMON: Well, if you were going to do a randomized trial, you would have the opportunity not just to look at response rate, but also to look at

symptomatic benefit and having a real control group to do that.

Whatever your endpoint is, essentially if you have a 0 percent or something very close to that in the one arm and a substantial in the other arm -- I don't have the numbers on my fingertip, but you could do it with a relatively small sample size.

DR. SCHILSKY: Dr. Kelsen.

DR. KELSEN: From what I've heard this morning, I think it would be really hard to do a placebo controlled, random assignment in this disease from that list of drugs that I saw. There are a number of agents that have activity, and the argument would be is this less toxic than those agents that have activity. It would be more of an equivalence trial or a less toxicity trial. I wonder if you could comment on the numbers that would be needed for that because had they done a placebo-controlled trial and brought that to us today, I think this would have been very straightforward.

But since that wasn't chosen, what would be required to address statistically a trial where you have equal response rates but you're looking for less

toxicity knowing the toxicity profile. This is hypertriglyceridemia and changes in hormone levels and methotrexate or cytoxan's toxicities are myelosuppression, nausea, vomiting, et cetera.

DR. SIMON: I think in that type of a trial, in that situation, the toxicities would be different. So, I think what you would be looking at is are the response rates or are the symptomatic benefits equivalent and for that really to have a narrow confidence, as to whether the tight confidence level for -- whether response rates or symptomatic benefits are equivalent, that could require a large sample size.

DR. KELSEN: I was thinking of the UFT trial we just looked at.

DR. SCHILSKY: Well, I want to just make a comment and then ask a question of the FDA. It seems to me that it should be feasible to do a randomized clinical trial against some other systemic therapy as sort of the first systemic therapy that this patient population receives. We've heard and I think the general clinical experience is that most of these patients initially get treated with topical therapy or

electron beam radiotherapy, skin-directed therapy. Not until later in the course of their disease did they usually require and receive a systemic therapy. And then there are a variety of systemic therapies that could be used. In the studies we've seen already today, most of those therapies were used. So, it seems perfectly conceivable to me that a trial could be done comparing this agent to some other agent as first-line therapy at the time that systemic disease is required.

My question to the FDA I guess is, are you asking us whether such a study should have been done or whether such a study should be done in the future?

DR. TEMPLE: Well, we were asking both. One possibility was that you might have thought or might think that given the availability of other therapies, the drug shouldn't be approved until they have some comparison, or you might think that that's critical information to get later, especially since the patients studied all had been refractory to one or another of -- the advanced patients, anyway, were refractory to one or another treatment. You might think it's of interest, as you just suggested, to see how it compares with the

alternative initial systemic therapy.

DR. SCHILSKY: To me it would make sense that if the drug were to get accelerated approval, that the follow-on phase III trials --

DR. TEMPLE: We're not talking about accelerated approval. We're just talking about approval. We can reach understandings with companies on further data, and they generally agree to those. Under accelerated approval, we can actually require things.

DR. SCHILSKY: I withdraw the comment.

Dr. Rook.

DR. ROOK: One of the problematic issues is that there is no landmark against which to base this. In other words, you heard from Dr. Foss that the only controlled trial that has been published to date was one I believe involving multi-drug chemotherapy that took 7 years to perform. There is no standard landmark with a single agent that has been used in a randomized trial in this disease against which to base these results. We only have anecdotal data in the literature. So, what is the landmark that you're going to require against which Targretin is going to be based to gain approval?

Any controlled trial in my experience that has been attempted in this disease has taken years to generate and has generally fallen apart. Let me give you an example.

A controlled trial was attempted with interferon compared to photopheresis. After 3 years, that trial was abandoned because of problems with patient entry and accrual of a satisfactory patient number. Even as such, comparing photopheresis to interferon as a two-arm trial ultimately was considered to be unsatisfactory because you didn't have a placebo arm, you didn't have a background response level against which to base it. So, these are all problematic issues.

DR. SCHILSKY: Dr. Temple.

DR. TEMPLE: It's hard simultaneously to think they've shown evidence of effectiveness and then believe you have to have a placebo in a controlled trial. Those two thoughts can't coexist.

You've all indicated that you think the observed responses are credible because you don't think that's what happens in the absence of therapy. If that's the case, a comparison could be done, and even if

you don't think there's one thing that's standard therapy, you still get a good description of what the response rates are and what the toxicity is, and it helps you locate the therapy in the therapeutic regimen. It's not a loss. This isn't a case where you'd say, well, if it's any worse than methotrexate, I won't approve it. You might just want to know how much worse or how much better than methotrexate it is. There's a lot of information.

Of course, the other thing you can do is you have a control group so you can make more credible observations.

DR. SCHILSKY: Any other comments on this particular question? Dr. Blayney?

DR. BLAYNEY: I have trouble if the question is should our advice be that another trial is required before approval, or in the abstract, should another trial be done. And I think should another trial be done -- as a clinician, I would like to see that done, but whether another trial with a pickier control group should be done before approval, I am not sure I could advise you that that's necessary.

DR. TEMPLE: I think we understand your previous answers to be saying the same thing.

DR. SCHILSKY: Dr. Lippman.

DR. LIPPMAN: I think one potential trial could be, for instance, comparing this to another retinoid since 20 percent of the advanced population in this study had actually used one retinoid, 13-cis, and maybe there are more that used others.

But I think there's so much data out there with these two agents in this setting and other settings. First of all, we know that the retinoids are active. There are a number of studies in this disease. And this drug is less toxic in many settings, including this. It's better tolerated.

So, one can argue whether it's more active than the other retinoids because at least these investigators have gone to quite a bit to define a refractory population which is I think probably more refractory than in the general studies in the literature. These are some of the issues and difficulties with the randomized study.

DR. SCHILSKY: I don't think we're being

asked to design the trial here today. We're only asked to comment on whether such a trial should be done.

DR. LIPPMAN: Like I say, this is the difficulty with it because of the --

DR. SCHILSKY: Dr. Johnson, did you have a comment?

DR. JOHN JOHNSON: Yes. I just want to comment there has bee more than one randomized trial. The committee was presented a year ago with a randomized trial of Ontak, randomized high dose and low dose, with a total of 71 patients.

DR. SCHILSKY: Dr. Simon.

DR. SIMON: Well, I feel what would have been valuable would have been to have had a trial -- in other words, we were shown data today that says after 4 weeks you have a difference in quality of life for the 300 dose group versus their baseline measurement. One could have done a trial, a short-term trial. If that's really credible data, which I question, it wouldn't take a very big trial -- to delay treatment for a few months and to do a trial to show whether that's real or that's just something else. That's the kind of trial that I would

have liked to have seen done to see whether we're really having symptomatic improvement here.

I think once you go beyond that -- and then the issue is it's always useful to have randomized trials when you have multiple treatments available even if they are phase II trials, even if it's not big enough to be an equivalence trial, so that you have sort of the response rates measured without bias selection from different studies and with the same kind of response criteria.

So, I think, in general, those kind of trials are very useful, but I think it's harder to see how those kind of trials would solve the problems that I think are facing us from the fact of the absence of a randomized trial against a delay in therapy.

DR. SCHILSKY: I think we've had sufficient discussion on this point, so let me suggest that we go ahead and vote on it. I'll reread the question.

Given the availability of other systemic chemotherapy agents active in this disease, should Targretin capsules be compared to another systemic therapy in a randomized, controlled clinical trial in

early disease?

All who would vote yes?

DR. LIPPMAN: Are we talking about prior to registration or just in the future?

DR. SCHILSKY: Do you want to clarify?

DR. JUSTICE: Can I just suggest maybe the committee table this question till after you answer the other questions? It will make more sense then.

DR. SCHILSKY: We're here to advise you. If that is more helpful to you for us to do it that way --

DR. ROOK: But the answer to that question is an important one when we come back to this issue.

DR. SCHILSKY: Number 5. In view of the risks, are the benefits adequate to warrant approval of Targretin capsules for treatment of the patient population in the early disease study?

All those who would vote yes?

(A show of hands.)

DR. SCHILSKY: 2 yes.

All who would vote no?

DR. MARGOLIN: Excuse me. We haven't had a discussion of question 5.

DR. SCHILSKY: No one offered to have any. Would you like to?

DR. MARGOLIN: This is the first time we've even talked about the risks. I think there may be some issues about long-term risks in early disease that at least one of us doesn't feel totally comfortable with.

DR. SCHILSKY: Since we didn't complete the vote, we'll allow Dr. Margolin to enter into some discussion.

DR. MARGOLIN: No. I don't have the answer. I'm just concerned that if this turns out to be the great drug that it looks like it may be, but the long-term risks of this significant hyperlipidemia, even on therapy, and maybe other problems that we haven't even seen yet or haven't seen the evolution of over time, I think there's going to have to be something to address that either in the package insert or some very carefully worded guidelines about how to follow patients who do well and therefore for whom a recommendation is made to have these patients on some form of chronic retinoid therapy.

DR. SCHILSKY: Any other discussion? Dr.

Kelsen.

DR. KELSEN: The indication that they're asking for for early disease is refractory early disease that's progressive under topical skin treatment? It will help me to know a little bit more about that because I agree with Dr. Margolin. If these patients have a good prognosis -- perhaps Dr. Rook could help here -- they're going to do well for a real long period of time.

DR. SCHILSKY: Well, the indication was restated by the FDA.

DR. JOHN JOHNSON: The first page of the FDA questions at the bottom.

DR. SCHILSKY: The proposed indication, at least as restated by the FDA, is treatment of cutaneous manifestations in patients with all clinical stages of cutaneous T-cell lymphoma in the following categories: patients with early stage CTCL who have not tolerated other therapies, patients with refractory or persistent early stage CTCL, and patients with refractory advanced stage CTCL.

Any discussion on that? Comment? Dr.

Albain?

DR. ALBAIN: Going back too, I'm concerned that there's no forum here to discuss the -- this is a point of order too -- the labeling and the duration of therapy, what dose to have them on, how to lower the dose, items we brought up earlier in discussion. That seems to be a big unknown, especially in patients with early stage disease.

DR. SCHILSKY: Well, we have had some discussion about each of those issues. My sense is that the committee has some concerns, particularly with proposed labeling that would suggest that the dose be increased in patients who don't do well with the initial dose. We haven't been asked a specific question by FDA with respect to that aspect of the labeling.

DR. ALBAIN: This just seems an open-ended dosing without a lot of guidance just because these patients are truly being followed in real time now and the data isn't there. Somehow that needs to be reflected.

DR. SCHILSKY: Well, I think they've heard your --

DR. PAZDUR: Assume that the dose is 300.

DR. SCHILSKY: Pardon?

DR. PAZDUR: Assume that the dose is what the sponsor is suggesting, 300.

DR. JOHN JOHNSON: I think in a question like this, you have to assume that the labeling is going to be adequate with respect to dose and precautions, warnings, and all that. You have to assume that you would be willing to approve it with what you consider adequate labeling.

DR. PAZDUR: Trust us.

(Laughter.)

DR. TEMPLE: Or you can write in suggestions.

DR. SCHILSKY: I think we have had good discussion on those issues, though. So, at least FDA is aware of some of the concerns that the committee members have.

Is everyone prepared to vote on question 5 now? Okay. In view of the risks, are the benefits adequate to warrant approval of Targretin capsules for treatment of the patient population in the early disease study?

All who would vote yes?

(A show of hands.)

DR. SCHILSKY: 4 yes.

All who would vote no?

(A show of hands.)

DR. SCHILSKY: 7 no.

Abstentions?

(A show of hands.)

DR. SCHILSKY: 4 abstentions.

Missed one. Can the abstentions please raise your hands again, all who are abstaining?

(A show of hands.)

DR. SCHILSKY: 4 abstentions. Still missing one. I'm sorry. We'll have to do it again.

All who would vote yes to question 5.

(A show of hands.)

DR. SCHILSKY: 5 yes, 7 no, 4 abstentions.

Question 6. In view of the risks, are the benefits adequate to warrant approval of Targretin capsules for treatment of the patient population in the advanced disease study?

Any discussion anyone wishes to have there?

(No response.)

DR. SCHILSKY: All who would vote yes for advanced disease?

(A show of hands.)

DR. SCHILSKY: 13 yes.

All who would vote no?

(A show of hands.)

DR. SCHILSKY: 2 no.

Abstentions?

(A show of hands.)

DR. SCHILSKY: 1 abstention.

You can only vote once, Dr. Zackheim.

(Laughter.)

DR. SCHILSKY: 13 yes, 2 no, 1 abstention.

Shall we go back to question 4 now? I think we've had plenty of discussion on that, so perhaps we can just vote it. I'll reread the question.

Given the availability of other systemic chemotherapy agents active in this disease, should Targretin capsules be compared to another systemic therapy in a randomized, controlled clinical trial in the early disease?

Dr. Lippman.

DR. LIPPMAN: Just a clarification again. Are we talking pre-registration or after, post-registration randomized trial?

DR. SCHILSKY: After?

DR. TEMPLE: Well, after. You've already voted on whether you think it should be approved. And it doesn't have those studies.

DR. SCHILSKY: So, we're voting for should there be a randomized trial performed after approval, assuming the approval is granted.

DR. ROOK: Question: Are we generically referring to the chemotherapy as chemotherapeutics, alkylating agents, and that, or does interferon get lumped into that? What do we mean by chemotherapy, since most of us will not do a randomized trial in early disease employing any kind of chemotherapeutic agent.

DR. SCHILSKY: Well, I'll ask the FDA. It's their question.

DR. TEMPLE: Well, I probably wrote the question. I think we're interested in your advice here. If you care to advise separately on early disease and

late disease, emphasizing cancer chemotherapy for late disease and something else for early disease, that's okay. This is a free opportunity to tell us what you think we should do.

DR. DAVID JOHNSON: Maybe what you're suggesting, not that I would try to tell you what you're thinking here, Dr. Temple, but perhaps what you were thinking at the time is that if one -- they obviously did a study in early stage disease, albeit it refractory early stage disease. It's sort of a bit of an interesting concept. So, maybe what you were thinking is taking the definition of the group that they studied in this trial that they've presented to us, maybe tightening the criteria a little bit and making sure, and then randomizing that group of patients, one might perhaps stratify. That's been done doing somewhat different therapies. I mean, there are ways I think one could think of this.

Now, whether it's practical to do it or not is a separate issue than should it be done and how one would do it. Those are actually three questions. The question of should it be done is sort of like do you

love your mamma.

(Laughter.)

DR. DAVID JOHNSON: Of course, it should be done.

DR. SCHILSKY: Dr. Justice.

DR. JUSTICE: I'll see if my colleagues agree with me on this, but the way I interpreted the committee's vote was that for early disease, you're recommending against approval. So, therefore, the controlled study would be before approval. In the latter case, you voted for approval, so it would be after approval.

DR. SCHILSKY: Does that make things more clear? Dr. Zackheim?

DR. ZACKHEIM: Yes. Well, the way the statement stands, nobody can argue against the desirability of having a randomized trial. You can't argue against that. But as Dr. Rook has said, in dermatology practically out of the question. We have never been able to do, except with the one study, a randomized trial in dermatology and probably never will because of so many difficulties.

So, if you would reword the question, should the availability of systemic therapy, et cetera, be compared before FDA approval is given, then I would say no.

DR. SCHILSKY: Let me suggest that we vote on two questions here. One question would be -- and we're going to forget the preamble about the availability of other systemic chemotherapy agents. Okay?

So, the first question is, should Targretin capsules be compared to another systemic therapy in a randomized, controlled clinical trial? It's understood that that would be prior to approval. We're talking about for early disease.

All those who would vote yes? All those who would vote yes for should this be compared to another systemic agent in a randomized, controlled trial in early disease. That's what we're voting on. Please raise your hands high.

(A show of hands.)

DR. SCHILSKY: 5 yes.

No. All those who vote no?

(A show of hands.)

DR. SCHILSKY: 6 no.

Abstentions?

(A show of hands.)

DR. SCHILSKY: 5 abstentions.

Next question.

DR. TEMPLE: Can I just ask a question? The vote initially on approval for early disease was I think 7 to 5 against. I'd be interested in what the people who were against it think would be needed to make the case for approval in early disease. Presumably it's some additional information of some kind.

DR. DAVID JOHNSON: Yes. I actually think Dr. Margolin touched on it, and that is in early stage disease that you're going to be treating an individual for a protracted interval of time. I think we need more long-term follow-up data. I'm not sure I necessarily need the comparative data. Again, ideally that would be nice. But I do think one needs long-term follow-up. If your ear lobes fall off after 5 years on this stuff, you know, it's not a good thing, if you wear earrings I mean.

(Laughter.)

DR. SCHILSKY: Dr. Margolin.

DR. MARGOLIN: But that's not to say that I think that we don't -- I would actually vote probably the most strongly in favor of exactly what Dr. Temple said earlier and what you also said earlier about the importance of these randomized data to tell us the real truth about drugs that look really great in phase II and where we don't have the heart not to approve them for such a small group of patients. I don't think the fact that we couldn't do randomized trials in the past means that we should stop all efforts to do them.

Furthermore, I think at this point there are probably some choices about potential comparators. My first choice would be interferon because it's not PUVA and it's not electron beams, and it's something that's probably the closest in terms of outpatient therapy and in terms of where it goes in the therapeutic armamentarium because I think the point was made that we need to know what's the place and time of this drug in the serial therapy of this disease.

DR. SCHILSKY: Can we vote on the last question before lunch? So, to restate the question,

should Targretin capsules be compared to another systemic therapy in a randomized, controlled clinical trial in advanced disease? Presumably this trial would be done post-marketing.

All those who would vote yes?

(A show of hands.)

DR. SCHILSKY: 8 yes.

All those who would vote no?

(A show of hands.)

DR. SCHILSKY: 4 no.

Abstentions?

(A show of hands.)

DR. SCHILSKY: How many times are you voting?

(Laughter.)

DR. DAVID JOHNSON: Every question I voted at least once.

(Laughter.)

DR. SCHILSKY: Can we complete the vote before you put up your hand to ask a question?

All those who would vote yes about a controlled trial in advanced disease.

(A show of hands.)

DR. SCHILSKY: 8 yes.

All those who would vote no?

(A show of hands.)

DR. SCHILSKY: 4 no.

All those who are abstaining?

(A show of hands.)

DR. SCHILSKY: 4 abstentions. I think that's 16.

Thank you. We will reconvene promptly at 2:15.

(Whereupon, at 1:37 p.m., the committee was recessed, to reconvene at 2:15 p.m., this same day.)

AFTERNOON SESSION

(2:20 p.m.)

DR. SCHILSKY: Good afternoon. I'd like to begin this afternoon's session. Our apologies to RPR for starting late.

We'd like to begin by reintroducing the committee because we have a few new people at the table. Let's begin with Dr. Simon again.

DR. SIMON: Richard Simon, biostatistics,

National Cancer Institute.

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

DR. LIPPMAN: Scott Lippman, medical oncology and cancer prevention, M.D. Anderson.

DR. PELUSI: Jody Pelusi, oncology nurse practitioner in Arizona and Consumer Rep.

DR. KELSEN: Dave Kelsen, medical oncology, Sloan-Kettering.

DR. ALBAIN: Kathy Albain, medical oncology, Loyola University, Chicago.

DR. SANTANA: Victor Santana, pediatric oncologist, St. Jude's Children Research Hospital, Memphis, Tennessee.

DR. DAVID JOHNSON: David Johnson, medical oncologist, Vanderbilt University.

DR. SLEDGE: George Sledge, medical oncologist, Indiana University.

DR. SCHILSKY: Richard Schilsky, medical oncologist, University of Chicago.

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

DR. BLAYNEY: Douglas Blayney, medical oncologist, Wilshire Oncology Medical Group, Pomona, California.

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

DR. RAGHAVAN: Derek Raghavan, medical oncology, University of Southern California.

DR. GRIEBEL: Donna Griebel, medical reviewer, FDA.

DR. BEITZ: Julie Beitz, medical team leader, FDA.

DR. JUSTICE: Bob Justice, Deputy division Director, FDA.

DR. PAZDUR: Richard Pazdur, Division Director, FDA.

DR. SCHILSKY: Thank you.

And Karen has a statement to read.

DR. TEMPLETON-SOMERS: First of all, I'd like to announce that we will be working without a patient representative this afternoon. Kenneth Giddes was taken ill and cannot be here.

The following announcement addresses the

issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

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

In accordance with 18 U.S.C. 208, full waivers have been granted to Dr. Derek Raghavan. A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, room 12-A30 of the Parklawn Building.

In addition, we would like to disclose that Dr. Dr. Raghavan's and Dr. Sledge's employers have interests which do not constitute a financial interest in the particular matter within the meaning of 18 U.S.C. 208, but which may create the appearance of a conflict. The agency has determined, notwithstanding these interests, that the interest of the government in the

participation of Dr. Sledge and Raghavan outweighs the appearance of the appearance of a conflict. Therefore, they may participate fully in all matters concerning Taxotere.

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

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

Thank you.

DR. SCHILSKY: Thank you, Karen.

We have several people who have requested an opportunity to speak to the committee during the open public hearing. I would ask each person to come to the podium and identify yourself and indicate whether you've received any financial support to be here. We'll begin with Gaetano Giorno.

MR. GIORNO: My name is Gaetano Giorno, 65

years old.

I was first diagnosed with non-small cell cancer over two and a half years ago, and according to the experts, my chances of survival were slim. And I was given two months to two years to live. You can imagine how those words sound to a person. You want to do everything you can to live, but at the same time, you realize everything you do will be in vain.

I was constantly coughing, feeling tired, short of breath, and my appetite was gone. I soon began to lose weight.

But giving up is not in my nature and I began chemotherapy, cisplatin and navelbine. The side effects to the drugs were bad. I was often sick, nervous, very tired, and feel always cold. Needless to say the chemotherapy treatment was not a success, and my hopes grew less and less.

I was referred to a Dr. Shepherd who was working with an experimental drug called Taxotere at the Princess Margaret Hospital in Toronto. At first I was not anxious to become part of a program. I was doubtful that this drug would work and also very worried about

the side effects. I delayed my decisions for a full week before finally deciding to join a program. In my heart there was still that faint hope.

After the second cycle of treatment, I was almost removed from the therapy due to a misunderstanding. Thanks to Manuela Muneroz, Dr. Shepherd's nurse, who managed somehow to get me back on the program and on the route to recovery.

After three sessions, I began to feel better. My appetite returned and I started working again. My outlook also improved, and I began to see a light at the end of the tunnel. For the first time I began to think that I could win. My energy and confidence grew. I replaced the shingles on my 30-foot high roof. I chopped wood in my back yard. I regained the weight I had lost before, and I felt as good as ever.

I have completed 10 sessions and I can say that this drug Taxotere has allowed me to speak to you today. I have hope and life again, and it is important that others will be given the same chance by having this drug approved for the use of lung cancer therapy.

Thank you.

DR. SCHILSKY: Thank you very much.

The next speaker is Scott Rivers.

MR. RIVERS: My name is Scott Rivers, and I'm with the Alliance for Lung Cancer Advocacy, Support and Education where I'm a program manager. We are a nonprofit organization dedicated solely to helping those at risk for and living with lung cancer. I'm here today on behalf of the Alliance for Lung Cancer and our constituents, both current and future, to encourage the ODAC to support approval of Taxotere as a second-line treatment for non-small cell lung cancer.

The Alliance for Lung Cancer feels tremendous responsibility to advocate for new and better therapies for people with lung cancer. Our representatives have appeared before this committee previously when other agents were being reviewed, and we hope to be here whenever a promising agent is under review for treatment for lung cancer.

Lung cancer is a formidable and insidious disease. Given the bleak survival statistices, especially those for late stage, recurrent and refractory disease, more and better treatment agents are

definitely needed now.

Through our toll-free hotline and our web site, we are in daily communication with large numbers of people from around the country and even around the world. Paraphrasing the question we hear most often, my therapy is not working anymore. What else is out there?

Hearing this question as often as we do and feeling the accompanying desperation and shattered hopes of the people who ask it, we are keenly aware of the need for more treatment options for this population. Many of those who have been successfully treated live with the unshakable anxiety that the disease will return or progress, and they will not have adequate treatment to combat the disease.

The demographics of lung cancer are changing. People are being diagnosed at earlier ages, and this allows some more vigorous therapies. In patients of all ages, we are seeing some longer survival times. We know many who have survived 5 years or longer, and some of those even with advanced disease. Unlike in days gone by, when patients were frequently offered one or

possibly even two regimens and then hearing the refrain, I'm sorry, that's all we have to offer, people can receive more regimens today, three, four. And we've talked to people who have even received five or more regimens.

Because of the better supportive care agents that are now available, people can manage the toxicities better and tolerate the treatments better with things to manage the myelosuppression and to manage the nausea and vomiting that are so frequently a part of chemotherapy treatments.

This is good but we must not rest on our laurels. If people are going to have fight left in them, then we need to have something for them to fight with. Taxotere appears to be a good tool for this fight.

I know that the presenters today will elucidate more about the drug and the science of it, but a recent article in the Seminars of Oncology, the abstract from Drs. Ganderra, Lao, and Edelman read: Single agent docetaxel appears to be most active agents in the therapy of advanced non-small cell lung cancer,

with response and survival data in chemo-naive patients comparable to that reported for combination chemotherapy regimens, and activity in platinum-refractory, non-small cell lung cancer superior to that reported with other agents to date.

Our callers have also reported to me feeling that they owe their lives to Taxotere, and as Mr. Giorno just told you about his experience, I've spoken with a number of patients with similar experiences. People have continued working while on Taxotere. I've also spoken with patients who have not had such good luck or have not had such an easy time, but that's going to happen with any chemotherapy.

The point is that we need more drugs in our stable of options for those that it will work for. So, for many, just knowing another option is available provides strength and hope, enabling to keep up their fight.

I find myself asking this question, with which I will conclude, how could Taxotere not be approved when, one, there's such a void of effective therapies for advanced and refractory non-small cell

lung cancer? Two, when Taxotere offers such promise in terms of response rates and 1-year survival in comparison to other regimens; and three, the toxicities are being noted as acceptable.

Thank you for the opportunity to speak and consideration of my remarks.

I forgot to mention that I have not received any financial support for being here. We have in the past received some grants from RPR, as well as we do other pharmaceutical companies, general grants for specific programs or unrestricted funds. Thank you.

DR. SCHILSKY: Thank you very much.

We have several letters that have also been submitted and Karen will summarize those letters for the record.

DR. TEMPLETON-SOMERS: Again, in the interest of saving time, I'll be summarizing the letters I've received in support of Taxotere.

Mr. Urmston, Mr. Ammerman, and Mr. Tyre all participated in the clinical trials for Taxotere. They all experienced benefit from the drug and recommend that it be made available as a chemotherapy for non-small

cell lung cancer.

The letters again are included in your blue folders for those of you at the table, and for the audience, they're available in the notebook which is at the meeting registration desk. They will also be included in the official meeting record.

Thank you.

DR. SCHILSKY: Thank you.

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

(No response.)

DR. SCHILSKY: If not, we'll proceed to the sponsor's presentation, and Dr. Chaikin.

DR. CHAIKIN: Good afternoon, Dr. Schilsky, Dr. Somers, members of the committee, Dr. Temple, Dr. Pazdur, members of the FDA Taxotere review team, ladies and gentlemen. My name is Dr. Philip Chaikin and I'm Vice President for Clinical Development at Rhone-Poulenc Rorer Pharmaceuticals. It is my pleasure to introduce this afternoon's presentation regarding our NDA 20-449, supplement 11 for Taxotere.

Taxotere for injection concentrate was

initially granted accelerated approval on May 14, 1996 for the treatment of patients with locally advanced or metastatic breast cancer who have progressed during anthracycline-based therapy or have relapsed during anthracycline-based adjuvant therapy.

Subsequently on June 22, 1998, the accelerated approval was converted to full approval, and the label was broadened to include the treatment of patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy. And that is the indication reflected today in the current package insert for Taxotere with a dose range of 60 to 100 milligram per meter squared.

Taxotere is approved in 87 countries worldwide for use in the treatment of breast, ovarian, and/or lung cancer. 44 of those countries, which include Australia, Canada, and Japan, have approved Taxotere for the use in the treatment of lung cancer.

In October of this year, the committee, for proprietary medicinal products, recommended approval of Taxotere to the European Commission for the treatment of patients with locally advanced or metastatic non-small

cell lung cancer after failure of prior chemotherapy. As of the middle of this year, an estimated 220,000 patients worldwide have been exposed to Taxotere in their fight against cancer.

We appear before you today regarding an efficacy supplement which we believe demonstrates the patient benefit associated with the use of Taxotere in the treatment of advanced non-small cell lung cancer. I refer to Taxotere supplement number 11. This supplement was granted fast track designation and priority review by FDA on February 19, 1999 based on the potential for Taxotere to fill an unmet medical need in previously treated patients with advanced non-small cell lung cancer, a setting which represents a serious and life-threatening disease and for which there is no FDA-approved agent and where treatment options have offered little hope for the future of these patients.

In addition, until now no phase III trials have evaluated the efficacy of chemotherapy in previously treated non-small cell lung cancer patients and evaluated its impact on quality of life. As a reminder, survival for patients with advanced non-small

cell lung cancer who have been previously treated with chemotherapy has been dismal, with a median survival of less than 5 months and a 1-year survival of 12 percent, as shown on this curve. This is the best supportive care arm from our pivotal phase III trial TAX317, which you will hear more about later this afternoon.

Supplement 11 is supported by two phase III trials. The total number of patients treated with Taxotere in this supplemental NDA is 618.

The first phase III trial is TAX317, a multi-center, randomized phase III study of Taxotere plus best supportive care versus best supportive care alone in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy.

The second trial was TAX320, a multi-center, randomized phase III study of Taxotere 100 milligrams per meter squared or 75 milligrams per meter squared versus vinorelbine or ifosfamide in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy.

In addition, data from six phase II trials were part of this submission.

Both of the phase III trials mentioned here today were designed with input from the FDA's Division of Oncology Drug Products at an end of phase II meeting on June 6, 1995. We will present survival data for both pivotal phase III trials as initially submitted in the supplemental NDA and will give an overview of the survival updates for both studies as part of the 4-month safety update as requested by FDA at our pre-sNDA meeting.

This slide reflects the indication for which we seek FDA approval in previously treated non-small cell lung cancer patients at a dose of 75 milligrams per meter squared. And that is Taxotere for injection concentrate is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.

This afternoon you will hear presentations regarding the efficacy and safety data for this new indication. Moreover, you will see consistency between the efficacy and safety results of the phase II program when compared with the phase III data. So, our agenda is as follows.

Dr. Mark Green from the Medical University of South Carolina will provide you with an overview of chemotherapy in advanced non-small cell lung cancer and will present the results of RPR's phase II data.

Dr. Frances Shepherd from Princess Margaret Hospital in Toronto, Canada, will provide an overview of study TAX317.

Dr. Frank Fossella from the University of Texas, M.D. Anderson Cancer Center will discuss study TAX320.

Dr. Richard Gralla from Ochsner Cancer Institute will provide an overview of quality of life and the methodology used in this dossier.

Then Dr. Mark Green will provide an investigator's summary of the benefit-risk for Taxotere in patients with advanced non-small cell lung cancer.

I will return to the podium to provide some concluding remarks.

I would like to thank all of you for your time and attention. I would also like to thank the FDA Oncology Division's review team for its rapid review of this application and for their expertise and guidance

along the way.

So, now I would like to turn the presentation over to Dr. Green.

DR. GREEN: Good afternoon. As Dr. Chaikin has just told you, I will begin the data portion of our presentation by providing a brief overview of non-small cell lung cancer with an emphasis on the current status of chemotherapy in previously treated patients.

Worldwide platinum combinations are the standard of care for first-line therapy in good performance status patients with advanced non-small cell lung cancer. Response rates in advanced disease range from 20 to greater than 50 percent. Cancer-related symptom improvement is frequently associated with treatment.

Individual phase III trials and the 1995 meta-analysis confirm a survival benefit for chemotherapy used in this setting compared to best supportive care. In the meta-analysis, median survival for the treated group was 7 months compared to 4 months in the patients assigned to best supportive care. 1-year survival increased to 25 percent with the use of

chemotherapy compared to 15 percent in the best supportive care managed patients.

Despite the increased activity of chemotherapy in first-line management, available treatment options remain less than optimum. Most first-line responses are partial rather than complete, and essentially all responding patients eventually progress.

Once progression after first-line chemotherapy has occurred, the therapeutic options have been quite limited. One option is best supportive care. However, with this approach, even good performance status patients can expect a median survival of only 4 and a half to 5 months. Given the fact that these patients are still quite fit and many have had a good experience with prior chemotherapy, a large number, especially in the United States, want additional therapy. In fact, additional chemotherapy is frequently offered despite the absence of FDA-approved agents for this indication.

In the most recent ASCO guidelines for management of patients with unresectable non-small cell

lung cancer -- these guidelines were published in the August 1997 JCO -- the guideline authors concluded that "there is no current evidence that either confirms or refutes that second-line chemotherapy improves survival in patients with advanced non-small cell lung cancer."

However, referring to the work of Fossella and colleagues, using single agent Taxotere in previously treated patients, they went on to say that "there are recent phase II data to suggest some of the newer agents under investigation may provide a survival benefit in non-small cell lung cancer patients who progress after receiving cisplatin-based chemotherapy."

Activity rates for several single agents as second-line therapy for non-small cell lung cancer have been reported. Among older agents, aggregate or single study second-line activity ranges have been described for vindesine, for epirubicin and etoposide, for cisplatin and ifosfamide. In each case, at least some activity has been reported, with the highest rate of 20 percent seen with ifosfamide. In most of these series, median survivals were not reported, although in at least one of the ifosfamide series, a median survival of 6

months was achieved.

For some of the newer agents, activity ranges are a bit broader, including 0 to 20 percent for vinorelbine, 0 to 21 percent for gemcitabine, 0 to 23 percent in an aggregate of 112 previously treated patients getting Taxol, and 8 to 21 percent among 272 patients treated on six different trials of single agent Taxotere. In addition to some responses in each of the Taxotere studies, very encouraging median survival rates of 6 to 11 months were reported for these individual series of Taxotere therapy in previously treated patients with non-small cell lung cancer.

A more detailed look at the activity of Taxotere in these 272 patients previously treated is shown on this and the next slide. The largest number of patients, 240 of the 272, were treated at the dose level of 100 milligrams per meter squared every 3 weeks. Response rates in these studies, two of which were multi-institutional phase II trials, range from 8 to 21 percent. In addition, one trial was done at 75 milligrams per meter squared and another at 60 milligrams per meter squared. While the numbers of

patients in each of these two series was modest, the observed response rates of 20 percent and 14 percent were well within the envelope of activity seen in the trials done with the 100 milligrams per meter squared regimen.

Other endpoints of importance are shown here. We can see that the median survivals following Taxotere therapy in these previously treated patients were quite encouraging, ranging from 5.7 to 11.2 months. 1-year survival, which is a benchmark that achieved substantial importance as a gauge of utility for first-line regimens, ranged from 18 to 41 percent in these six trials with patients who had already received prior chemotherapy.

Based on the unmet need, which was clearly articulated in the ASCO guidelines, for proven effective second-line therapy in patients with non-small cell lung cancer, the poor outlook with best supportive care in these patients, and the consistent and encouraging activity of second-line Taxotere in six phase II trials, Rhone-Poulenc Rorer undertook the two phase III trials introduced by Dr. Chaikin: TAX317, a test of Taxotere

plus best supportive care compared to best supportive care alone, and TAX320, a test of two different doses of Taxotere or a control regimen of either vinorelbine or ifosfamide. These studies were done in order to definitively evaluate the potential of Taxotere in patients with previously treated non-small cell lung cancer.

The results of these two studies, which will be presented by Drs. Shepherd and Fossella, demonstrate that Taxotere, in particular Taxotere at 75 milligrams per meter squared, improves survival for these patients and, as will be presented by Dr. Gralla, is associated with an improvement in clinical benefit parameters as well.

With this as background, I would now like to introduce Dr. Frances Shepherd to present the first of these phase II trials.

DR. SHEPHERD: Good afternoon, ladies and gentlemen. My name is Dr. Frances Shepherd from the University of Toronto and the Princess Margaret Hospital, Toronto, Canada.

It is my pleasure to present the results of a

prospective, randomized, multi-center trial of Taxotere plus best supportive care versus best supportive care alone in non-small cell lung cancer patients previously treated with platinum-based chemotherapy. This is one of only two phase III trials ever undertaken in this setting. This was an international study conducted in 36 centers in 8 countries.

The primary objective of the study was to compare survival with Taxotere versus best supportive care. Secondary objectives included response time, time to progression, safety, quality of life, and clinical benefit.

Patients in the trial were stratified based on their ECOG performance status of 0,1 versus 2 and on whether while on platinum-based therapy they had demonstrated progressive disease or complete response, partial response, or stable disease.

Patients were randomized to receive either Taxotere 100 milligrams per meter squared, given as a 1-hour infusion every 3 weeks, or best supportive care. This methodology of comparing against best supportive care is the most pure and rigorous way to assess the

efficacy of new agents.

Routine monitoring of safety data revealed 5, or 10 percent, early toxic deaths in the chemotherapy arm. Therefore, after discussion with the principal investigators and the FDA, the Taxotere dose was reduced to 75 milligrams per meter squared in the second half of the study.

The sample size was maintained at 200 patients as originally planned due to difficulty in accruing patients to this study because of the control arm being best supportive care.

Premedication with dexamethasone for the first 100 patients was given at a dose of 8 milligram b.i.d. for 10 doses, but for the second 104 patients only 5 doses were given. The first dose of dexamethasone began the night before the first Taxotere infusion. Treatment was administered every 3 weeks until disease progression or unacceptable toxicity.

Although we will present the study in its entirety, we would like to emphasize now that Taxotere 75 milligrams per meter squared plus best supportive care versus best supportive care alone will be our

primary comparison because 100 milligrams per meter squared was discontinued due to unacceptable tolerability in this patient population.

Patients were required to have documented non-small cell lung cancer and they must have received at least one platinum-based chemotherapy regimen. They could be of ECOG performance status 0 to 2. They had to have adequate hematology and biochemistry, and 21 days must have elapsed from their last chemotherapy. Patients who had treated brain metastases were eligible if they were asymptomatic. In contrast to the TAX320 trial, patients were excluded from this study if they had received prior Taxol.

A total of 204 patients entered the study. Initially the first 100 patients were randomized to receive either Taxotere 100 milligrams or best supportive care designated group 317A. As mentioned previously, due to greater than expected toxicity in the 317A phase, subsequent patients were randomized to a reduced dose of Taxotere 75 milligrams or best supportive care, designated group 317B.

The arms were well balanced with respect to

performance status and best response to prior chemotherapy, the two stratification parameters. Approximately 20 percent of the patients had demonstrated progression while receiving platinum-based chemotherapy.

They were also well balanced for age, gender, stage, and number of prior regimens in both phases of the study. Please note that about one-quarter of the patients had received two or more prior regimens and approximately 80 percent of the patients had stage IV disease.

6 patients responded to Taxotere, for an overall response rate of 6 percent, 3 patients treated at 75 milligrams and 3 at 100 milligrams. The median duration of response in both dose levels was 6 months. Disease control with either partial response or stable disease was achieved in 49 percent of all Taxotere patients and 53 percent of Taxotere 75 milligram patients. This observation is very important in view of the survival benefit seen in Taxotere treated patients.

The median time to disease progression was 9.1 weeks for the Taxotere 100 milligram treated

patients compared to only 5.9 weeks for corresponding best supportive care patients. The median time to progression for the 75 milligram cohort was 12.3 weeks compared with only 7 weeks for best supportive care, both statistically significant with log rank test p values of 0.037 and 0.004, respectively.

The results of time to progression for Taxotere 75 milligrams are depicted graphically on this slide.

Survival for Taxotere 75 milligrams was significantly better than best supportive care, with a p value of 0.016 by the log rank test. The median survival for Taxotere 75 milligram treated patients was 9 months compared to only 4.6 months for corresponding best supportive care patients. 1-year survival was 40 percent for the Taxotere 75 milligram patients compared to 16 percent for corresponding best supportive care.

As requested by the FDA for the 4-month safety update, we performed an updated survival analysis with a cutoff date of October 1, 1999. The survival comparison between Taxotere 75 milligrams and best supportive care confirms the advantage for Taxotere with

a log rank test p value of 0.010, as seen on this slide. In addition, 1-year survival favors Taxotere with a chi-square test p value of 0.003.

Despite the early toxic death rate seen in the first phase of the study, the survival update is also favorable for all Taxotere treated patients in the full study with a log rank test p value of 0.047.

Hematologic toxicity was clearly dose-related with higher neutropenia seen in patients treated with 100 milligrams versus 75 milligrams. Febrile neutropenia was seen in 22 percent of the higher dose Taxotere patients compared to only 2 percent at 75 milligrams. There were 5 toxic deaths in the patients treated with Taxotere 100 milligrams and 1 at the 75 milligram dose.

The greater toxicity seen with the Taxotere 100 milligram dose led to fewer treatment cycles being administered at this dose. The total number of cycles delivered to patients randomized to Taxotere 100 milligrams was only 187 compared to 264 cycles in those randomized to 75 milligrams per meter squared, with a median cumulative dose of 211 milligrams per meter

squared for Taxotere 100 and 299 milligrams per meter squared for Taxotere 75 milligram patients. The median number of cycles delivered was 4 for Taxotere 75 milligrams, but was only 2 for Taxotere 100 milligrams.

With respect to non-hematologic adverse events, with few exceptions, similar toxicities were seen also in the best supportive care group. In particular, the patients who had the most severe asthenia were in the best supportive care group. This serves to emphasize the point that treatment emergent symptoms may be disease related as well as treatment related in this population of patients with advanced lung cancer.

Patients completed either the Lung Cancer Symptom Scale or the EORTC quality of life instrument. Advantages in several quality of life and clinical benefit parameters were shown. This will be discussed in detail by Dr. Gralla.

Briefly, though, Taxotere provided significant clinical benefit to the patients over best supportive care as supported by the observation that tumor-related medication use was significantly less in

patients treated with Taxotere 75 milligrams. In addition, significantly fewer patients treated with Taxotere required palliative radiation.

In conclusion, this is a landmark study that clearly shows that Taxotere is an appropriate therapy in previously treated patients with non-small cell lung cancer. Taxotere results in significant improvements in overall and 1-year survival and offers meaningful clinical benefit. As you will hear from Dr. Gralla, the quality of life analysis also favors Taxotere over best supportive care. We believe that Taxotere 75 milligrams per meter squared is safe and effective for non-small cell lung cancer patients previously treated with platinum-based chemotherapy.

Dr. Fossella will now present the results of the TAX320 trial.

DR. FOSSELLA: Good afternoon.

In confirmation of the data from TAX317 just presented by Dr. Shepherd, I will now discuss the details of the other phase III trial which was TAX320. TAX320 was a randomized, multi-center, phase III trial conducted at 23 U.S. sites comparing two different doses

of Taxotere versus a control regimen of vinorelbine or ifosfamide for patients with non-small cell lung cancer previously treated with platinum-based chemotherapy.

The primary study endpoint was survival with secondary endpoints of response rate, time to progression, duration of response, and quality of life.

Patients were stratified by their best response to prior platinum-based chemotherapy and performance status and were then randomized to either Taxotere 100 milligrams per meter squared every 3 weeks, Taxotere 75 milligrams per meter squared every 3 weeks, or a comparator regimen. In the absence of an approved agent in this setting and after discussion with consultants and with the FDA, it was decided to select as an appropriate control arm either vinorelbine 30 milligrams per meter squared per week or ifosfamide 2 grams per meter squared times 3 days every 3 weeks. For patients randomized to the control group, the choice of treatment was left up to the treating physician. Responses were assessed every 2 cycles.

Eligible patients had locally advanced or metastatic non-small cell lung cancer which had

progressed on or after at least one prior platinum-based chemotherapy regimen. There were no restrictions on the number of prior cycles or regimens of chemotherapy, and in particular, patients treated with prior Taxol were eligible for this study. Prior radiation therapy was permitted. Patients must have had a performance status of 0 to 2, and patients with treated brain metastases were eligible as well.

373 patients were enrolled in this trial. The three arms were well balanced with regard to the two stratification factors of performance status and best response to prior platinum-based therapy. Fewer than 20 percent of patients had a performance status of 2, and best response to prior therapy was progressive disease in 24 to 33 percent of patients.

Other key patient characteristics of age and gender were similarly well balanced across the three arms. About 90 percent of patients across the three groups had stage IV disease. About 30 percent of patients had received two or more prior chemotherapy regimens, and prior treatment included Taxol in 30 to 40 percent of patients.

The total number of cycles delivered was highest in patients treated with Taxotere 75 milligrams per meter squared. The median number of cycles received was 3 for both of the Taxotere arms and for vinorelbine and was 2 for ifosfamide.

The median cumulative dose of drug was highest for the Taxotere 100 milligram group, and this was a result of the protocol dose modification schema which stipulated that patients in the Taxotere 100 milligram group would receive G-CSF support to maintain that dose intensity. Consequently, G-CSF use was highest in that arm at 28 percent of cycles, but was comparable in the other two treatment arms.

Partial response rate was 11 percent with Taxotere 100 milligrams and 7 percent with Taxotere 75 milligrams, both significantly greater than the 1 percent response rate noted in the control group, with p values of 0.001 and 0.036. It is notable that an additional one-third of patients maintained stable disease.

The median duration of response was over 7 months with Taxotere 100 milligrams and was 9.9 months

with Taxotere 75 milligrams.

Time to progression curves are shown here. By log rank analysis, overall time to progression had favorable trends for both Taxotere groups. The p value was 0.044 for Taxotere 100 milligrams, 0.093 for Taxotere 75 milligrams, and 0.046 for both Taxotere arms combined in comparison with the control group.

Median time to progression was 8.4 weeks for Taxotere 100 milligrams, 8.5 weeks for Taxotere 75 milligrams, and 7.9 weeks for the control group.

Survival curves are shown here. There was a trend favoring survival in the Taxotere 75 milligram group, which is shown in the blue curve, with a p value by log rank test of 0.14. The median survival was equivalent in all three groups at about 5.6 months.

However, the 1-year survival favored treatment with Taxotere 75 milligrams per meter squared. 1-year survival was 32 percent for the Taxotere 75 milligram group compared with 21 percent with Taxotere 100 milligrams and 19 percent in the control group. The difference in 1-year survival favoring Taxotere 75 milligrams was statistically significant with a p value

by chi-square test of 0.025.

As requested by the FDA for the 4-month safety updated, we performed an updated survival analysis with a cutoff date of September 20, 1999. These updated survival curves are shown here. 1-year survival was 30 percent with Taxotere 75 milligrams, again shown in the blue line, versus only 20 percent in the control group. The associated chi-square p value of 0.05 serves to reinforce the favorable survival data presented earlier.

The incidents of grade 3 and 4 neutropenia and febrile neutropenia were greater in both Taxotere arms compared to the control group. However, documented infection was equivalent in all three arms, as were grade 3 and 4 anemia and thrombocytopenia.

The incidence of severe non-hematologic adverse events is shown here, and I should point out that this data is tabulated here regardless of relationship to study drug. These adverse events, as you can see, were comparable across the three treatment groups.

The incidence of treatment discontinuation

due to adverse events was highest with Taxotere 100 milligrams, but was similar between Taxotere 75 milligrams and the control group.

Treatment-related deaths were equivalent across the three treatment arms.

In this study, patients completed the Lung Cancer Symptom Scale instrument and advantages in several quality of life and clinical benefit parameters were shown. This will be discussed in detail by Dr. Gralla.

In conclusion, in this randomized phase III trial of chemotherapy for previously treated non-small cell lung cancer, significant differences favoring Taxotere were observed for response rate, time to progression, and 1-year survival with acceptable toxicity. This was especially so for patients treated at the 75 milligram per meter squared dose level.

The data from TAX320 strongly support the results of the TAX317 data presented by Dr. Shepherd. Both trials consistently demonstrate the clinical benefit of Taxotere 75 milligrams per meter squared for these patients with non-small cell lung cancer whose

disease has progressed after prior chemotherapy.

I'll now turn the podium over to Dr. Richard Gralla who will present the quality of life data from these two trials.

DR. GRALLA: Thank you, Dr. Fossella, ladies and gentlemen.

Quality of life assessment is becoming a mandatory part of treatment evaluation. The ASCO Outcomes Research Committee reinforced that quality of life is one of the three key endpoints in clinical research in addition to response and survival, echoing prior publications from the World Health Organization and the FDA.

In all advanced malignancies, and especially in second-line treatment of non-small cell lung cancer, enhanced control of symptoms is a crucial goal for patients, family, and health care professionals. Several studies have demonstrated that modest response rates with anticancer treatment can be associated with larger symptomatic or palliative benefits. Any treatment has some risk. Quality of life assessment as evaluated by patients can help ascertain that

improvements in response or length of life with chemotherapy do not occur at the expense of patients' quality of life.

Two terms have become common when evaluating palliative or subjective benefits of chemotherapy in patients with cancer. Both terms can be useful and it may be helpful to review briefly the advantages or limitations of each.

Clinical benefit refers to the control of common cancer-related problems. This has previously been defined in new agent testing to include specifically the three areas of pain control, weight loss, and performance status.

Quality of life evaluation differs in that it is multi-dimensional. It includes clinical benefit aspects as part of the physical and functional domains or dimensions, but it also includes social, psychological, and spiritual dimensions. While all are important considerations, many of these dimensions are unlikely to be affected by chemotherapy agents being tested. A new agent is less likely to affect, for example, social relationships within a family than it is

to help control pain. Thus, while all dimensions of quality of life are important, to evaluate a new treatment, it may be relevant to concentrate on those aspects most likely to be influenced by the intervention.

Without consensus in this area, these trials examine both quality of life and clinical benefit. Two validated instruments were used. The EORTC QLQ-C30/LC-13, which includes 43 items with general and lung cancer modules, was used in the 317 trial of Taxotere versus best supportive care. The LCSS, which was developed specifically for the evaluation of treatment in a clinical study, was used in both trials. It contains 9 patient-rated items and 6 observer-rated questions.

Quality of life evaluation was conducted every 3 weeks, an interval which has been demonstrated to be particularly appropriate for quality of life evaluation in advanced lung cancer. Patient compliance with the quality of life instrument was good in both trials, comparing favorably with the best reported compliance rates in recent large randomized trials assessing quality of life in this disease. It should be

noted that these trials were powered to examine the primary endpoint, survival, not the quality of life or clinical benefit endpoints.

Three different analysis methods were used. ANCOVA, or analysis of covariates, was used to evaluate change from baseline to the last assessment. A longitudinal method was used to evaluate changes in quality of life over time. Additionally, a pattern mixture method, as suggested by the FDA, was used to deal with the problem of attrition of patients and to account for any differential attrition that could occur.

This presentation will focus on Taxotere 75 milligrams per meter squared comparisons in both trials.

First, examining clinical benefit, this graph looks at a degree of weight loss generally considered to be of importance, that is, the percentage of patients in each trial with 10 percent or greater weight loss displayed by treatment assignment. As is seen in the graph, less major weight loss occurred in patients randomly assigned to receive Taxotere in each trial. The difference was marked in the 317 trial comparing Taxotere with best supportive care and only minor in the

320 study.

Perhaps most important is the consistency of less weight loss and the degree of less weight loss in the Taxotere groups in both trials. That is, there's an average of fewer than 4 percent of the patients treated with Taxotere experiencing major weight loss during treatment.

Weight loss is not only an important factor as related by patients and families, but it also represents a parameter that can be objectively measured and it indicates a consistent benefit over the entire course of treatment.

This graph displays the results of the measurement of pain as reported by both the patient and by the medical and nursing observer. The control of pain is often considered one of the most important, if not the most crucial, palliative goals of treatment. The data point for each of these measures is the mean score, displayed with the 95 percent confidence interval. The vertical middle line represents a no-difference result. The placement of the mean score value to either the left or to the right of the no-

difference line indicates a score that favors the treatment group listed for that portion of the graph.

In study 320, the results are similar, but in study 317, there is a modest trend toward improved control of pain with Taxotere treatment as rated by both the patients and by the observers.

Still focusing on study 317, the comparison of Taxotere with best supportive care, it is interesting to see that the trend toward better pain scores is achieved with less additional use of pain medications when viewed against the comparison group. Significantly less additional opiate-based pain medication was required for those patients randomly assigned to receive Taxotere. At pretreatment baseline there was similar use of opiates by both assignment groups. However, those given best supportive care more frequently required additional opiates or required initiation of opiate medications.

Also, the significant differences demonstrating less additional pain medication initiation or additional use was found when one examines all pain medication use, not just opiate-based pain medications.

No significant differences in pain mediation use was seen in the Taxotere 320 comparison study.

Of interest is the finding that patients on best supportive care more frequently required supplemental radiation therapy, as mentioned by Dr. Shepherd, that is, 41 percent versus only 16 percent for the Taxotere group. This difference was statistically significant with a p value of less than 0.01. Palliative RT was allowed in the protocol for any assignment group if needed.

Performance status, often viewed as an activity scale but relating also to functioning in the physical, social, and psychological dimensions in quality of life evaluation, represents one of the most frequently measured areas in new agent testing for palliative benefit.

To examine all time points for assessment, performance status was analyzed after each treatment cycle, at the last assessment, and as a mean across cycles 1 to 3 of Taxotere treatment. No matter which time point is used, consistent results demonstrating performance status benefits associated with Taxotere

treatment are reported in both trials. Using the ECOG performance status scale, in both trials better performance status ratings are reported with Taxotere treatment at all of the time points. The degree of benefit reaches statistical improvement for most of the time points and in both trials.

Quality of life is a multi-dimensional concept that includes areas likely and unlikely to be affected by chemotherapeutic agents. On the contrary, negative aspects of chemotherapy could produce a detrimental effect on quality of life even if gains in response or survival occur.

In that quality of life instruments evaluate several dimensions and often include many questions to evaluate these areas, controversy continues whether to examine an aggregate total score of all areas or a single global quality of life question which allows the patient to globally rate his or her quality of life.

Because of this controversy, both aggregate scores and global scores of quality of life are displayed for both trials using both instruments in this graph. As can be seen, no negative effect on quality of

life, as rated by the patients or by observers, is found whether looking at aggregate total scores or the single global question for both the LCSS and the EORTC instruments.

In both the Taxotere 317 and the Taxotere 320 trials, important clinical benefit and quality of life advantages were found for the patients randomly assigned to the Taxotere arms. Patients receiving Taxotere used fewer pain medications and achieved better pain control, experienced less severe weight loss, and had better performance status than patients on the comparison arms. In several instances, these quality of life and clinical benefit improvements were statistically significant even though these trials were powered to examine the primary endpoint, survival, rather than quality of life differences. This was particularly notable when contrasted to the results of the patients assigned to best supportive care in the Taxotere 317 study.

While potential difficulties of chemotherapy could produce detrimental effects on overall quality of life, there was no evidence of this using the LCSS and

the EORTC quality of life instruments.

The results were consistent with all three analysis methods that were used. Whichever term is used, quality of life, clinical benefit, or palliation, benefit was consistently associated with Taxotere treatment in both trials and with all evaluation instruments.

Dr. Mark Green will speak next to summarize these presentations.

DR. GREEN: As I noted in the first of these four clinical presentations, the ASCO guidelines from August of 1997 for management of patients with unresectable non-small cell lung cancer state that "there is no current evidence that either confirms or refutes that second-line chemotherapy improves survival in patients with advanced non-small cell lung cancer."

Now in late 1999, things have clearly changed. Study TAX317B, which compared Taxotere at 75 milligrams per meter squared plus best supportive care with best supportive care alone, shows a significant overall survival difference favoring Taxotere 75 milligrams per meter squared versus best supportive

care.

The updated 1-year survival estimates for the two treatments are 37 percent and 12 percent, respectively. The survival curves begin to diverge at about 3 months and continue to diverge leading to a 25 percentage point difference in 1-year survival.

Time to progression is also significantly superior for the Taxotere 75 arm.

Quality of life for Tax 75 was at least as good as for best supportive care and in some assessments showed favorable trends for Taxotere.

Clinical benefit was improved for Tax 75 treated patients as measured by opioid analgesic use, positive changes in performance status, and less weight loss during study treatment.

In TAX320, comparing Taxotere at 100 milligrams per meter squared, Taxotere at 75 milligrams per meter squared, or vinorelbine or ifosfamide, the survival curves diverge after the 8-month time point in favor of the Taxotere 75 patients compared to the vinorelbine or ifosfamide treated comparators.

In the updated survival analysis, the 1-year

survival advantage of 30 percent for Taxotere 75 versus 20 percent for vinorelbine or ifosfamide, has a p value of 0.05.

In addition, overall response rates are significantly better for both Tax 75 and Tax 100 versus vinorelbine or ifosfamide.

And quality of life for treatment with Taxotere at 75 milligrams per meter squared is at least as good as vinorelbine or ifosfamide, with some assessments showing favorable trends for Taxotere over the vinorelbine or ifosfamide comparator.

The risks associated with Taxotere 75 milligrams per meter squared compared to the control arms of both Taxotere 317 and Taxotere 320 trials are shown on this admittedly complicated summary slide. These are treatment emergent data, not necessarily related to the Taxotere or to the control treatments themselves. The Taxotere related safety profile for the approved use of Taxotere in patients with breast cancer is shown in the far right-hand column for reference.

With the exception of grade 4 neutropenia and febrile neutropenia, the risks are very similar for

Taxotere at 75 milligrams per meter squared and each of the control arms. Despite the higher rates of grade 4 neutropenia and febrile neutropenia, treatment related mortality in the Taxotere 75 milligrams per meter squared arm was essentially identical to that seen in the active control arm of vinorelbine or ifosfamide. Overall, the risks shown here are not unexpected and are readily managed by practicing oncologists.

Based on these data, we believe that Taxotere at 75 milligrams per meter squared represents a significantly effective treatment option with a favorable therapeutic index for patients with non-small cell lung cancer who have already received platinum-based chemotherapy.

Now I'd like to turn the podium over to Dr. Chaikin for his concluding remarks.

DR. CHAIKIN: To summarize, this NDA supplement was granted fast track designation and priority review by the FDA based on the potential for Taxotere to fill an unmet medical need in the therapy of previously treated patients with advanced non-small cell lung cancer.

We believe that Taxotere at a dose of 75 milligrams per meter squared has been shown to be safe and efficacious and to provide meaningful clinical benefit to patients who have limited therapeutic alternatives. We believe these data presented today justify the expansion of the current labeling for Taxotere at a dose of 75 milligrams per meter squared to include the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of previous chemotherapy. This will help fulfill the unmet medical need in this patient for which there is no FDA-approved therapy and where treatment options to date have offered little hope for these patients.

Finally, I would like to recognize the many investigators and patients that made these studies possible and meaningful. We have several experts with us here today to help in fielding your questions, and their names are included on this slide and the next slide.

Thank you all very much for your attention. We will now be pleased to answer any questions that you may have.

DR. SCHILSKY: Thank you very much.

This presentation is open for discussion from the committee members. Dr. Margolin?

DR. MARGOLIN: I just have a couple of very small questions to Dr. Gralla about the validity of two of the claims made about the quality of life improvement. I just wonder whether 5 or 3 doses or 10 or 5 doses of Decadron every 3 weeks, as well as the slight fluid retention associated with multiple cycles of Taxotere, could have complicated the analysis of the difference in weight gain among patients on therapy versus best supportive care.

DR. GRALLA: As far as the weight gain is concerned, you saw that the fluid retention percentage is 4 percent for the Taxotere arms. So, it's a very low percentage. It's really no different than otherwise.

What I showed you in the weight loss was those with severe weight loss of 10 percent or more. This would represent taking on 5 to 7 liters of fluid, and I really don't think that that occurred, seeing no additional edema. So, I really don't think that that's there.

The other thing is that the weight gain is over the entire time, and it's a little hard for me to believe that 2 to 4 days a month of dexamethasone would lead to improving a weight gain over the entire treatment time.

DR. MARGOLIN: The related question has to do with the need for radiation. I think we've dealt with studies before where some bias could be introduced into something that happens to patients on two arms, depending on how much the patient or the doctor believe in the treatment arm.

In patients being treated with best supportive care, it would seem that palliation is first and foremost and that a lower threshold for palliating a painful bone lesion with radiation might be used, whereas both the doctor and the patient could be counting on the effects of the Taxotere in the treatment arm, as well as wanting to avoid the risks of any potential overlap with radiation, and therefore there might be some bias introduced into that.

DR. GRALLA: Surely I agree with that, but actually the context that I meant to try to present it

in was over pain control. With pain scores being relatively similar, there were larger doses of pain medications needed, more initiation of pain medication, more radiation, and still with less radiation, with less additional pain medicines, the pain control was at least as good with Taxotere. So, I agree with your first point, by all means, but the context in which I wished to show that was in terms of the pain control.

DR. SCHILSKY: I have a couple of questions, and maybe I'll just ask them and we'll get on to the other committee members.

I guess for Dr. Fossella, with respect to the TAX320 study, I'm a bit confused regarding how the choice of vinorelbine or ifosfamide was made. Was that a choice that the investigator made with respect to each individual patient or did each site have to declare which regimen they were going to use and they used it in all the patients randomized at that site? Could you just clarify that please?

DR. FOSSELLA: Yes. At any given site, the attending at that site on a case-by-case basis had the option of offering the patient randomized to the control

arm either vinorelbine or ifosfamide. And that was because some of the patients had already received either ifosfamide or vinorelbine. It was just a way of being able to enroll more patients.

DR. SCHILSKY: So, if it was done on a case-by-case basis, do you have any sense as to what parameters the physicians used in making the choice as to which therapy would be offered to the patient?

DR. FOSSELLA: No, I don't. I can tell you that at our site at M.D. Anderson where we enrolled 53 patients, our preference at that time was to use vinorelbine. The occasions when we would use ifosfamide is if a patient had already received platinum/vinorelbine in the first-line setting.

DR. SCHILSKY: Another question for you regarding TAX320. I noticed that the data on time to progression was statistically significantly in favor of Taxotere, although if I do a quick calculation, it strikes me as being an improvement in median time to progression of about 4 days. Would you consider that to be clinically meaningful?

DR. FOSSELLA: The time to progression I

think statistically it was, but I think the clinically meaningful benefit we saw I think was more in the survival and the quality of life.

DR. SCHILSKY: Questions from others? Dr. Johnson?

DR. JOHNSON: I have several questions, if I may, and these are directed to the sponsor and any of their experts who wish to address them.

Was there stratification by time off prior therapy in either of these two trials?

DR. DURRLEMAN: No. I am Sylvain Durrleman from Biostatistics at RPR.

There were two stratification factors used in those two trials, one being the PS 0,1 versus 2 and the other being the best response to the previous cisplatinum-containing regimen.

DR. JOHNSON: So, the answer is no.

DR. DURRLEMAN: The answer is no.

DR. JOHNSON: Do you have that data?

DR. DURRLEMAN: We know that the time since the last platinum-containing regimen has a median of 3 months.

DR. JOHNSON: And did it differ between the best supportive care and the others?

DR. DURRLEMAN: No. It is similar across the groups.

DR. JOHNSON: Can you show us those data?

DR. DURRLEMAN: Do we have a backup slide showing those data?

DR. JOHNSON: And while you're pulling up those data, I want to go back to an issue that was asked by Dr. Margolin and the weight gain. Actually, if I read the sponsor's submission correctly, if one goes, for example, to table 30 on page 56, you actually show a marked difference in peripheral edema for those who received Taxotere versus those who got vinorelbine and ifosfamide. For example, 40 percent of patients on Taxotere 100 are listed as having peripheral edema, 32 percent with 75 versus 14 percent. That seems to me to be more than just a trivial difference.

DR. GRALLA: That is not level 3 and 4.

DR. JOHNSON: Excuse me?

DR. GRALLA: That's not grade 3 and 4. So, I think if we're going to talk about a 10 percent

difference in weight loss or gain, 5 to 7 kilos, that grade 1 and 2 probably won't do it.

DR. JOHNSON: No, but it might well have other implications as well. So, there is a substantial difference there and it could account for weight difference. What you're doing is speculating, Dr. Gralla. These are the data.

DR. GRALLA: But actually the only slides that I showed you were on severe weight gain, a 10 percent difference, not on the others. So, again, I'm not speculating when it comes to that degree. There is no analysis of the overall weight change.

DR. JOHNSON: Did patients with performance status 2 who received therapy experience greater toxicity than those individuals with performance status 0 and 1? Or did those patients who experienced toxic deaths have a PS of 2?

DR. SHEPHERD: Approximately 20 to 25 percent of the patients in the 317 trial had a performance status of 2. None of those early toxic deaths that led to our dose reduction occurred in a performance status 2 patient. They were all performance status 1.

DR. JOHNSON: And the overall toxicities of the PS 2 were identical to those that were 0 and 1?

DR. SHEPHERD: Similar.

DR. JOHNSON: A major concern I have is with hyperglycemia, which I personally have found to be a major side effect of Taxotere. How many patients were actually hospitalized and/or went on to some form of hyperglycemic type therapy, either oral medications or insulin, as a complication of the premedication regimen? I didn't see those data in the submission.

DR. SHEPHERD: I'm sorry. I can't answer that question. Do we have that?

DR. JOHNSON: I suspect the sponsor can.

DR. HAMMERSHAIMB: Unfortunately, we haven't documented any hypoglycemia.

DR. JOHNSON: Hyper.

DR. HAMMERSHAIMB: But we can look deeper into our database to provide that to you.

DR. JOHNSON: You haven't documented whether patients had hyperglycemia or not?

DR. HAMMERSHAIMB: We haven't had any reports of it.

DR. SCHILSKY: Would you please identify yourself for the record?

DR. HAMMERSHAIMB: It is Luz Hammershaimb, clinical research oncology.

DR. JOHNSON: I guess I find that a little bit difficult to believe. You do not have data about hyperglycemia for your patients? Are you suggesting no patient had hyperglycemia on the premedication?

DR. BIZZARI: Yes, but this has not been reported as an issue in our database. So, we have no patients with hyperglycemia in our database.

DR. SCHILSKY: And would you also please identify yourself for the record?

DR. BIZZARI: Excuse me. Jean-Pierre Bizzari, clinical oncology. I'm sorry.

DR. JOHNSON: Okay.

DR. GRALLA: David, can I just make one point?

DR. JOHNSON: Yes.

DR. GRALLA: I can only indirectly approach that and that is that if we look at the use of all medications, not just the pain medications, there's less

use of all medications on the Taxotere arms than there is on the comparator arms.

Another thing that could confound that kind of an evaluation is that again there's only about 2 and a half days of corticosteroid use. In fact, the majority of patients, for instance, on 320 in the comparator arm used corticosteroids for various reasons on the comparator arm as well. So, it might be difficult to come up --

DR. JOHNSON: I guess I'd want to know why they were done, but it just goes completely against my own personal experience and I have some experience with lung cancer and this drug. So, I'm surprised.

Let me ask then surely a multivariate analysis was done to look at the responses, which again are not an endpoint that we normally accept as particularly relevant in this disease since response and survival don't correlate in this disease all that well. But I'd be interested knowing what the multivariate analysis demonstrated were the pretreatment parameters that predicted for a good outcome in this group of patients.

And then while you're doing that, you're going to go back and tell me about the other stratification data I asked for.

DR. DURRLEMAN: Yes. We have not performed a multivariate analysis on the response rate because the overall response rate is not as large, and so we would not have enough data to conduct a meaningful multivariate analysis in this particular endpoint. We have done it, however, on survival.

DR. JOHNSON: Well, that's fine. I'll be happy to hear it on survival.

DR. DURRLEMAN: Okay. So, can you provide me with the statistical slide on the multivariate model on 317B and 320?

DR. JOHNSON: I mean, the difference you show in your best supportive care, the amount of survival benefit you show is actually greater than anyone has ever reported for first-line therapy in comparison to supportive care. This is an amazing product.

DR. DURRLEMAN: Yes. We have done several things to confirm the results and show the robustness of those results. One was to conduct, in addition to the

straightforward log rank test, which is a primary analysis for this study, also stratified log rank test based on the two stratification factors that we had incorporated in the randomization. As a matter of fact, when we look at our study TAX317 in the group of 75 milligrams, the primary p value based on the log rank would have been .016. It becomes .007. So, it's even stronger.

So, here is the multivariate analysis that we have performed on the overall database consisting of TAX317B, 75 milligram per meter squared patients on Taxotere and BSC patients, and the TAX320 using the 75 milligram arm again and the control arm. So, we have -- in order to have a larger database and do this exploratory analysis.

So, you can see the covariates appear to be significant in this multivariate analysis. First of all, performance status 0,1 with those patients having a better survival overall as patients with PS 2. Stage IIIB disease, those patients also fair better than patients in stage IV. Number of organs involved, 1 or 2 or more than 2 was also febrile prognostic factors.

Similarly, weight loss less than 10 percent at baseline was also a febrile prognostic factor for overall survival, as well as the absence of full liver involvement. The better baseline patients total score for LCSS was also febrile prognostic factors. We do not have here the hazard ratio because a continuous variables interpretation would be less clear.

Now, when you adjust for all those covariates that are prognostic factors, you can --

DR. JOHNSON: May I interrupt you one second?

DR. DURRLEMAN: Sure.

DR. JOHNSON: Let me be sure I understand. Liver involvement is bad? Good?

DR. DURRLEMAN: Liver involvement is a bad prognostic factor.

DR. JOHNSON: Absence of liver involvement.

DR. DURRLEMAN: So, it should read no liver involvement. As you can see, those patients without liver involvement would have about a 25 percent reduction in overall risk of death with the hazards ratio of about .76.

Now, when you adjust for all those

covariates, you see that the primary results are even strengthened. We have a p value which is .004 in this exploratory analysis, and again an overall hazard ratio here of .71, which suggests 29 percent reduction in risk of mortality.

DR. JOHNSON: Well, actually the question I'm asking is as a clinician surely you're not suggesting that all patients who fail front-line therapy should receive this drug. And you want to take these data and try to come up with some parameters that would allow one to predict who is more likely to benefit from the therapy. We do this in front-line therapy. We call it performance status. Some people we treat, some we don't.

For example, in your own data set, you show that patients that lose more than 10 percent of their weight, none of those patients responded to this agent. None. So, I would assume you would tell me that you would not treat as second-line therapy someone with a 10 percent weight loss based on these data. That's what I'm asking.

DR. KOCH: Gary Koch, University of North

Carolina, statistical consultant to Rhone-Poulenc Rorer.

My understanding is the sponsor has taken this model and evaluated whether there are any statistical interactions between the prognostic variables that are listed, together with the treatment effect, to identify whether treatment effects are bigger in certain subgroups than others. That kind of analysis does not have a great deal of statistical power, but to the extent to which they have evaluated it, they did not find any noteworthy interactions. So, for the most part, the treatment effects are more or less homogeneous across the factors identified here.

DR. JOHNSON: It's sort of surprising, isn't it, that it would be that way in second-line therapy but not in first-line therapy?

DR. SHEPHERD: Perhaps I can add something to this from the perspective of the 317B part of the trial. Patients with performance status 0,1 or 2 both benefitted from Taxotere. Now, patients with performance status 2 did worse overall, as we would expect, with either best supportive care or with Taxotere. The magnitude of the benefit that they

derived from Taxotere was similar. They doubled their median survival and they had 0 1-year survivors with performance status 2 in the best supportive care group, whereas there were 15 percent 1-year survivors with Taxotere. So, although the survival was less, as we would expect, the magnitude of benefit was similar in both PS 2 patients and PS 0,1.

DR. JOHNSON: And I have one final question. I've never seen the statistical analysis looking at 1 year and doing a chi-square or a Fisher's analysis. That doesn't seem statistically appropriate to me at all.

DR. KOCH: That analysis is basically taking the Kaplan-Meier estimates at 1 year, identifying their standard errors, as provided by software such as Life Test or any other standard package -- when you get the Kaplan-Meier curve, you get the survival rate at 1 year, you get a standard error as well. You can then take the difference between the Kaplan-Meier estimates and divide that by the standard error of that difference which is the square root of the two summed standard errors.

So, this is a direct comparison of Kaplan-

Meier estimates. It's not the usual kind of chi-square test. It is not a Fisher's test. It is a comparison of Kaplan-Meier estimates, which with sample sizes this large, approximately has a chi-square distribution.

And this is Gary Koch again, statistical consultant.

DR. JOHNSON: So, if we had done this at 1 week, it might have looked different is what you're telling me.

DR. KOCH: Yes. This kind of comparison can vary from one time point to another. So, this comparison is most useful when looked at time points that would be identified as of clinical interest. The log rank test, which is the primary method the sponsor had, is an overall assessment of the survival curves, and that was why that was relied upon to get an overall assessment. And this 1-year time point is one that has been, according to my understanding, identified as being of clinical interest, and this assessment was done then.

DR. SCHILSKY: So, I know a number of other committee members have questions, but I want to ask Dr. Simon if he would like to comment on this particular

issue or ask another question.

DR. SIMON: Well, I don't disagree with anything that Gary Koch said.

I think to me the concern, though, is what was specified in the protocol as the primary endpoint. Unless 1-year survival was specified in the protocol as the primary survival endpoint, I personally discount the 1-year findings because it's easy to look at the survival curves and see where they're furthest apart and then do the test at that point.

The test, as you're describing it or any other way -- you'd have to do a totally different test if you're going to try to adjust for the fact that you could do it at any point in looking for the maximum difference between the curves.

DR. KOCH: And relative to Dr. Simon's comment, the log rank test was the one specified in the protocol.

DR. SCHILSKY: I'm going to go to Dr. Raghavan. Dr. Raghavan next.

DR. RAGHAVAN: I have a couple of questions about 320. The first one is you gave us information

about the distribution of prior Taxol treatment, and I'm interested to know whether you can give us information on the respective response rates in Taxol pretreated and un-pretreated patients. Do you have a slide you can show us on that?

DR. FOSSELLA: Across the board, about 30 to 40 percent of patients had received prior Taxol.

This is the survival curves looking at the Taxotere 75 versus the control arm. The panel on the left is the cohort of patients who had received prior Taxol. The group on the right had not received prior Taxol. The Taxotere curve is the blue curve and you can see that there's no difference on the survival curves whether patients had or had not received prior Taxol.

Now, this shows the amount of prior Taxol was a median of 4 cycles. The median number of cycles in the group that we looked at at Anderson because this data wasn't collected prospectively in the case report forms, but in my group at Anderson, the median number of prior cycles of Taxol was 3.5 cycles with a total cumulative dose median of 525 milligrams per meter squared.

On the next slide, it shows the response rate. As you can see in the Taxotere 100 milligram group, patients who had received prior Taxol, the response rate was 8 percent versus 12 percent in the patients who had not received prior Taxol. In the Taxotere 75 group, patients who had received prior Taxol, the response rate was 12 percent. Patients who had not received prior Taxol, the response rate was 3 percent.

DR. RAGHAVAN: My second question is -- and I understand how the stratifications were done -- can you give us some information about the distribution of platinum-containing regimens in each of the arms? In other words, I figured it out there's platinum in each of them, but what are the other drugs' frequency of use in each of the arms?

Presumably ifosfamide came up, vinca alkaloids came up. In my experience, the V/I arm has done, at least in terms of response rate, a little less well than I might have predicted, although I don't see V or I as a panacea. And I'm interested to know what went into the mix.

DR. FOSSELLA: Okay, hold on one second.

So, this slide shows the prior carboplatin and prior cisplatinum. Most of the patients had received prior cisplatinum.

The next slide shows the other drugs, not necessarily which regimens, but prior vinorelbine, ifosfamide, and etoposide. I think those three drugs probably accounted, it looks like, for the majority of the drug with which platinum was paired.

DR. SCHILSKY: Dr. Albain.

DR. ALBAIN: Thank you.

The sponsors and investigators were very careful to elucidate prior IIIB disease versus stage IV. I think another important question would be how many of the patients that entered this trial were truly failing front-line therapy for metastatic non-small cell lung cancer?

In other words, patients may have entered this trial having had a few cycles of neo-adjuvant therapy or concurrent chemoradiotherapy for earlier stage disease and this would be their first chemotherapy, Taxotere, for metastatic disease. So, how

many were truly second-line for metastatic disease? And if you know that, how did those patients fare in the two trials?

DR. FOSSELLA: Half of the patients were enrolled on this trial within 3 months of having had prior platinum. That is, they progressed while on platinum or within 3 months of having failed or having received the platinum regimen, and we might consider those patients platinum -- is that what you're asking?

DR. ALBAIN: No.

DR. FOSSELLA: No, okay.

DR. SHEPHERD: I'm not sure that we actually have the answer for you, Kathy, because I do not think that that was in the case report forms.

We know that at the time of the study, 80 percent of the patients had stage IV disease and only 20 percent had stage IIIB. So, presumably the 20 percent that had stage IIIB had all had either neo-adjuvant or adjuvant study for either stage disease.

What we cannot tell you, because it was not captured on the case report forms, is how many of the stage IV's had distant metastases after having had

induction chemotherapy for earlier stage disease. Those data were not captured, unfortunately, on the case report forms.

DR. ALBAIN: I think that might explain why the survival figures, at least in part, apart from treatment are so high, to go back to your question, David.

But I'd like to re-ask Dr. Johnson's first question. Do we know time from previous therapy on both of these studies, and in particular, the 75 dose, which wasn't in the materials?

DR. BIZZARI: May we get the slide? So, this is on 75, and you see that the time between last infusion and docetaxel is 3.3 months in the 75 milligram dose and 3.4 months in the 100 milligram dose. When you look at the best supportive care in the 317 study, we have exactly the same figure, 2.8, 3.4.

DR. ALBAIN: Another question in the best supportive care trial. What happened to these patients afterwards in terms of subsequent therapy? Frances, do you have that data?

DR. SHEPHERD: Yes, we do. You may be very

surprised, actually to find how little subsequent therapy was given. Only 6 patients in the best supportive care arm received second-line chemotherapy and only 3 patients in the Taxotere arm received subsequent chemotherapy. For the 317B, the 75 milligram dose, the survival curve remains statistically significantly better with Taxotere even when we do not censor for subsequent chemotherapy. So, there was very little subsequent treatment given.

DR. SCHILSKY: Dr. Blayney, do you have a question?

DR. BLAYNEY: Yes. I don't think Dr. Margolin's first question was answered to my satisfaction. You cannot distinguish in the quality of life data between Taxotere and Decadron versus best supportive care from my reading of this. I accept your survival benefit and other things, but the quality of life I think is a bit disingenuous if you don't include the Decadron as a perhaps mood elevator or getting people to answer those quality of life questions that they feel better at that particular time.

DR. GRALLA: Right. Despite the fact that

corticosteroids have been available for 40 years, there's really no study that demonstrates that there is an improvement in quality of life in patients with cancer who get corticosteroids. But our clinical feeling would be, remember, these patients only had it for 12 hours prior to their evaluation and that 3 weeks, almost, have gone since their last administration. And recall that a pretty good percentage, although a lesser percentage, of patients on the comparator arms also have corticosteroids.

The only thing I can tell you in terms of the quality of life is that we actually have a small study in which we analyzed this, and there was not a difference in quality of life in a 24-hour period after giving corticosteroids. But there's no doubt that corticosteroids have been documented to be helpful. Corticosteroids have been shown to help with pain, but in the peer-reviewed literature, this has been documented only by Dr. Bruera's paper which shows benefit in bone pain, not in other kinds of pain, and about 15 to 20 percent of the patients had bone metastases in the group as compared to nearly 90 percent

who reported pain at some point during the analysis. So, whereas there might be an effect of the corticosteroids, there's nothing in the literature to say what our clinical impression might differ from in the very short 12 hours between giving the corticosteroids and evaluating the quality of life.

DR. BLAYNEY: Thank you.

DR. SCHILSKY: Other questions from the committee members? Dr. Simon?

DR. SIMON: I had a couple of questions. One, the design of study 320. Was it designed as an equivalence trial or was it designed as a superiority trial? How was the sample size chosen for that study?

DR. DURRLEMAN: This trial was designed in late '94, early '95 with FDA input, and we had discussion at the end of phase II meeting in '95. At that time, we discussed with FDA the choice of the comparator, ifosfamide or vinorelbine, and we discussed the study design in terms of sample size.

The sample size calculation was based on trying to detect an increase of about 50 percent in time to progression, but it was agreed, however, that

survival would be the endpoint. So, it was some sort of a compromise. It's a difficult study to run, as you know.

At that time as well, we were advised by the FDA to introduce a 75 milligram dose group into this study. So, this is the basis for sample size. It was really detecting 50 percent increase in TTP.

DR. SIMON: In survival, okay. I'm sorry. In time to progression.

DR. DURRLEMAN: No. The basis for sample size calculation from the meetings we had with the FDA was detection of a 50 percent increase in time to progression. However, it was felt necessary by FDA that we looked, obviously, at survival as a primary endpoint.

DR. SIMON: You showed some information about comparing -- if you subset with regard to patients in 320, whether they had received Taxol or not, you showed some information with regard to response rate. But with regard to survival, if you take the patients who had not been pretreated with Taxol and then compared the three arms with regard to survival, did it make any difference?

DR. DURRLEMAN: Can you show the slide on TAX320 by prior Taxol use? Survival curves, yes.

Again, we have about 40 percent of the patients who had received Taxol. On the left-hand side, you have the group of patients who had received prior Taxol as part of their previous regimens. Again, some of those patients in those studies actually had, obviously, more than one previous treatment. Sometimes they had already two lines of therapy or more.

But at least here, they had the Taxol usage on the left-hand side. As you can see for the 75 milligram group, as the active control, we have the same pattern as we observed in the overall study and also on the right-hand side where you have the patients without prior Taxol usage. So, it looks from those very consistent patterns that use of prior Taxol was a significant factor.

DR. SIMON: I had one other question. It was about study 317. I'd like to compliment the company for the design of 317. But I guess there's one aspect that's sort of gnawing at me a little bit.

You found a survival difference there, but I

guess because I don't treat lung cancer, whereas to Dr. Johnson, it looks large a difference, to me it looks like a small difference.

DR. JOHNSON: That's a huge difference. It's an amazing difference.

DR. SIMON: But, nevertheless, the curves all go down to 0 and it's a difference in median of a few months, 4 months maybe. So, I look for the other endpoints, the symptomatology, the clinical benefit endpoints, the quality of life endpoints, to see that.

I guess the one question I had then is, was the protocol more specific in terms of objectives? What did the protocol say in 317 with regard to endpoints?

One problem I have with quality of life and symptomatology issues is that there are so many potential endpoints that you can look at, that it's a problem, unless you start doing multiple comparison corrections, or unless you've specified ahead of time what are the main dimensions or the main endpoints you're going to look at, it's difficult to interpret the findings.

You've sort of showed findings with regard to

weight loss and with regard to pain. I'm wondering, are these 2 of the 20 things you looked at?

DR. KOCH: Gary Koch.

My understanding, although Dr. Shepherd can verify, is that study 317 was originally powered for survival. Is that correct? Yes.

Now, what happened in study 317 is that part-way through the study, they identified this tolerability issue, and they identified that from routine safety analyses, not from any kind of efficacy analysis. That led to the dose reduction to 75. So, the original study 317, as it was originally conceived, was completed halfway through, identifying the dose of 100 as unsatisfactory for tolerability reasons. So, essentially a new study was started when the 75 was compared to the best supportive care. But the primary endpoint remained the same.

Now, there did become some difficulty in analysis because what would be the primary comparison? Would it be all patients randomized to Taxotere, or would it be the comparison of 75 against best supportive care?

From the point of view of interpretation, the comparison of 75 is meaningful because that's a potentially tolerable dose. But from the point of view of sample size, looking at all patients would be informative and helpful and give an overall assessment for the trial as a whole.

Now, the sponsor had good fortune. 75 turned out to be significant in its own right with half the planned sample size for the original study.

But it was important to confirm robustness of this finding, and study 320 is helpful for confirming robustness by showing good trends on survival and other endpoints. An overall analysis of study 317 is helpful for supporting robustness by again showing in the survival update a favorable p value. And then one can do an integrated analysis like that shown with the proportional hazards model where all patients with Taxotere 75 are compared against all patients on comparator, and that also, with favorable p values, supports robustness. So, one has on the original primary endpoint a significant result at the .05 level and certain robustness assessments as well.

DR. SIMON: Maybe I haven't expressed myself clearly because you haven't addressed my question at all. My question is not about the primary endpoint. My question is about the secondary endpoints, quality of life and clinical benefit. What I'm asking is, did the protocol specify how that data was going to be analyzed? That's one of the problems.

Two of the problems we typically see with quality of life type endpoints. One is missing data, and two is multiple comparisons, picking and choosing endpoints from among all of the numerous scales and ways you can analyze symptomatology data.

So, I'm asking in 317 did the protocol specify anything about how the clinical benefit or quality of life data was going to be analyzed?

DR. DURRLEMAN: It's obviously difficult especially in this clinical setting. But the protocol specified that quality of life would be one secondary endpoint, and it was clear on the LCSS, Lung Cancer Symptom Scale, that was introduced in the study and also I think the performance status as being part of any quality of life analysis that we would do. So, I

believe that those are prospective, although the issue of multiplicity still exists.

I would like also to stress that we have looked at various analyses to try to convert the lack of deterioration in quality of life in those patients, and some of those analysis methods were actually suggested by the FDA, such as the pattern mixture model, and we implemented those, although they were not part of the protocol originally.

DR. KOCH: Time to progression was also specified as a secondary endpoint with log rank tests and response rates were secondary endpoints with Fisher's tests. But there was no multiplicity adjustment for any of the secondary endpoints in study 317. Survival was the primary endpoint. The secondary endpoints were supportive. There were preplanned methods for the secondary endpoints, but there was not a prespecified method for managing multiplicity of the secondary endpoints. Their role was supportive.

DR. SCHILSKY: Dr. Kelsen.

DR. KELSEN: In the data you showed on 320, the survival curves seem to be very close, one on top of

another, until 8 months and then they diverge. The time to progression is measured in weeks. It's about 2 months. So, what do you think happened at 8 months?

DR. FOSSELLA: Well, I think the -- can you state the question again?

DR. KELSEN: As I was looking at the slides for Taxol prior and no Taxol and you look at the curves, they just sort of lie one on top of another until about 8 months.

DR. FOSSELLA: Right.

DR. KELSEN: And then they diverge, and the experimental arm is slightly better in both previously Taxol treated and previously un-Taxol treated. I'm just wondering what happened at 8 months since it looks like most of the patients were probably not -- or maybe they were. It looks like most of the patients weren't getting Taxotere at 8 months, or with your little tail on the curve that's getting the Taxotere.

DR. FOSSELLA: The median number of cycles received across the board for all patients was 3, but if you look at patients in the Taxotere 75 arm that were responding, those patients received a median of 10

cycles of treatment. And even the patients with no change received a median of 6 cycles of treatment. I think those patients were just being maintained on treatment longer.

DR. KELSEN: It's pretty clear that very few patients actually respond in this. This treatment stops the growth of the disease --

DR. FOSSELLA: Yes. I mean, few patients respond and then a fairly large proportion, about a third, have stable disease. So, if you count the stable disease nd the responders, you're talking about 40 percent, 40 to 45 percent, of patients that received a median, if you count both groups, of about 8 cycles of treatment, if you count both groups.

DR. KELSEN: So, your answer is at the 8-month divergence is because there are some patients who were still doing well and remaining on Taxotere.

DR. FOSSELLA: Right.

DR. JOHNSON: The only problem with that explanation, Frank, is that the same number of patients on the vinorelbine and ifosfamide arm had stable disease. You showed it was a third, a third, and a

third.

DR. FOSSELLA: The median number of cycles that those --

DR. JOHNSON: But that could be due to investigator bias as well. You know, I think it's working, so therefore I'm going to continue to give it. It's not working, so I'm going to stop giving it. I mean, the number of cycles to get the same survival means you gave more toxicity to get the same survival that you got with an ineffective regimen. That's how I would interpret those data.

There are several ways of looking at that. You've chosen to look at it in a positive light. I'm just saying there's another way of looking at that data. An ineffective regimen that you stop is as effective as an alleged effective regimen. That's how you can interpret those data.

DR. FOSSELLA: Difference of opinion.

DR. JOHNSON: It is an opinion and I think it's a good one.

(Laughter.)

DR. SCHILSKY: Dr. Temple.

DR. TEMPLE: If the drug only worked in a small fraction of the people who got it, wouldn't that be exactly what you'd expect to see? The 80 percent of people who got no response would just follow the usual curve, and any benefit you would see would occur later when the people who did get a response didn't stay on that curve. It doesn't seem so surprising. That's why 1-year survival is sort of attractive even though it wasn't specified as a secondary endpoint in this trial.

DR. KELSEN: Another explanation is -- and this is not the only disease we see this in. It's a very bad disease. If it progresses, patients do extraordinarily poorly and if you have a drug that even just stops the growth of the tumor for that period of time, the shape of the curve changes.

DR. TEMPLE: Right, but it won't affect the ones who get no response, and therefore the early part of the curve looks like the early part of the curve usually does, sort of what you'd predict.

DR. KELSEN: Yes. Their argument is that no growth and response have the same clinical benefit to the patient.

DR. TEMPLE: Yes, but then the other therapy, which had no responses at all, did almost as well on stable disease. So, that's not --

DR. KELSEN: Yes.

DR. TEMPLE: Can I ask one other question?

Not to be too picky about this, but wasn't the designated primary endpoint of the study the combination of both 75 and the 100 survival? That might have been an unwise choice. In retrospect, surely it was. And how much do you think that matters? Because that was not significant until the update. Again, Rich is here to be picky as needed, so I don't want to do it too much.

DR. DURRLEMAN: The primary objective and primary analysis for the trial was, originally when we started, to compare 100 milligrams versus best supportive care. Obviously, after a number of patients were entered and routine safety monitoring, we had to discuss with our experts and with the FDA to reduce the dose.

At that time, we had discussion with the division and given the difficulty of accruing patients

in such a study with a best supportive care arm, we discussed with the FDA the possibility to envision not to increase the sample size to again enter 200 patients in 75 or best supportive care, but to have the option to pool the 75 milligram plus 100 milligram dose versus best supportive care because we had obviously some concerns about the power of the trial. This, I would say, was agreed upon by the FDA.

DR. TEMPLE: So, that was the primary endpoint. It seems mean-spirited to mention it, but that was the primary endpoint. Right?

DR. KOCH: Well, my understanding in discussions with the sponsor is that when the 75 was introduced, it was difficult to say where the primary comparison would go because it was recognized, as you're aware --

DR. TEMPLE: That's a problem with prospectively designating endpoints.

DR. KOCH: -- that the 75 would be underpowered. So, what was identified was a possibility of combining the two doses in an overall comparison in the eventuality that the 75 could not stand on its own.

Now, a hypothetical question that is of interest is suppose that on the combined comparison you had had a p value of .02 and on the 75 versus comparator you had had a p value of .10. Now, then you would have a dilemma where you would be basically trying to make a decision about a mixture of a dose that was found to be not tolerable with a dose that was found to be acceptable.

So, in a certain sense the way things worked out is probably the most logical way in the sense that you have a dose that stands on its own, and the only concern that remains is whether there's enough robustness from other sources of information to make you believe a large difference in a small number of patients.

Now, one way to do that is to go back and look at the combined analysis, and the updated survival analysis is helpful. It gives an .047 p value for that.

And another way to look at it is to do an integrated analysis of 317 and 320, 75 against comparator, and that's also supportive.

The third way to do it is to look at 320 on

its own, and although there's not clear significance in 320, there is enough trends in 320 to be helpfully confirmatory.

But you're right. It's a difficult assessment.

DR. JOHNSON: I have one last question. Maybe you can convince me on the basis of this. Do you have your survival curves with the number of patients that are still on the curves? Can you show me the number of people that have been followed out beyond 1 year? None of your curves show that data.

DR. DURRLEMAN: I don't think we have those data here. But clearly in the survival data we have observed a number of the events, and the number of patients at risk remaining is not that great. I think the amount of censoring is quite small.

DR. SCHILSKY: We're going to take a break for 10 minutes and reconvene at 4:25.

(Recess.)

DR. SCHILSKY: We'd like to go ahead with the FDA presentation. For the committee members, I'll point out that copies of the FDA slides are in the blue

folders.

Dr. Griebel.

DR. GRIEBEL: Good afternoon. I'm Donna Griebel. I'll be presenting the FDA's review of this application, and a lot of it you will have heard already. So, hopefully I can speed through.

I'd quickly like to acknowledge the other members of the review team, particularly Clara Chu from Biostatistics.

The proposed indication we're considering today is for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy.

The sponsor has already reviewed in detail the clinical trial design, and we've talked about it in detail in the discussion after the presentation from the sponsor. I'd quickly like to touch on some of the salient points that are pertinent to the discussion.

The control arm of TAX317 was the best supportive care arm. The control arm of TAX320 contained chemotherapeutic agents, but these agents have not been established as efficacious in the second-line

treatment of non-small cell lung carcinoma.

The safety monitoring in 317 prompted the dose reduction of Taxotere in 317 from 100 milligrams to 75 milligrams, and because there was difficulty in accruing to this study with the best supportive care arm, the sponsor requested that the primary efficacy analysis of this study be a pooled analysis of the 100 milligram dose level and the 75 milligram dose level. This had relevance to the remaining discussion because technically the 75 milligram dose level of this study is a subgroup. You'll see that dose level was prespecified in 320, and you have a larger number of patients, 125 in 320 versus 55 in 317.

Both studies required that patients had been treated with prior platinum-based chemotherapy, and in TAX317 prior taxane exposure was excluded. However, that was not the case in TAX320, as you've already heard, and approximately 40 percent of the patients in the 75 milligram arm of 320 and the control arm of 320 had been treated with prior paclitaxel.

The primary endpoint in both studies was overall survival to be examined with a log rank test,

and the secondary endpoints were the same.

The major efficacy issues for the FDA boiled down to whether clinical benefit had been established in a prespecified analysis or whether you had to go to other analyses, analyses that weren't prespecified, to establish that clinical benefit; and then, second of all, whether the clinical benefit was consistent across the two studies.

This is a slide of the prespecified analyses for the primary endpoint, survival, from the two studies. Remembering that in TAX317 the primary analysis was the pooled analysis, you see that in the final analysis that was submitted in the application, in both studies there was no statistically significant difference between treatment arms in either of the studies.

However, the sponsor conducted a survival update which was submitted as a safety update and in TAX317 only, using the pooled data of the two doses, the p value came out as significantly different with a p of 0.047, 7 months versus 4.6 months.

We had some reservations regarding embracing

this with unbridled enthusiasm because the planned final analysis for the study to be submitted was not statistically significant in this study and it took going to the survival update to get this p value. This p value had been prespecified in the protocol itself as being the maximum p that would be considered significant, not the usual .05 because of a planned interim analysis.

Moving on to non-prespecified analyses, in the application itself, the sponsor presented a number of non-prespecified analyses. We've limited our discussion to those non-prespecified analyses which we thought were clinically relevant. As we've already discussed, the 75 milligram dose level is the dose level that the sponsor and the FDA feels is clinically relevant in this population. If you go to a dose higher than that, you get prohibitive toxicity in this population.

When you look at the 75 milligram dose level, again in this study, a smaller number of patients compared to 320, in 317 only there is a significant difference compared to best supportive care, the control

arm, with a p of .016. We've put asterisks with these p values because they weren't prespecified analyses and are technically unadjusted p values.

We were troubled with this data because the 9 months was so much larger than 5.7 months in TAX320. When we got the survival update, however, that median survival in 317 dropped down to 7.5 months, more in line with what was seen in TAX320 at the same dose level. The p value, despite that drop, appeared statistically significant. Again, this was not a prespecified analysis. So, you get the asterisk.

If you go across and look at the confidence intervals, which are tighter in 320 with this larger number of patients, you see that these confidence intervals almost fall completely within the confidence intervals of the same dose level in 317. However, the control arm comes pretty darned close to doing the same thing when you move those confidence intervals over as well.

These are the Kaplan-Meier plots for the two studies. The best supportive care study is on the left, TAX317; TAX320 is on the right. I've only put the

survival curves of the 75 milligram dose level in these plots. Taxotere is the red curve in both plots. The control arm is in green. You can see in the best supportive care study the dramatic difference in appearance of these curves compared to best supportive care.

If you shift your view across to 320, you lose some of that drama. However, you see that, as you look at the curves, there is splitting of the curves as you follow out, getting out close to a year, a little bit before a year, suggesting that there is some late clinical benefit in that study compared to the control arm of vinorelbine/ifosfamide.

Which takes us to the next non-prespecified analysis that we thought was worth discussing because of clinical relevance in non-small cell lung carcinoma, and that's the 1-year survival rates. As we've already discussed, the 1-year survival analysis in both studies was not a prespecified analysis. However, it's a frequently reported endpoint in non-small cell lung carcinoma and is felt to be clinically relevant, and it was striking in these two applications that in both

studies the 75 milligram treatment arm was higher than that of the control arm. And this continued out at the survival update.

Now, the asterisks are there because these were not prespecified analyses and have to be considered unadjusted p values. The sponsor has reported the p values that they got with chi-square analysis. We've marked them less than .05. They weren't prespecified analyses.

I did not put an asterisk here because the p value at this comparison, 30 percent to 20 percent, was right on the money of .05.

I did want to mention that in my review, I spent a lot of time critiquing the chi-square comparison of 1-year survivals. When we got the 317 data and talked to the sponsor about the methodology that was used, our concern had been that censoring was not incorporated into the analysis. They gave us their methodology, and when this was applied, our biostatisticians did think this was a valid methodology, the one incorporating the censoring.

So, how do we put this in historical

perspective? You've already heard that we don't have phase III data in the second-line setting. Although the agency had a number of applications in the second-line setting in other diseases, non-small cell lung carcinoma isn't one of those diseases. Most of the efforts have been working toward finding effective therapy in the first-line setting, and it hasn't been until fairly recently that the controversy has died down regarding whether chemotherapy was even indicated in non-small cell lung carcinoma. This is not a population of patients that has been targeted for phase III trials.

If you look at the first-line data, there's lots of phase III data in the literature, and first-line rates of survival at 1 year are reported in the 18 to 43 percent range. With the newer agents that are out and newer combination regimens, we've seen a drift upward in that rate of 1-year percent into the 30 percent range. Rather than try to list an exhaustive list of 1-year survival rates that have been reported in the literature, I just focused on the three applications we've most recently considered in the first-line setting: gemcitabine, paclitaxel, and vinorelbine, all

in combination with platinum. You see that the 39 percent, 36 percent, and 35 percent compare very favorably with what we have seen in this application in the second-line setting, and we were struck by that.

So, to quickly review the review issues with regard to the primary endpoint in this application, the important endpoint, survival, there was a significant difference between arms that was demonstrated in a prespecified survival analysis in only one of the studies, the pooled data of 317, and that only occurred in the updated survival analysis.

The overall survival at the 75 milligram dose level favored Taxotere in a single study, again TAX317, in an analysis that was not prespecified.

The exploratory analyses of rates of 1-year survival favor Taxotere in both studies, and those rates of 1-year survival were comparable to what has been reported in the literature for the first-line setting.

Moving on to clinical benefit parameters, Dr. Gralla very nicely explained to me how I shouldn't have lumped this slide. The Lung Cancer Symptom Scale quality of life instrument doesn't really technically, I

guess, fall under clinical benefit parameters.

I'll move down to that instrument quickly. The FDA has consistently approached quality of life data using the longitudinal analysis with pattern mixture modeling, and when we applied that to the data in TAX317 and 320, we found no evidence of significant benefit for Taxotere in this setting. However, we found no evidence that there was detriment to quality of life in this data using Taxotere as well.

Moving up to the other three endpoints, these were prespecified in the protocol as secondary endpoints to be examined. They were prespecified to be evaluated with an ANCOVA analysis, which I took to mean a comparison of baseline to the last assessment on study.

So, if you stick to that, which is my interpretation, a comparison of baseline to end of study, for performance status there was significant benefit associated with Taxotere in 317. In 320 there was no significant benefit, but there was no evidence of detriment with Taxotere.

Weight loss, the same pattern was seen. The

10 percent or greater cutoff point was not prespecified in the protocol. I just wanted to make that point.

And in terms of analgesic use, the protocol did not clearly set forth how analgesic use was going to be examined. There was no clear plan of optimizing analgesic coverage, pain control, at the start of the study across all the treatment arms, and when the data was rolled into the FDA, the initial data just compared overall percentages of patients on analgesics across the two treatment arms, which was not a very meaningful comparison.

The sponsor subsequently submitted an analysis looking at adding in additional morphine-type opioid analgesics and looking at, actually starting de novo, morphine on study. That type of analysis, although not prespecified in the protocol, favored Taxotere in TAX317. The numbers went against Taxotere in 320, but were not statistically significant, and those numbers are shown here. This is 320, the 75 milligram dose arm, and there was a greater percentage of patients with additional morphine and new morphine, but it was not significantly different.

In terms of safety, I've not put up an exhaustive list of toxicities. I focused on febrile neutropenia, grade 3/4 infection, and treatment related mortality.

Again, the sponsor and the FDA both agree that a dose greater than 75 milligrams is not indicated in this population. It's not safe. But to drive home that point, we've included for these particular endpoints the 100 milligram dose level in the white font. 75 milligrams is in yellow, and the last column, much like the sponsor's slide, is what's currently labeled, based on the breast cancer trials, for a higher dose, 100 milligrams. You can see, if you look at the 75 milligram dose level, you don't really get numbers that fall far out of line of what would already be anticipated with this drug based on the current labeling except perhaps in 320 in grade 3/4 infection, 12.4 percent versus 7.1 percent.

However, if you look at the same dose, 100 milligrams, in this population of second-line treatment of non-small cell lung carcinoma, and move down to treatment-related mortality, 14.3 percent versus 1.5

percent and 5 percent versus 1.5 percent. This is clearly not an acceptable dose for this population.

So, in quick summary, in terms of safety, as long as we are looking at a dose of 75 milligrams or less, the FDA did not have a lot of issues with safety based on the data presented in this application.

In terms of quality of life, we did not see definitive, statistically significant improvement in quality of life, but we did not also see a consistent trend for deterioration in quality of life in this population with 75 milligrams of Taxotere.

Finally, in terms of survival, we're asking the ODAC's input today in helping us determine which one of these faces to slot over as our final assessment of the data presented in this application.

To quickly reiterate, our issues were whether the clinical benefit was demonstrated in a prespecified analysis versus an analysis that was not prespecified and whether there was consistency across the studies.

This is actually the third table in the questions that you'll be looking at. This is just the data for the 75 milligram subgroup of TAX317 and the

prespecified arm of 320. Favorable median survival in that subgroup in 317, 9 months versus 4.6 months. In both studies in a non-prespecified analysis, favorable 1-year survival across both studies. Then there was a prespecified analysis, TAX317 pooled data, that in the survival update did favor Taxotere.

DR. SCHILSKY: Thank you very much.

Questions from the committee? We're being asked to decide whether or not to put on a happy face.

(Laughter.)

DR. SCHILSKY: Dr. Johnson.

DR. JOHNSON: Let me just ask a question about the clinical benefits parameter and the FDA's assessment of the performance status. About, as I recall, a third of the patients on 317 were PS 0. Is that correct?

DR. GRIEBEL: That's what I remember.

DR. JOHNSON: So, they can't improve their performance status.

The others were 1 or 2. Did we, in fact, see evidence of benefit in both of those subsets of patients; i.e., did the 1's go to 0 and the 2's go to 1,

or was it only in the 1's?

DR. GRIEBEL: I didn't look at those subsets. My recollection of the data that was presented in the application was that that was actually looking at proportions of deterioration and the amounts of deterioration.

DR. JOHNSON: So, it wasn't that anyone improved. It's just that no one got worse.

DR. GRIEBEL: A comparison of the proportions that got worse.

DR. JOHNSON: Okay.

I'll ask you the same question I asked the sponsor. Safety. Was there an analysis done by FDA or did you have the ability to analyze the outcome in PS 2 patients? Were they more likely to have life-threatening -- Dr. Shepherd told us there was no difference in treatment-related mortality, but were the opportunities for death greater in that group of patients?

DR. GRIEBEL: I myself did not specifically look at that. I could definitely do that myself, but did not do it. My understanding of the data from TAX317

when the patients were having the problems at 100 milligrams, there was an exhaustive look at those patients from my reading back at what happened at that time, and nothing definitive could be pointed out as the underlying common factor in that. But I could certainly go back and look at that.

DR. JOHNSON: Along that line, the 14 percent treatment-related mortality for the 100 milligram dose is really very high. So, you don't know the reason why those patients died? It wasn't fever and neutropenia. I mean, it wasn't infection. Is that correct? Because that data was not shown on that group of patients.

DR. SHEPHERD: I can address that question. 3 patients clearly died of febrile neutropenia. 1 patient was found dead at home unexpectedly, but it was at the time at which it might be related to neutropenia, but we have no documentation of that. And 1 patient was found subsequently at autopsy to have had an aspiration pneumonia.

DR. JOHNSON: So, they were all infectious related deaths in some fashion, presumably.

DR. SHEPHERD: Well, the aspiration

pneumonia, maybe not, and the one suddenly at home, we don't know. 3 definitely were and 2 possibly were.

DR. JOHNSON: The sponsor did not have. Do you have the median follow-up times? Do we know what the ends of those curves look like? I mean, that's a pretty good confidence interval you have out there.

DR. GRIEBEL: Right. I don't have the actual Kaplan-Meier plots. At the survival update of TAX317, the best supportive care study, there were 25 percent of patients in both arms who still had not had an event.

DR. SCHILSKY: Dr. Blayney?

DR. BLAYNEY: As I understand it, the asterisks which you placed around your p values and confidence intervals are unadjusted. That's a rubric for multiple looks at the data. So, if all we were looking at was the initial input that they received 4 months before this safety update, the significance would not be there. Is that correct?

DR. GRIEBEL: If you looked at the prespecified pooled data, the p was 0.14.

DR. BLAYNEY: And the survival advantage and these other things that we're impressed with, we

wouldn't be talking about them if we were meeting 3 months ago.

DR. GRIEBEL: Exactly. The others were not prespecified.

DR. BLAYNEY: And you can't rule out that there were multiple looks at the data and they happen to, at 4 months, look impressive, so then that's when they submitted the updated data?

DR. GRIEBEL: I can't exclude that, but they did ask if our preference would be the normal safety update that we always get with an application, that that application be a survival update, and we very enthusiastically said, yes, we'd like to see a survival update.

DR. BLAYNEY: Thank you.

DR. SCHILSKY: Other questions from the committee? Dr. Albain?

DR. ALBAIN: Another spin you might consider putting on why there may not be a quality of life or at least clinical benefit in the TAX320 to the same degree you see is that these other agents may, in fact, be doing something. Bearing in mind that some of the

patients have not seen chemotherapy for metastatic disease that are on these trials -- unfortunately, we don't know how many, but vinorelbine as a single agent may, in fact, improve quality of life also, even though it isn't as dramatically doing so. I wondered what you thought of that interpretation.

DR. GRIEBEL: I thought of that. It was in 317 that the time to progression p value was there, and it wasn't there for the 75 milligram comparison to vinorelbine/ifosfamide in 320. So, that might even further bastion up that argument that there may have been activity there in that arm.

DR. SCHILSKY: Dr. Simon?

DR. SIMON: Can you summarize the analysis that the FDA did on the clinical benefit endpoints in 317, namely weight loss, changes in performance status, and analgesic use? Well, for example, performance status. Was it just looking at the performance status when the patient went off study either because of progression or death versus the baseline?

DR. GRIEBEL: What I did was I used the analyses from the sponsor that appeared to be closest to

what was prespecified in the protocol, which I took to be a last assessment for any reason on the study to the baseline assessment.

The sponsor did look at this in two different ways. They looked at absolute numbers, looking at averages and how much it changed from that time, and they also looked at proportion. So, there are multiple comparisons in this.

DR. SIMON: For example, with weight loss, you would just take the weight at the most recent visit compared to the baseline weight?

DR. GRIEBEL: That was my understanding of what it was.

DR. SCHILSKY: Dr. Margolin?

DR. MARGOLIN: I don't whether you can answer this question, but I'd like to hear at least your hypothesis. The sponsor tried to show us on a retrospective look that prior Taxol-based therapy didn't seem to matter in that study that did allow prior taxane. I think it was the second study. Obviously, that's retrospective and the study was not powered to prospectively look at that.

Also, since there wasn't much in the way of traditional antitumor objective response, you have to sort of take on faith that whatever is happening with this Taxotere has to do with kind of holding back the tumor without showing objective responses.

So, the question I have is do you think that it make sense perhaps to approve this for patients who have not had prior Taxol, that if they're resistant to Taxol, they're far less likely to benefit, although the data don't really show that because they weren't designed to show that? Or do you think if it's approved, it should just be across the board and let people make their own decision?

DR. GRIEBEL: We asked this question of ourselves, and we ran the Kaplan-Meier plots ourselves. If you look at them, the numbers are approximately 70 patients versus 50 patients in each split of prior Taxol versus non-prior Taxol. You just could not convince yourself that there was a difference. If you look at no prior Taxol, the curve for the Taxotere arm was over that of the control arm for a greater period, but it was just eyeballing and there's not enough there.

DR. SCHILSKY: Other questions?

(No response.)

DR. SCHILSKY: If not, thank you very much, Dr. Griebel.

We have again a number of questions we've been asked that are in the blue folders. Does anyone care to make any general comments about this application before we address the questions? Any of the committee members? Any of the committee members. Dr. Nerenstone?

DR. NERENSTONE: I just wanted to address this to Rich. I know we usually don't like subset analysis, and I think that's part of the problem here. But this isn't the usual subset analysis in terms of the original trial of 75 and the 100 dose. Clearly the 100 was too toxic. So, it's not a question of fishing around and looking for subsets to show that in this subset it really works even though it doesn't work in all the others. This was clearly a clinical decision made because the dose that was chosen was not appropriate for the patients. So, they sort of started again.

Clinically that's very important, or at least

for a nonstatistician. I can understand the difference in theory. Does that hold any argument with you from a statistical point of view?

DR. SIMON: We talked a little bit about this before. For 317 it looks like, with regard to survival, you get a statistically significant difference with the log rank test if you just look at the 75 milligrams compared to the patients who were randomized against 75, or if you pool the 100 and the 75 and you compare it to the entire control group. With the updated survival analysis, it comes out statistically significant either way.

I guess my take on it is that the company was incredibly lucky, with only 50 patients per arm, that they could get a statistically significant difference in survival for the 75 milligram arm alone or that they would have gone forward with the same sample size in the face of a 12 percent treatment-related mortality with a plan to sort of pull together the 75 and the 100 milligram dose group. So, I guess I'm not so concerned about the subsetting of the 75 in 317 because it looks like you sort of get statistical significance either

way.

I guess what I am concerned about more is I generally really like to see two studies showing basically effectiveness. Here I don't see that 320 really confirms 317. The p value is .14 or .13 for the 75 milligram arm, but it's really not significant. Certainly if you pooled the 75 and 100 in 320, I guess that sort of dilutes the difference there. So, I don't know. I'm more concerned myself about the fact whether 320 really can be viewed as sufficiently confirmatory rather than how we analyze 317.

DR. SCHILSKY: Dr. Raghavan.

DR. RAGHAVAN: Well, I want to step out of character and actually congratulate the company, which is a first. You heard it here at the FDA. I generally don't do that. But I think they took on a tough target.

Lung cancer is difficult. Dr. Johnson and others have shown over many years that there is a huge disconnect between response rate and survival in front-line studies, let alone second-line studies. I think that the company took a gamble, and to their great credit, it paid off. I mean, this is second-line

treatment.

Median survival is not of huge interest, and I think one of the things people are forgetting, or maybe just not stating, is the fact that we're still really in the stage of trying to model what is the right statistical approach to this clinical problem. Nothing is etched in stone. So, the fact that we find it difficult to identify median differences and the fact that the confidence intervals for medians overlap in a disease where there is a low response rate and so many people die makes the problem a little tougher.

So, while it wasn't preplanned, I think that increasingly in the year 1999 and probably 2000 and henceforth, people will be looking for landmark points like 1 year because the clinicians who treat lung cancer second line know that there are very few people that are seen at 1 year second line.

So, I think one of the things we look at here is, is there chicanery afoot? Are we looking for companies that are trying to cheat? And just once in a while we find companies that are not absolutely true blue. I don't think that's what we're seeing here. I

think we're seeing a company that's looked at data as they come off the production line and have tried to look at them in a creative way and provide data that I think are actually clinically useful. I guess we should all be careful not to fall into a forest and trees problem here.

DR. SCHILSKY: Dr. Albain.

DR. ALBAIN: Yes. I'd like to respectfully disagree with my colleague, Dr. Simon. I think the second trial does provide confirmatory evidence, and if you look at the 1-year survivals in each of the T75 groups, they're very similar, 40 percent and 32 percent. I think you have that problem of some efficacy in the, quote/unquote, ineffective arm in that trial. And fortunately we do have I think the robustness of the best supportive care trial, and I look at the two as very complementary and a major advance for lung cancer survivors worldwide.

DR. SCHILSKY: Dr. Sledge.

DR. SLEDGE: Yes. I'll respectfully disagree with my colleague, Dr. Albain.

(Laughter.)

DR. SLEDGE: I look at these two trials, and it appears to be one of them is negative and one is positive.

The 1-year analysis, let's face it, is essentially irrelevant and illogical. There's no reason to believe that a 1-year point logically is any different than, say, a 6-month point or an 18-month point. But if you'd run the statistics at 6 months or at 18 months, you would have got a totally different answer.

In study 320, we've got Taxotere being essentially equivalent to a toxic placebo. In essence, we're being asked to approve Taxotere based on 317, in essence to say that Taxotere is better than nothing.

How robust is any study that's got 50 patients in each arm? My real concern here is that we're basically dealing with a small number artifact. To me the most telling thing here is that that dose of Taxol, 75 milligrams per meter squared in 320, is 5.7 months versus 9 months in the original analysis. It really makes me wonder whether or not we're just dealing with a small numbers' artifact.

DR. SCHILSKY: Kathy?

DR. ALBAIN: Well, I would just say that in taking care of lung cancer patients, you never see patients living first line to 1 year and now second line. I think there is a lot of data here that's very encouraging. You could say 8 months. You could say 12 months, 14, but the point is we never used to have them around to be discussing before.

DR. SCHILSKY: Dr. Johnson.

DR. JOHNSON: I actually can give you some information that may help with that. Because of this question about what is the survival of patients second line, actually Dr. Fossella did a nice review at his institution looking at these data and came up with a median survival of around 16 weeks in a group of patients who had had prior platinum, and I think he selected a group of around 30 or 40 patients. I don't recall the exact number.

Prior to that, this was a question that I had in my mind. And so we looked at the ECOG database at a set of patients of roughly 2,000 who had received platinum-based chemotherapy, and what we found was that

after progression or at the time that the physician said that the patient was no longer responding, median survival in that data set was around 16 weeks.

However, the range of survival was 0 to over 280 weeks. 280. Let me repeat that figure. With no further therapy. So, there is a subset of patients in there that survives for a long time.

We don't know why that is. We don't know how to characterize patients prior to any therapy terribly well, and that's one of the issues that I think, if the committee votes to approve, that I would ask the FDA to work with the sponsor to look at their data set to begin to try to characterize those patients who do well and don't do well.

An issue that wasn't discussed at all is the gender of the patients that survived a long time. We know, for example, that women, good performance status, do well. If there was any imbalance there, that could explain some of these marked differences, for example. I still say that their own data set showed that a weight loss of greater than 10 percent suggests you should not treat that patient under any circumstance.

And I do think time off therapy is a critical issue. It has been proved to be a critical issue in all diseases that I know of where it has been looked at. Certainly it's true in small cell lung cancer. Again, subtle differences, which may not seem like a lot, 4 weeks' difference in the median time off therapy, could make a huge difference in outcome, especially if it were in favor of the group in the 75 milligrams per meter squared arm.

Lastly, let me comment about the 1-year survival. I'm probably as responsible as some of the other people in this room for using that as a benchmark, but it's only that. I agree completely with Dr. Sledge's comments. There's nothing magic about 1 year. It just happens to be a time. And you're right. We don't see a lot of people walk in the door after 1 year. But by the same token, these are preselected patients by virtue of the fact that they're well enough to go to a second-line therapy, and that alone puts them in a unique group of patients in my experience. And many of those patients do well with or frankly without chemotherapy in my experience. That's not speaking from

a small number of patients that I've treated over the last 25 years.

DR. SCHILSKY: Other comments from committee members? Dr. Temple.

DR. TEMPLE: I just wanted to ask a little more about the median, 1 year, et cetera. Tell me if this is wrong thinking. It seems fairly obvious that if you have neither delay of progression -- I mean, stable disease nor a response in more than half of the patients, you're unlikely to affect the median very much. So, the other analyses, whether it's Kaplan-Meier or survival at 1 year, could detect a subset of people who do better than that. Is there something wrong with that?

DR. SIMON: Yes, there is.

DR. TEMPLE: Okay.

DR. SIMON: The log rank test has nothing to do with median survival.

DR. TEMPLE: Yes, that's what I said.

DR. SIMON: The log rank test is not a test of whether the medians are equal. It's a test of whether the survival curves are equal, and it's actually

more sensitive to late differences than other tests that had been previously used. So, people seem to assume that the log rank test is somehow being linked to the median.

DR. TEMPLE: Actually I thought that I said that. So, we use either log rank or something cruder and simpleminded like a 1-year survival to deal with the fact that only a small fraction of people respond. Even in 320, which certainly isn't robust support, the log rank is trending, whereas the median looks right on top of each other. So, it seems reasonable to use tests that are sensitive to a small number of people who do better.

DR. JOHNSON: I hear what you're saying, and there is this disconnect between response and outcome in lung cancer and frankly in some other diseases as well. So, it's not unique to lung cancer. It's just that there's a lot of data in lung cancer.

Again, we've looked at this in a couple of data sets, for what it's worth, where we looked at responders, the classic responders and nonresponders, which we all know statistically drives everyone right up

the wall. But we've looked at this in locally advanced as well as advanced and compared our stable disease or minimal responders to see if, in fact, they had a survival that was equivalent to those who had major responders, not to nonresponders, but to those who are stable.

Actually there is a difference in outcome. Those who are stable or minimally responding do not do as well as those who truly have a major, classic response in our experience or in the ECOG experience. So, it isn't as if there's something magical about that group of patients.

Now, it is also true that that group of patients seemingly does better than those who progress. That seems self-evident, that those who just grow right through -- and it may well again be simply the biology of the tumor. I'm not sure it has anything to do with the effectiveness of the treatment per se.

DR. TEMPLE: Just to follow up my thought, do you think there's any reason for us to advise companies to prospectively identify such things as 1-year survival as an alternative to a log rank, which they're already

doing?

DR. JOHNSON: Yes.

DR. SIMON: Well, for example, Genentech did that with Herceptin. Right? They had written it into the protocol and they had used 1-year survival.

DR. TEMPLE: So, is that a good thing or do life tables really handle that?

DR. SIMON: I think it depends on where you think the effect is going to be, and if you think the effect is going to be something like that, then it's fine.

DR. TEMPLE: So, it's a choice. Either would be reasonable.

DR. SIMON: Yes.

DR. JOHNSON: I think we've done that, have we not? We approved some biologicals for melanoma, for example, where there was absolutely no difference in median survival, but we accepted the fact that there was a subset of patients who enjoyed prolonged survival that none of us had anticipated would have occurred.

So, I do think as a prespecified endpoint, it should be considered. I don't think any of us have

thought about that because, frankly, there's not a lot of long-term survival in this disease. So, it's unusual to see it.

DR. TEMPLE: That analysis -- I don't remember whether it was prespecified or not. I don't think so -- was certainly influential in the gemcitabine pancreatic cancer --

DR. JOHNSON: Absolutely.

DR. TEMPLE: -- determination where medians might have differed by 5 weeks, but nobody was impressed by that, but the 18 percent versus 2 percent 1-year survival looked dramatic. I think that's why that provoked interest in the endpoint.

DR. SCHILSKY: Dr. Raghavan.

DR. RAGHAVAN: I would like to answer Dr. Temple's question as well. I'd say be careful because while I'm one of the people who has advocated the fact that live bodies at 1 year is an important endpoint in the discussion, I got nervous when you said either/or. I think that you don't want to be advising companies in discussion next week that they can have a 1-year survival and expect the committee to buy it in 4 years'

time. So, I think you can identify that this is an area of evolving thought. I think it's very hard to be doctrinaire.

As I said before, I think we're trying to evolve our understanding of the relationship between biology and statistics in some of the diseases that are around. I think to give alternatives as opposed to giving other indices that might be viewed as other secondary indices and that would then be evaluated at a committee like this, I think to provide alternatives could get you into tiger country later on because they're unvalidated at this point.

DR. TEMPLE: So, we should tell them a Kaplan-Meier analysis, log rank.

DR. RAGHAVAN: I personally think you can tell them stick with log rank, and you can then comment honestly and say in melanoma, in lung cancer, the committee has looked at other finite endpoints. I think it's what Richard Simon has often said. You want to prespecify. You don't want to do it ad hoc afterwards just because it's convenient. So, you can prespecify some other indicators. But I wouldn't get rid of the

log rank at the moment because we haven't really tested the robustness of the other finite landmark points.

DR. SCHILSKY: Scott, do you have one final comment before we go to the questions?

DR. LIPPMAN: Just a comment, yes, about the 1-year time point and what that means. I think that, at least in this case in 320, where the curves remain separate -- obviously, we'd all be very concerned if they were going back and forth and a certain time point was picked. But the fact that they seem to remain separated is encouraging, although as Dr. Johnson mentioned, it's not clear how many people are out that far and how robust they are. But in general I think I'm more encouraged by the 1-year figures if the differences remain.

DR. SCHILSKY: I'm going to ask that we go to the questions now. The first few pages of the questions are again the tables on the efficacy analyses. Just to draw your attention to the fact that the table on the bottom of the first page are the original prespecified analyses of survival for the pooled data and demonstrate no significant difference across the treatment arms for

median survival in either study.

The next table at the top of the second page are the updated survival analyses for the two trials and for the pooled results demonstrate a significant benefit for Taxotere in the TAX317 study, with a p value of .047, and in the TAX320 study demonstrate no significant difference in survival among the three arms.

The next table at the bottom of the second page are the original analyses just for the 75 milligram per meter squared dose level in the two studies and again demonstrate a significant advantage for Taxotere in median and 1-year survival compared to best supportive care and demonstrate no difference in median survival in comparison to the active control, but an advantage with respect to 1-year survival.

And in the final efficacy table are the updated analyses for the 75 milligram per meter squared dose level which in the TAX317 study again continued to demonstrate a significant advantage in favor of Taxotere in both median and 1-year survival, but failed to demonstrate an advantage in TAX320 with respect to the active control.

So, on to the first question. Are the median and 1-year survival data presented for docetaxel 75 milligram per meter squared adequate to demonstrate a survival benefit associated with this docetaxel dose in the second-line treatment of non-small cell lung cancer?

Does anyone wish to discuss that before we vote?

(No response.)

DR. SCHILSKY: All those who would vote yes, please raise your hand?

(A show of hands.)

DR. SCHILSKY: 10 yes.

All those who would vote no?

(A show of hands.)

DR. SCHILSKY: 2 no.

Abstentions?

(A show of hands.)

DR. SCHILSKY: 1 abstention.

You guys have got to raise your hands high. Don't give me these little fingers down next to the table.

10 yes, 2 no, 1 abstention.

Moving on to other efficacy analyses. So, here we have comparisons in the table of time to progression and response rate for the prospectively defined analyses demonstrating a significant advantage for Taxotere in time to progression in the TAX317 study and I guess no significant difference in the TAX320 study.

Then there are a number of additional efficacy analyses that are summarized for us. If you'll bear with me, I'm going to read this because I think it's important to focus everybody's attention on these three issues.

So, the first is the Lung Cancer Symptom Scale. In TAX320, the pattern mixture model for the longitudinal analysis of the LCSS data found no significant difference between docetaxel 75 milligrams per meter squared and the control arm, vinorelbine and ifosfamide. In TAX317, the same model suggested benefit favoring docetaxel in the pain subscale for the docetaxel arm, but there was no difference between the docetaxel 75 milligram subgroup and best supportive care.

For analgesic use, in TAX320 the proportion of patients on the docetaxel 75 milligram per meter squared arm starting morphinic analgesics was not significantly different from the control of vinorelbine and ifosfamide. In TAX317, fewer patients on the docetaxel 75 milligram per meter squared arm started morphinic analgesics than those on the best supportive care arm.

Then the third point is change in performance status from baseline to last assessment on study. No significant difference was observed in TAX320 between the docetaxel 75 milligram per meter squared arm and the control arm. The same analysis performed in TAX317 did suggest a difference between docetaxel 75 and best supportive care, favoring the docetaxel subgroup.

So, we have somewhat divergent results, although there seems to be some consistency of benefit for docetaxel in the TAX317 study compared to best supportive care and not a consistent benefit or less evidence of a consistent benefit in comparison to the active control in TAX320.

So, the questions. Do the data on median

time to progression, morphinic analgesic use, and mean change in performance status from baseline to last assessment presented in this sNDA adequately demonstrate that therapy with docetaxel 75 milligram per meter squared in second-line treatment of non-small cell lung cancer confers clinical benefit?

All those who would --

DR. JOHNSON: Rich, may we --

DR. SCHILSKY: Yes, we may have a moment for discussion. Dr. Johnson.

DR. JOHNSON: This goes to the heart of many of the questions that I was trying to get at, and that is, there may be a survival advantage and I believe there is. I think the best supportive care study, the 75 versus best supportive care, demonstrates that in my personal opinion.

However, I'm less impressed by these data. The survival benefit may well be conferred on those patients who are already in relative good shape. I realize that the data that were shown to us does not necessarily bear out my bias that the survival benefit is likely to have been seen in those with PS 0 and 1.

It's very difficult for me to imagine that those patients will derive, quote/unquote, clinical benefit from this. They may certainly derive survival benefit.

So, as I look at these data, both from a statistical perspective but also as a clinician, I am concerned that the benefits that we saw in a survival sense are just that, and they're likely to be in those just like in first-line therapy where those that are of good performance status, good health, apart from their terminal disease, benefit from this type of therapy.

So, I guess it's very difficult for me as a committee member to vote in the affirmative on this second question largely because I have some doubts in my own mind about where the benefit really actually exists, what group of patients. In any case, even if I'm looking at the pooled data, I have some difficulty accepting -- those quality of life issues, if you will, or clinical benefits are all pretty much right on the line of 0, as I look down those lines. So, it's very difficult for me personally to say yes in response to this question.

I'd be interested in the other committee

members' thoughts.

DR. SCHILSKY: Does anyone want to discuss it, or do you just want to express your opinion in your vote?

(No response.)

DR. SCHILSKY: Okay, no discussion. So, I think we'll go ahead with the vote then. So, let me reread the question. Do the data on median time to progression, morphinic analgesic use, and mean change in performance status from baseline to last assessment adequately demonstrate that therapy with docetaxel 75 milligrams per meter squared in second-line treatment of non-small cell lung cancer confers clinical benefit?

All those who would vote yes, please raise your hand.

(A show of hands.)

DR. SCHILSKY: 4 yes.

All those who would vote no?

(A show of hands.)

DR. SCHILSKY: 6 no.

Abstentions?

(A show of hands.)

DR. SCHILSKY: 2 abstentions.

Sorry, guys. All those who would vote yes, please raise your hand again.

(A show of hands.)

DR. SCHILSKY: 4 yes.

All those who would vote no.

(A show of hands.)

DR. SCHILSKY: 7 no.

And all those who are abstaining?

(A show of hands.)

DR. SCHILSKY: 2 abstentions.

The next question relates to the safety data. I won't summarize this table except to just state that the table again summarizes the major adverse events reported for the two studies that we've been discussing this afternoon and also includes incidence data on the currently labeled dose of 100 milligram per meter squared for breast cancer.

The question is, do these data demonstrate acceptable safety associated with docetaxel when administered at a dose of 75 milligrams per meter squared in this population of patients with non-small

cell lung cancer?

Any discussion before we vote?

(No response.)

DR. SCHILSKY: All those who would vote yes?

(A show of hands.)

DR. SCHILSKY: All those who would vote no?

(No response.)

DR. SCHILSKY: So, it's 13 yes, no no.

Any abstentions? I don't think there are any abstentions.

(No response.)

DR. SCHILSKY: 13 yes, no no.

Question 4. Is docetaxel 75 milligrams per meter squared approvable "for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy"?

Does anyone wish to discuss that? Dr. Nerenstone.

DR. NERENSTONE: I guess I was just a little surprised at the vote on number 2, and I just wanted to say in terms of somebody who treats these patients, if you were to give a patient an option of perhaps

surviving longer, at least being alive, at 1 year with treatment and the treatment, although you can't say it's going to make them feel better, it's not going to make them feel worse. If you want to argue that the data showed it didn't make them feel better in a meaningful way, but it didn't make them feel worse, would the patient want to take that therapy?

DR. JOHNSON: That was question 1. We asked that in question 1. Was there survival? And we said yes.

DR. NERENSTONE: Well, you just asked the survival. Now you're going to have to decide that's enough of an indication to approve this. I guess it's just my feeling that I think it should be approved even if you don't think that there was enough clinical benefit to warrant that.

DR. JOHNSON: Well, I'll just quote Dr. Temple. Survival trumps all other endpoints.

(Laughter.)

DR. NERENSTONE: I agree with that, but I wasn't sure that would necessarily be the --

DR. JOHNSON: It's one of my favorite quotes

of all time along with turtles on fenceposts.

(Laughter.)

DR. SCHILSKY: Dr. Albain.

DR. ALBAIN: I too was surprised by the vote on the other question. I think that you really have to give more weight to the best supportive care trial when you're looking for clinical benefit here. In that study, there were a number of parameters that had the smiley face by it. I just think that in my practice as well when you can offer an agent such as this, there is a clinical benefit.

DR. JOHNSON: On mine, it's one frowny face, one frowny face, and some question marks.

(Laughter.)

DR. SCHILSKY: I would just say as someone who voted no on that question that the reason I voted no is because I'm not persuaded that there is clinical benefit, nor am I persuaded that there's not clinical benefit. I just think that the data are too sparse and too ambiguous for us to know for sure, although I'm reasonably convinced that people who receive the drug don't do substantially worse. It's just not so clear

that they do substantially better in terms of some of these other parameters except for survival.

Derek.

DR. RAGHAVAN: I think the message that the companies can get out of that vote is if you have the option of getting the numbers up, take the option. They got away with it because survival trumps, but I think for future reference, whenever you have the option of increasing your numbers to -- when an unexpected event occurs, you could get caught at this committee by saving yourself a couple hundred thousand dollars and 6 months of accrual.

DR. SCHILSKY: Dr. Kelsen.

DR. KELSEN: I think the other message we might give -- and I don't know. It's not such an easy thing to do -- is I think it's a tenable hypothesis that if a tumor stops growing, the patient's symptoms are delayed. What we're really seeing here is, since they all die, is a delay in symptoms because the drug works well enough to stop tumor growth. If they would look at quality of life or whatever parameter they want to look at, more than just at the beginning -- I think we heard

this. They looked at the beginning and the very end, but rather looked at it over time, we might have a better feel for if these patients really are doing better because that's what one would expect.

DR. SCHILSKY: I might just comment for the interest of those in the room that the FDA has appointed a quality of life subcommittee that will be meeting for the first time in early February, February 10th I believe. Some of us who are members of ODAC will be sitting on that committee, as well as other people who are bona fide quality of life experts, and I think we're all looking forward to benefitting from the deliberations of that committee in the future.

So, having said that, can we -- Dr. Blayney.

DR. BLAYNEY: The indication is both studies were people who had failed platinum-based chemotherapy, and what we're asked to vote on is prior chemotherapy. I'd just point that out. Does that make a difference in terms of the indication?

DR. SCHILSKY: It's a bit broader the way it's currently written.

DR. JUSTICE: You can certainly amend it to

reflect the patient population.

DR. SCHILSKY: Would you like to propose something different from what's written?

DR. BLAYNEY: No. I'd just point out that that's the limits of the data.

DR. SCHILSKY: Dr. Albain?

DR. ALBAIN: I would just endorse that the labeling reflect the patient population that accrued to these trials because otherwise there will be greater toxicity with this agent if more indiscriminately applied to patients with poor performance status or who had not received as much prior chemotherapy.

DR. SCHILSKY: Would you like to propose a change in the wording of the proposed indication, or are you just sending a message to the FDA?

DR. JOHNSON: In the past what we've done is approved it and then put in the appropriate data in the package insert so that the physician who treats the patient can make that decision. So, if we were to do that, it would be a departure from our previous precedents. I'm happy for us to do that personally.

But I think one of the issues -- and this

again goes to some of the questions that I was asking. I was hoping that the sponsor itself had gone back and looked at some of these data to help us as clinicians select patients that would be appropriate for this type of therapy as opposed to just blanket just use it second-line. And I hope that they will do that.

DR. PAZDUR: We will work on the specifics of the indication and the labeling with the company.

DR. BLAYNEY: But last time when we discussed the package insert with another drug, the comment was made that nobody reads the package insert. I think the package insert, though, does influence the advertising and the other things. Clearly, with some of the journals with which I'm involved, there have been surveys done showing that physicians do read advertisements and it does influence their use of this drug. So, I would encourage us not to be so --

DR. PAZDUR: There will be lengthy discussions with the company about the exact indication.

DR. BLAYNEY: -- flip about the package insert because it does influence what happens.

DR. SCHILSKY: Any further discussion?

(No response.)

DR. SCHILSKY: If not, let me reread the question so everybody is clear on what we're voting on. Is docetaxel 75 milligrams per meter squared approvable "for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy"?

All those who would vote yes, please raise your hand.

(A show of hands.)

DR. SCHILSKY: All those who would vote no?

(A show of hands.)

DR. SCHILSKY: 1 no.

Any abstentions?

(No response.)

DR. SCHILSKY: So, 12 yes, 1 no.

Okay. We can be adjourned for this afternoon. The committee will reconvene at 8:00 a.m. tomorrow morning.

(Whereupon, at 5:30 p.m., the committee was recessed, to reconvene at 8:00 a.m., Tuesday, December 14, 1999.)