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FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

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C O N T E N T S

C O N T E N T S (Cont'd.)

NDA Supplement 20-671 Hycamtin (topotecan), SCLC, SmithKline Beecham Pharmaceuticals

Sponsor Presentation:

P R O C E E D I N G S

Call to Order, Opening Remarks and Introductions

DR. DUTCHER: Good morning. We are going to get started. We have a very full agenda. This is the Oncologic Drugs Advisory Committee. I would like to start by having introductions around the table. We have a very interesting agent this morning. We have a mixed group of people on the Committee, from NCI, from the FDA Dermatologic Committee, and from the FDA Biologics Committee. So, we will just start with you, and if you will introduce yourself and where you are from.

DR. BERMAN: I am Ellen Berman. I am on the Leukemia Service at Memorial Sloan-Kettering Cancer Center.

DR. SAUSVILLE: My name is Ed Sausville, I am from the Developmental Therapeutics Program at NCI.

DR. MARGOLIN: Kim Margolin, Medical Oncology and Hematology, City of Hope, Los Angeles.

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

DR. KROOK: Jim Krook, medical oncologist.

MS. BEAMAN: Carolyn Beaman, Sisters Network, consumer rep. to the Committee.

MS. HEINEMAN: Christina Heineman. I am the patient rep. on the Committee.

DR. VOSE: Julie Vose, University of Boston

Medical Center, and I am the Chair of the Biologics Committee.

DR. DUTCHER: Janice Dutcher, from Albert Einstein, in New York.

DR. SOMERS: Karen Somers, the Executive Secretary to the Committee, FDA.

DR. BERGFELD: I am Wilma Bergfeld, Cleveland Clinic, dermatologist and dermatopathologist, former Chair of the Dermatology Advisory Committee, now a consultant of 20 years with FDA.

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

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

DR. SANTANA: Victor Santana, St. Jude's Children's Research Hospital, in Memphis, Tennessee.

DR. KEEGAN: Patricia Keegan, FDA, Center for Biologics.

DR. DUTCHER: Thank you. Dr. Somers will now read the conflict of interest statement.

Conflict of Interest

DR. 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 interest 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:

Full waivers have been granted to Dr. Victor Santana, Dr. Sandra Swain and Dr. Kim Margolin. A copy of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office, Room 12-A30 of the Parklawn Building.

In addition, we would like to disclose for the record that Dr. Robert Ozols and Dr. Richard Schilsky have interests which do not constitute a financial interest in the particular matter within the meaning of the 18 USC 208, but which could create the appearance of a conflict. The Agency has determined, not withstanding these interests, that the interest in the government and Dr. Ozols' and Dr. Schilsky's participation outweighs the concern that the integrity of the Agency's programs and operations may be questioned. Therefore, Drs. Ozols and Schilsky may participate fully in today's discussion and vote concerning ONTAK.

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

DR. DUTCHER: Thank you. We now have the open public hearing, and we will be hearing from four people today. The first will be Mr. William Smith. If you will please come up to the podium and use the microphone, identify yourself and identify any support from the sponsors.

Open Public Hearing

MR. SMITH: Good morning. My name is William Smith. I reside at 36 Bel Air Road in Hingham, Massachusetts. I want to thank you for giving me the opportunity to speak before the Committee.

Miracles can happen. In October of 1986, I was diagnosed with non-Hodgkin's B-cell lymphoma, a slow developing but treatable form of malignant cancer. After three years of seemingly effective treatments, I was then diagnosed with cutaneous T-cell lymphoma, a uniformly fatal form of cancer that often progresses very rapidly.

Beginning in November of 1989, under the care of

Dr. Robert Carey at Massachusetts General Hospital, I was treated with conventional chemotherapy and radiation. For the next three months the disease became progressively worse. The cancer had caused severe skin lesions on my face, scalp, forehead and legs. In fact, the chemotherapy that was administered in Dr. Carey's clinic, which was Adriamycin, cytoxin and vincristine combined, was so strong that it burned the inside of my mouth. I had to swab my tongue with novocain to be able to eat.

After several weeks, Dr. Carey told me that he was sorry but there was no other medicine he could use for this cancer. Conventional chemotherapy was not effective. However, he did tell me that clinical trials were being started at the University Hospital in Boston for the treatment of cutaneous T-cell lymphoma. He then called Dr. Paul Hesketh and said, "I have a patient who may be a candidate for the clinical trials now starting at the University Hospital."

In the middle of February of 1990, I became a patient of Dr. Hesketh at the University Hospital. Biopsies were taken to confirm that I was a candidate for the T-cell lymphoma trials. Starting in March of 1990, I had four courses of treatments, each one lasting five days, and I stayed in the hospital for all five days, ending on May 29, 1990. After three weeks of extensive outpatient testing,

which included bone biopsies, eye-field tests and CT scans, I was admitted for a five-day stay and received one injection of the medicine each day. The staff would then keep me under observation. Between hospital stays, I participated as an outpatient for several weeks, undergoing more of the intense testing. The process was then repeated for the duration of my treatments.

During my entire treatment period I experienced no side effects from the medicine. In fact, during my weekly stays, I was allowed to dress in my own clothing, leave the hospital, have dinner with my wife, and was also able to enjoy an evening at the Boston Symphony and return to the hospital that night. By the second cycle, my skin lesions had significantly improved and had almost disappeared. In May, after four courses of treatment, I was taken off the therapy. As of this date, I have had no treatment for cutaneous T-cell lymphoma -- truly a miracle.

I was free of medicine from May, 1990. A scheduled CT scan in May of 1997 showed evidence that the B-cell non-Hodgkin lymph nodes in my abdomen had increased in size from the previous CT scan of November of 1996. From May of 1997 to November of 1997 I was put on chemotherapy by Dr. Paul Hesketh, who is now in charge of oncology at St. Elizabeth's Hospital, in Boston, for the B-cell non-Hodgkin lymphoma. A recent CT scan, taken in February of 1998,

showed that the lymph node had again receded.

In conclusion, there has been no evidence of the cutaneous T-cell lymphoma recurring. I am living a normal life, enjoying my retirement. Because we believe in this drug, developed by Seragen, our family does own stock in the company. Thank you for giving me the opportunity.

DR. DUTCHER: Thank you very much. The next person to speak is John Morissette.

MR. MORISSETTE: Good morning, Committee members, ladies and gentlemen. It is my pleasure to be here today, and my name is John J. Morissette, Jr. I am from Mobile, Alabama and I am happy to be here today to speak of the results of the drug, and I have some pictures that I am going to pass around to you all before I took the treatment.

After suffering from severe eczema during most of my adult life and treatments with various steroids and antibiotics, in January of 1989 I tested positive for cutaneous T-cell lymphoma, CTCL, by Dr. Neal Capper, a Mobile, Alabama dermatologist.

He explained the disease to me and told me I had possibly five years to live. At that time, that was quite a shock, as I am sure you know, and he recommended I take a PUVA treatment which was available on the Eastern Shore by Dr. James Earl Jones, who I believe formerly was with Emory University.

I took the treatment for about a year, and then he referred me to a Tulane dermatologist, Dr. Larry Milikin. In Tulane, in New Orleans, I received photopheresis, which is the blood exchange where they separate the red cells from the white cells and run it under radiation for approximately an hour and a half, and then put it back into your body. Also, I took PUVA treatment at Tulane from 1990 through January, 1994, every 3-6 weeks.

Due to the severity and discomfort of my skin lesions, I went on medical disability from my business in December of 1993. In the fall of '93 I became aware of the trial study by Seragen Drug Company that was available at the University of Alabama at Birmingham medical Center's Kirklin Clinic. This study was with the use of interleukin-2 with a diphtheria toxin, which I understand is now called ONTAK.

Dr. Mitchell Sams, the head of dermatology at UAB interviewed me and tested me for admission to treatment. After my test fir the protocol, he told me there was only a 15% or 20% chance of my receptors meeting the protocol that would allow me to take this drug. He called me right after Christmas -- the best Christmas present I ever had, and told me I had been admitted to the Phase II study for interleukin-2. Dr. Sallen, who is a dermatologist scientist at UAB, after I had been tested and admitted to treatment in

January of '94, I took 5 days -- I was the second person treated and in Alabama with Seragen with interleukin-2, the diphtheria toxin. I took 5 days of the drug every 21 days for approximately 8 treatments. After the second series I began to improve, and after receiving 4 treatments I was able to return to work on a part-time basis. By the sixth series my lesions and symptoms showed complete remission. Now, after 4 years I have been clear of the disease.

One thing that happened to me, I had been taking blood pressure medicine for hypertension since I was 35 years of age. The treatment lowered my blood pressure, and I have not had a blood pressure pill in three to four years.

[Laughter]

Needless to say, that was a great thing for me because I never did like those things anyway, and I had my blood pressure taken the other day and it was 143/78.

I had a CT scan every 6 weeks, I believe, during the treatment. The treatment took approximately 6-8 months. But I have had no contact with Seragen drug and they have not paid any of my expenses. My only financial connection with Seragen is ownership of stock in that company, which I was pleased to buy because of the dramatic results I had had from the treatment.

One thing I would like to mention to you, which is a personal thing, the way I found out about the drug study

and availability of it was that my daughter-in-law is a drug detail person for Eli Lilly, and she was at school in Indianapolis and living with a girl, and they were talking one night and she said, "my step-father works for a drug company called Seragen drugs and they're studying a new drug for the treatment of cutaneous T-cell lymphoma, and also Hodgkin's disease at that time." She said, "well, my father-in-law has cutaneous T-cell lymphoma and is really suffering from it very badly, and is not doing well at all." She said, "well, I'm going to call Dick Seluga, who's my step-father, and I'm going to see where the trial's offered so you can tell your dad." Well, definitely I am a Christian person and I felt like this was really a divine type of thing, that I would come in contact over at Tulane -- my doctor at Tulane knew nothing about it and he didn't mention anything to me about it. So, after 30 days I got an appointment with Dr. Sams at UAB and that is how it got started, and I thought that was very interesting.

I would ask you today to please consider recommending this drug for approval so other people can have the pleasure and the quality and the gift of life that I have been given through this drug. Thank you very much for your time. Have a nice day. If you have any questions, I would be glad to answer any questions.

DR. DUTCHER: No, that is fine. Thank you very

much. I appreciate your comments. The next person is Phyllis Harris. She is not here? Thomas Cascio.

MR. CASCIO: My name is Tom Cascio. I am from Monroe, Louisiana. My profession, I am a registered entomologist and I have spent a lifetime in crop protection in Louisiana. Presently, this morning, I am here as a courtesy of Dr. Madeleine Duvic at the MD Anderson, who has directed my treatment with this wonderful new drug that has saved my life.

In August of 1985, I was diagnosed with a rare form of cancer known as T-cell lymphoma. As I could not be treated in Monroe, I chose to go to the MD Anderson Cancer Center in Houston. There, I was placed under the direction and supervision of Dr. Madeleine Duvic. Beginning in September of 1995, I have been afforded the latest and most progressive treatment under her supervision. I received much help and hope from Dr. Duvic throughout my treatment.

About three years ago, actually a little longer than that, an ugly, fast-growing tumor appeared in the right inner side of my leg. Chemotherapy did not help. My situation was hopeless. The tumor had grown and was now larger than the size of a lemon, infected and still active. Dr. Duvic again came to my rescue. She indicated that there was a new trial drug becoming available, but I must undergo testing to determine whether the tumor had the correct

receptors to match the new drug, known as Dabble, according to the protocol.

Fortunately for me, I had a proper match and arrangements were made for me to receive the new research drug. Upon receiving my first treatment by infusion in my right hand, some discomfort and chills were experienced. As I walked away from the treatment room after my first infusion, the tumor in my right leg felt warm, and then I experienced extreme and intense pain in that tumor. It appeared the drug had specifically attacked that tumor, a very, very unusual and fascinating thing.

I was rushed to the emergency room, where I stayed until I recovered enough from the pain. Following the next six or so treatments, the tumor completely disappeared, leaving a recess in my skin at the tumor site. The tumor has completely gone now and has not returned. It has been two or three years that the last treatment with Dabble was completed. This has been the most dramatic thing that has ever happened to me. No new tumors have appeared either.

With this story of effectiveness, even though each infusion caused some discomfort and general malaise, I stand before you as living testimony that this drug is absolutely necessary. Please help me and others by registering this drug. i wish for others who suffer from this terrible condition to have the same chance to live as I have had.

I have been under intensive medical observation plus laboratory testing monthly since completing the therapy and no particular problem has manifested itself three years post treatment.

Please let me point out to you that this is the least stressful treatment that I had throughout my 13 years of battling with T-cell lymphoma. I thank you for giving me the opportunity to comment to you on my story. It is an amazing story and it is a miracle. Thank you.

DR. DUTCHER: Thank you very much. We appreciate all of you coming and sharing your experiences with us.

We are now going to proceed -- well, let me ask, is there anyone else in the audience that wishes to speak at the open public hearing? No? All right, thank you, all.

We are now going to proceed with the sponsor's presentation. Dr. Kassis, from CBER, is going to introduce the topic.

Product Overview, FDA

DR. KASSIS: Thank you. I am just here to introduce the product.

[Slide]

Well, as you are all aware, we are here today to discuss $DAB_{389}IL-2$ for the treatment of cutaneous T-cell lymphoma. I am Judith Kassis, from the FDA. I am the chairperson of the review committee for this product.

[Slide]

USAN name for this product is Denileukin Diffitox, and the trade name will be ONTAK. The indication is for use in patients with cutaneous T-cell lymphoma, CTCL, which is persistent or recurrent despite prior therapy.

[Slide]

The committee for review of this product was myself. I was the chairperson and the product review, Bernard Parker, who you will hear from today. He did the clinical review. Dr. Gupta, who was the statistical reviewer, Mercedes Serabian, who is the preclinical reviewer, Carol Trapnell, who was the pharmacokinetic reviewer. You will also hear from her today. Pat Hasemann, who did the bioresearch monitoring. Malcolm Moos, who reviewed the product with me. Lloyd Johnson, Deborah Marie Trout, who reviewed the establishments, and Andra Miller was the regulatory coordinator. I would just like to thank everyone on the committee for working very hard to get this product reviewed in this short time period.

[Slide]

DAB_{389}IL-2 is a novel fusion protein of diphtheria toxin fused to interleukin-2, and it is produced in E. coli. It consists of fragment A, which is the enzymatically active domain of diphtheria toxin, and fragment B, the membrane translocation domain of diphtheria toxin, and they have been

linked to human IL-2.

DAB_{389}IL-2 will bond to cells which contain IL-2 receptors, be taken up and kill the cell via inhibition of protein synthesis.

[Slide]

There are 3 forms of IL-2 receptors; A high affinity form made up of 3 distinct proteins, one called p55, one called p75 and one called p64. There is an intermediate affinity form, made up of p75 and p64, and there is a low affinity form, made up of p55 alone.

[Slide]

IL-2 receptors are present on activated T lymphocytes, B lymphocytes, NK cells, macrophages and certain malignant cells of T- and B-cell origins such as CTCL. That is the rationale for this therapy, since CTCL cells express IL-2 receptors, this drug will be targeted to those cells and kill those cells.

Today we seek advice regarding clinical data on studies with DAB_{389}IL-2. We are working very closely with the company to resolve outstanding manufacturing issues, which will not be discussed today.

DR. DUTCHER: Thank you very much. We will proceed with the sponsor's presentation. Dr. Nichols?

Sponsor's Presentation

Introduction

DR. NICHOLS: Good morning, Dr. Dutcher, members of ODAC, consultants and representatives from the FDA.

Seragen is seeking approval for ONTAK, which will hereafter be referred to as $DAB_{389}IL-2$ or $DAB_{389}IL-2$. As you have just heard, for the treatment of patients with cutaneous T-cell lymphoma who have either recurrent or persistent disease.

[Slide]

$DAB_{389}IL-2$, which you see here in a cartoon diagram, is a novel compound, a receptor-active, cytotoxin fusion protein which is expressed in E. coli as a single polypeptide and has 3 functional domains, shown on the right-hand part of this slide, a receptor binding domain, the translocation region, and a catalytic domain which confers toxicity when inside a target cell. $DAB_{486}IL-2$, shown on the left-hand part of the slide, was a first-generation version of the fusion protein and was larger in molecular weight than the $DAB_{389}IL-2$.

[Slide]

Two of the functional domains are catalytic, and the catalytic and the translocation are derived from diphtheria toxin. The crystal structure of diphtheria toxin is shown on the left-hand part of this slide. The catalytic domain, in the upper left-hand corner, and the translocation domain are retained in $DAB_{389}IL-2$, the molecular model of

which is shown on the right-hand part of this slide. Sequences for interleukin-2, shown here in green, replace the receptor binding domain of diphtheria toxin.

[Slide]

The mechanism of action of $DAB_{389}IL-2$ is to bind to a cell surface IL-2 receptor. There is then entry into the cell via receptor-mediated endocytosis. Once inside the endocytic vesical, the acid environment lead to a confirmational change in the translocation domain that creates a port in the endocytic vesicle which then allows access of the catalytic or toxic domain to the cell cytosol where, as a consequence, elongation factor 2, a mammalian factor required for protein synthesis, is ADP ribosylated. This leads to an inhibition of protein synthesis and results then in cell death.

[Slide]

Proof of principle was first established with the first-generation molecule I mentioned, $DAB_{486}IL-2$, which began clinical evaluation in 1988.

We saw, in a Phase I trial, that 6/36 cutaneous T-cell lymphoma patients responded to treatment. We then transitioned, in 1988, to the current product we are discussing, $DAB_{389}IL-2$. This was due to greater potency, a longer half-life and increased stability.

In 1988, we began a first study. Subsequently,

the compound was evaluated in a number of different indications. In those studies we observed that 13/35 patients with cutaneous T-cell lymphoma responded.

Based on the encouraging results in those Phase I/II studies, we moved on to design a Phase III program. That was in conjunction with input and guidance from the Agency. We then initiated that program. Orphan drug designation has been granted for this indication.

We submitted our biologic license application in December of 1997, and there was subsequent designation for a priority review.

I just want to acknowledge here something that Judith Kassis just mentioned. We are very appreciative of the collaborative spirit of our interactions with the Agency, and we especially appreciate the guidance that has been given to us by representatives from CBER in our first time through this process.

[Slide]

The overall clinical program includes a larger pivotal study in heavily pretreated patients with cutaneous T-cell lymphoma, with supportive data from a Phase I/II study with $DAB_{389}IL-2$. There are 2 ongoing CTLC studies, a blinded study that is enrolling patients who had less prior treatment than the pivotal study that we will discuss today, and an extension study that allows rollover from other

studies.

[Slide]

The remainder of our agenda includes a description of CTCL by Dr. Paul Bunn; pivotal trial results, from Dr. Madeleine Duvic and Timothy Kuzel. Dr. Kuzel will go on to give some integrated summary statements, and I will come back for a few concluding remarks. I would like to turn the podium over to Dr. Bunn.

CTCL Description

[Slide]

DR. BUNN: Dr. Dutcher, ODAC members, FDA staff and guests, Mycosis fungoides, the original disease in the CTCL spectrum, was first discovered by Alibert, in 1906. The term Mycosis fungoides was coined from the mushroom-like appearance of the facial tumors on this original patient.

I was not until Calusen and his fellow workers reported, in 1971, that the malignant cells proliferated in response to lymphocyte mitogens that the disease was first recognized as a malignant lymphoma.

[Slide]

The T-cell nature of the malignant lymphocytes, and the fact that they were derived from the helper subset and express cell surface T-cell antigens, was described in the mid-1970s.

This slide shows the collection of malignant

Mycosis fungoides cells in the epidermis, a so-called pautrier micro-abscess which is pathognomonic of the disease. As shown on the slide, the malignant T-cells all express the cell surface T-cell antigens.

Later, it was recognized that the Sezary syndrome was part of this spectrum of cutaneous lymphomas, and the term cutaneous T-cell lymphoma, or CTCL, was coined.

[Slide]

While the original lymphoma pathologic staging classifications did not recognize CTCL, the most recent classification, termed the real classification, does. In this classification Mycosis fungoides and the Sezary syndrome are recognized as low-grade T-cell lymphomas. These lymphomas must be distinguished from peripheral T-cell lymphoma and adult T-cell lymphoma which also may involve the skin, but which are intermediate or high-grade lymphomas.

Mycosis fungoides and the Sezary syndrome are uncommon cancers. There are only 800 cases every year in the United States compared to 56,000 cases of all non-Hodgkin lymphomas. Because there are only 800 cases, and because some are cured and many die from other causes before progression, there are very few refractory patients available for study. Since there are more than 350,000 new cases of breast cancer and lung cancer every year, and we

still don't know the optimal dose and schedule and duration of new treatments like taxanes, it would not be surprising that we still don't know the optimal dose and schedule for new agents, but these certainly will be worked out over time.

[Slide]

Classically, Mycosis fungoides begins as small patches and plaques on the skin. Over a period of years these lesions become larger, raised, and spread over increasing areas of the skin. As you can imagine from the slide, these lesions are extremely troublesome to the patients because of the itching they produce, the susceptibility to infection they bring, not to mention the disfiguring appearance that they cause.

With respect to staging, the skin is considered as the primary stage or T stage. T1 lesions are plaque lesions which cover less than 10% of the body surface, where the palm of your hand represents about 1% of your body surface. Patients who have plaques covering more than 10% of their body surface -- generalized plaque disease is shown on the slide -- are scored as T2.

[Slide]

Tumors, as illustrated in the original patient, are classified as T3. Finally, patients who have generalized erythroderma, shown in the upper part of this

figure, are scored as having T4.

In 1939, Sezary recognized that the majority of erythroderma patients also have circulating malignant cells. Thus, this group with leukemic proliferation and erythroderma are referred as having the Sezary syndrome. They are truly part of the same spectrum of disease because pautrier's micro-abscesses are seen. The cells have the same appearance. They have the same cell surface characteristics, and patients with generalized erythroderma may also develop plaques or tumors, and there are transitions between the skin manifestations.

[Slide]

Although involvement of blood, nodes and organs is detected most frequently with electron microscopic cytogenetic and molecular studies, the staging classification first developed by The Mycosis Fungoides Cooperative Group, shown on the slide, uses only light diagnostic procedures.

As shown on the slide, stage I patients are those who have plaque disease without adenopathy, blood, node or visceral involvement. Stage IIa patients have plaques, pus, and palpable adenopathy. However, biopsy of lymph nodes must not show involvement of lymphoma or, if it does, it becomes stage IVa. Stage IIb patients are those with cutaneous tumors who do not have nodal or visceral

involvement. Stage III patients are patients with generalized erythroderma without lymph node or visceral involvement. Stage IVa patients have any T stage with nodal involvement. Stage IVb patients have any T stage with visceral organ involvement.

[Slide]

This slide, thanks to Ed Sausville, shows the survival from the time of diagnosis by stage. As shown on the top line, patients with plaques who have no nodal involvement have the best survival, and about three-quarters of the patients are still alive at 10 years.

Patients with tumors, erythroderma, and nodal involvement have an intermediate survival, with median survival of 5 years or less. Patients with visceral organ involvement have the worst survival, with a median survival of 2.5 years or less.

Patients enrolled in the $DAB_{389}IL-2$ studies to be presented have failed multiple therapies and a much worse prognosis than these patients from the time of diagnosis. The arrows at 5 years show the median starting point for patients to be described subsequently.

[Slide]

Essentially all CTCL patients are symptomatic and, therefore, they require some form of therapy. Nearly all patients receive one of the three types of topical treatment

listed here, of which none is approved by the FDA. The total body application of nitrogen mustard produces responses in the majority of patients but a minority have a complete response. Responses for these early stage untreated patients generally last several years, but nearly all patients progress and become refractory to further topical therapy.

Total skin electron beam therapy produces response in nearly all patients, and complete response in more than half. Like topical nitrogen mustard, the average response lasts about 1.5 years, and few patients remain disease free for extended periods.

PUVA stands for the combination of oral psoralin plus ultraviolet A light irradiation. It produces response and response durations similar to those produced by electron beam irradiation.

Each of these therapies have major limitations. Topical mustard must be mixed and applied every day, and many patients become allergic. Electron beam irradiation requires daily trips to a major center for a period of months, and it can be used only once. PUVA requires visits to a major center three times weekly at the outset, and the treatment averages one year. Each of these therapies is extremely toxic to the skin. In addition to, again, scarring and telangiectases, second skin cancers, including

melanoma, are common.

[Slide]

Systemic chemotherapy, especially in combination, produces response in the majority of patients. But, as you have heard, the response duration is short, less than 5 months from the start of treatment for systemic chemotherapy. In addition, complete remissions are uncommon and no patients are cured. Toxicity from chemotherapy, especially infections, are common.

[Slide]

When it was recognized that CTCL disseminates early, the NCI conducted a randomized trial. The scheme is shown on this slide. Patients were randomized to receive either conservative therapy, beginning with topical nitrogen mustard, or combined modality treatment consisting of whole skin electron beam radiation and 4-drug chemotherapy, consisting of cyclophosphamide, Adriamycin, VP-16 and vincristine.

I would like to point out that this is the only large randomized trial ever done in this disease until the studies you are going to hear about later.

The study showed no differences in survival between the 2 groups. Subset analysis showed there was no difference for survival by any stage.

[Slide]

The complete response rates by stage and treatment groups are summarized on this slide. Despite the fact that these patients were newly diagnosed and untreated, aggressive combined modality treatment with chemotherapy and radiation produced a complete response in only 32% of the patients with stage IIb to IV, the population most similar to those you are going to hear about later.

The median response duration for the stage II to IV patients given combined modality treatment in this NCI and other NCI series was 6.5 months from the start of treatment -- 65. months from the start of treatment in untreated patients.

Chemotherapy had considerably toxicity in these patients, and 70% of these patients had grade 3 or grade 4 neutropenia; 20% of these patients were hospitalized for complications from the treatment, most often febrile neutropenia; 61% of these patients had severe infections; 10% developed congestive heart failure, and 7% developed a second primary cancer. Please remember that 20% were hospitalized and 61% had severe infections in this untreated population.

[Slide]

Infectious complications are common in all series of advanced refractory CTCL. They are severe and often fatal. These patients have an altered skin barrier, and

they are chronically immunosuppressed. Prior therapy increases the risk of infection. Bacterial infections, specially with staph species, are most common but viral and opportunistic infections are also common.

This slide summarizes 5 series from the literature. In several of these series the rate of sepsis ranged from 10% to 23% of the patients. The series of Duvic et al. was evaluating just staph infections. Staph infections in the skin or the blood occurred in 76% of the patients in her series.

In a recent chemotherapy series, not shown on the slide, of APIC chemotherapy, there was a 40% rate of sepsis and a 20% rate of opportunistic infections. Viral infections and other fungal and opportunistic infections were common in each of these series. I conclude that standard chemotherapy produces a very high rate of sepsis.

[Slide]

Recombinant alpha-interferon was the first biologic agent to receive widespread use in CTCL. This slide shows serial photographs of one of the responding patients from the first NCI series. This patient had received several prior treatments and had generalized plaque disease at the outset. After 3 months of continuous interferon therapy the skin was much improved, as was his pruritus. Skin biopsies showed persistent disease and he

was scored as a partial responder. He continued on interferon throughout the first year of therapy, showing progressive improvement. After 1 year he had no pruritus and no visual skin lesions. A skin biopsy was normal and he was scored as a complete responder. His skin obviously does not appear completely normal to you and me. That is because of the scarring and telangiectases from his prior electron beam irradiation. Please keep these photographs in mind as you see other patients treated with $DAB_{389}IL-2$.

It should be noted that numerous toxicities also occur from interferon, including near-universal constitutional or flu-like syndromes, with fever often of 102 degrees or greater at the outset; frequent transamination elevations, CNS symptoms, cardiac events and occasional severe renal toxicities. However, there is a tachyphylaxis over time to most of these.

[Slide]

The objective response rate in the original NCI interferon series was 45% in less heavily pretreated patients, and the response duration had a median of 5.5 months from the time of the start of treatment, not from the time of best response. Several of these responses, however, lasted several years. Such long durations of response are unusual with systemic chemotherapy.

[Slide]

This slide summarizes the results of recent series of other systemic agents, taken from a review in the Annals of Internal Medicine. With rare exceptions, these are small, single-institution trials, without confirmation of objective responses and without evaluation of quality of life.

The average number of patients in these studies is less than 15, and no study had more than 50 patients. Remember, these are rare diseases. Recombinant interferon is by far the most widely studied agent, and probably the most frequently used in clinical practice. The overall response rate in these series, usually with less heavily pretreated patients, was 52%, with a 17% complete response rate, and response lasting a median of 4-28 months from the start of therapy.

The purine analogs have also received considerable evaluation and have activity. Although the overall response to DCF, deoxycoformycin, and 2-CDA was 41%, complete responses occurred in only 3% to 6% of the patients and the response durations were less than 6 months from the start of therapy.

There was only one cooperative group multicenter study which had review of objective response. This was the study of fludarabine, conducted by the Southwest Oncology Group. This multicenter trial had only 31 patients which

took over 3 years to accrue, and showed an objective response rate of 19%, with 8% CRs. This most likely represents the true response rate to the purine analogs. These purine analogs have considerable toxicities as well, including myelosuppression, permanent lymphopenia, permanent immunosuppression, infections and CNS toxicities.

Various retinoids, cyclosporine and acyclovir have been tried in some patients who are less heavily pretreated, with some objective response, but these are extremely small series.

Photopheresis, shown at the bottom of the slide, described by one of the patients earlier, is the only therapy approved by the FDA, although this was approved as a device for erythrodermic patients. As shown on the slide, even in a small number of patients the response rate was reported to be 50%, with 20% CRs. In my opinion, these res were scored without rigorous criteria, without confirmation or independent review, and many of these patients received concomitant therapies.

No study, including these trials of photopheresis, evaluated the quality of life or the meaning of an objective response to the patient, as assessed by the patient symptoms or quality of life. The fact that no subsequent series has ever confirmed the responses to photopheresis suggests to me, at least, that the true response rate is much lower.

This is not in my text, but I would like to add that I personally believe that interferon should be approved for this disease. The two large pharmaceutical companies that make interferon were unwilling to spend the money to come before this Committee to present the data with interferon, and I congratulate the sponsor for doing that in this unusual disease. I want to point out that this very expensive, perhaps inactive treatment is the only thing approved for this disease.

[Slide]

Based on information from the literature, it is reasonable to conclude that the cutaneous T-cell lymphomas are uncommon. Like other lymphomas, they disseminate early but, unlike their B-cell counterparts, they always produce symptoms and are extremely disfiguring. It is not uncommon to find these patients actually on psychiatric wards, or to know when they arrived in the clinic because of the odor.

For patients who have failed multiple therapies, the disease process and its infectious complications are frequently life-threatening. There are no FDA approved systemic therapies, and systemic therapies are all non-curative, produce short-lived response and are toxic. Thus, new systemic therapies with non-overlapping toxicities and differing mechanisms of action are sorely needed.

I believe that $DAB_{389}IL-2$ is such a new agent, and

I am pleased to present Dr. Madeleine Duvic, who will describe the pivotal trial efficacy results.

[Slide]

Dr. Duvic is professor of medicine and dermatology at the MD Anderson Cancer Center, one of the largest accruers to the study. As she comes to the podium, I would like to thank the FDA for putting this new biologic in front of a cancer committee used to evaluating cancer agents. I would also like to thank Dr. Parker for an outstanding review, one of the best I have seen. I might add, it is the first time I have ever seen FDA with a higher response rate than the sponsor, and I actually agree with Dr. Parker's response assessment.

[Laughter]

Pivotal Trial Results

DR. DUVIC: I too would like to thank the ODAC Committee and the FDA for the opportunity to present the efficacy results of the $DAB_{389}IL-2$ pivotal study, 93-04-10.

[Slide]

This study was designed as a blinded, 2-arm parallel study, with randomized blocks. Patients were stratified by stage of disease as either Ib to IIa or as IIb to IVa. Disease burden and response were assessed by standardized, rigorous outcome measures which were prospectively defined. Responses wee confirmed by an

independent data efficacy review committee.

The objectives of this study were to evaluate safety, tolerability and efficacy, and to assess changes in symptoms and functional activity.

[Slide]

Patients included in the study all had advanced or refractory CTCL. Those with stage Ib to III disease must have had at least 4 or more therapies. Stage IVa patients must have failed at least 1 prior systemic therapy. All patients had biopsy-proven CTCL. At least 20% of the lymphocytes in the skin biopsies were required to be positive for the alpha chain of the IL-2 receptor, CD25. Half of the CTCL patients screened were positive. All patients had ECOG performance status of 0-2, adequate organ function and no systemic infection at time of entry.

[Slide]

DAB_{389}IL-2 was administered as an outpatient IV infusion of 15-60 minutes duration for 5 days, at a dose level of either 9 or 18 mcg/kg/day. Therapy courses were repeated every 3 weeks for up to 8 cycles in the absence of progressive disease or severe toxicity. No dose adjustments were allowed, but it was possible to delay the next course by up to 1 week for abnormal lab values. Of note, premedication was limited to acetaminophen and antihistamines only. Steroids were not permitted.

[Slide]

As you have heard from Dr. Paul Bunn, it is often difficult to assess response in patients whose disease is limited to the skin. Standard oncologic measures of tumor burden, as well as dermatologic assessments of specific symptoms, were included in the objective response. In addition, we built in ways to quantitate improvement for each patient.

To assess tumor burden we used a weighted extent scoring tool, initially developed for atopic dermatitis and adapted to CTCL by Drs. Kevin Cooper and Seth Stevens. The components were weighted equally and included a skin tumor burden score, bidirectional lymph node measurements confirmed by CT scan, and FACS measurements of circulating lymphocytes.

For patients with T1 skin stage, the skin burden score required 2-dimensional measurements of 5 representative index lesions. For patients with stage T2 to 4 skin disease the extent and severity of the score was calculated, as shown next, and was performed by the same trained observer in each site.

[Slide]

This is an example of a skin evaluation tool in a patient with generalized disease. Each type of lesion was placed on the body chart. Areas were measured three times,

and the mean areas were multiplied by a weighted factor for patch, plaque or tumor. To this were added scores for the lymph node burden and blood, if applicable, to assess the entire tumor burden.

The diagram shown here at baseline is an actual scoring tool used by my patient, whom I will show you next. This 26-year old, married female, with stage IVa CTCL, had 80% of her body surface area involved at baseline.

[Slide]

She achieved a PR after 3 courses of $DAB_{389}IL-2$. This is the change in the tumor burden. There was a 68% reduction in tumor burden after course 3, and she received a total of 6 courses.

[Slide]

These prospectively defined and standardized skin assessment tools were established by a team of oncologists before the study was initiated, and set a new standard for the evaluation of CTCL patients.

[Slide]

Serial photographs were also taken for all patients. This patient had disfiguring skin tumors at baseline that were significantly improved after 5 months of therapy. Although this is just an aside, what I am going to tell you may not show up on a quality of life assessment, but by the end of treatment this patient's 2-year old son

was no longer afraid of his mother's face.

[Slide]

The primary efficacy endpoint was the objective response rate that was based on the weighted disease assessment. Objective responses were defined as complete or complete clinical responses depending on biopsy confirmation. Partial responses were defined as 50% or greater improvement in disease burden. Objective responses were required to be maintained for at least 6 weeks, rather than 4 weeks required in most other oncology studies. Six weeks was chosen because courses were administered at 3-week intervals.

[Slide]

Objective responses required confirmation by biopsy with histologic review, as this case will illustrate. Over 3 years ago, a rapidly growing tumor appeared on the right thigh of one of my patients. The tumor grew rapidly through multi-agent chemotherapy. When $DAB_{389}IL-2$ was infused rapid tumor necrosis, as shown here, was observed. After 3 courses of $DAB_{389}IL-2$, the tumor was gone and only residual hyperpigmentation and scarring remained.

[Slide]

In the baseline biopsy, shown here, CD4 positive lymphoma cells filled the dermis. At the time of first response when the biopsy was taken again, some perivascular

lymphocytes remained. Therefore, the response was first graded as only a complete clinical response. It was later upgraded to complete response, later confirmed by repeat biopsy.

[Slide]

To validated response reported by the investigators all data were assessed by an independent endpoint review committee whose members were blinded as to dose and response. Each member of the team reviewed each patient's disease assessments, photos, pathology and symptomatology. Members of this review committee are provided in your briefing document.

[Slide]

Because CTCL patients are so symptomatic and devastated by this disease, we included measurements to confirm the beneficial effect of objective responses. Instruments commonly used in other diseases were brought into this CTCL study to capture patient symptoms. These were patients' evaluations of global skin score, pruritus, use of medications for symptoms of disease and serial quality of life assessments as measured by a FACT-G tool, which is validated for other cancers, and were completed by the patients.

[Slide]

Physician subjective measurements were also

evaluated for secondary endpoints of degree of erythroderma and CTCL severity.

[Slide]

The pivotal trial enrolled 71 patients at 20 sites, and 87% of the patients had received 4 or more previous therapies. The intent-to-treat analysis includes 2 ineligible patients, one was HTLV-1 positive and the other had ongoing toxicity related to recent prior therapy.

[Slide]

This slide shows the age, gender and race of the patients enrolled. The 2 arms were well balanced for these factors, and 52% of the patients were male, and the median age for all patients was 64 years. Seventy-five percent of the patients were Caucasian, 17% were Black and 9% were Hispanic.

[Slide]

These patients were also evenly balanced with respect to stage of disease, time from diagnosis and prior therapies. Two-thirds of these patients had advanced stage CTCL. The median time from diagnosis was 5 years, with a range of 3 months to 20 years. Patients had received a median of 5 other therapies, with a range of 1-12.

[Slide]

This slide summarizes the huge extent of prior therapy in these patients. The percentage of patients

treated with each class of therapy shows no significant differences between the 2 arms. Three-quarters had received topical chemotherapy or phototherapy, and two-thirds had received electron beam irradiation. One-third had received photopheresis. About half had received interferon, and about half had also received some form of chemotherapy. In addition, a large group of patients had received unique combinations of 2 or more of these therapies including chemotherapies or other experimental agents.

[Slide]

DAB_{389}IL-2 is a new form of therapy and most of the treating physicians had no prior experience with this type of agent. Therefore, the spectrum of toxicities and the methods of dealing with them presented new challenges. Despite this fact, 42% of all patients received all 8 courses of therapy. Thirty-seven percent of the patients withdrew for adverse reactions. This was in part, I think, because no dose adjustments were allowed and no steroids could be given to alleviate their symptoms. Twelve percent of patients had progressive disease and others withdrew because they worsened but did not meet the definitions defined for progression.

As you will hear from Dr. Kuzel later, there are ways to manage toxicities which should decrease the dropout rate for adverse events.

[Slide]

This slide summarizes the independently confirmed objective response lasting 6 or more weeks. The overall response rate for this pivotal trial was 30%. In the group receiving low dose $DAB_{389}IL-2$, 9 mcg/kg/day, the overall response rate was 23%. In the high dose group, receiving 18 mcg/kg/day, the response rate was 33%. These 2 results were not statistically different. Responses occurred at 11 of the 20 sites enrolling patients.

As shown on this slide, 3 patients had complete response confirmed by biopsy; 4 patients had complete clinical response and 14 patients had partial responses.

[Slide]

The overall objective results for this study are, again, shown on the top line compared to objective response rates stratified by stage or by dose. Patients with earlier stage disease, on line 2, who received the lower dose, had a response rate of 43% compared to a response rate of 30% at the higher dose level. For advanced patients, shown in yellow, the highest dose was associated with a 38% response rate compared to a 10% response rate on those advanced patients receiving the low dose.

By regression analysis, there was a trend favoring the higher dose level for the advanced patients. That p equals 0.07. Of note, advanced patients had a greater tumor

burden than the earlier patients, as the next slide will illustrate.

[Slide]

This patient had extensive erythema with plaques at baseline. She achieved a PR and, as you can see, at the end of therapy remains with post-inflammatory changes resulting from her previous therapy.

[Slide]

Her weighted disease burden was 82.8 at baseline and was 12.4 at the end of treatment. The reduction in the weighted tumor burden was 85%, as shown here.

[Slide]

For this study we calculated the duration of response in two ways. Time from first dose is plotted here. Time from date of first response was also calculated, as shown here. The low-dose arm is shown in yellow and the high-dose arm in blue. They were not significantly different.

For the low-dose group the mean duration of response from first dose was 6.8 months, and from the first response was 5.7 months. For the higher dose arm the median duration of response were 6.9 months from the first dose and 4.4 months from the first response respectively.

[Slide]

For all study patients we determined the

progression-free interval. This was calculated from the time of first dose until documented progression of disease or institution of other therapy. In this slide you will note that 20% of patients receiving the low dose and 10% of patients receiving the high dose had progression-free intervals consisting of up to 2 years.

[Slide]

Although we can look at objective tumor response, it is important also to understand how the patient feels during and after therapy. Patients graded changes in their overall global skin condition using a 7-point scale, from definitely worse to normal. They also used a VAS scale to indicate their degree of itching or pruritus, which in many patients is their most disabling symptom. All patients had improvements in their assessments of global skin scores, shown here, as well as in their pruritus, shown here, when the values are plotted from baseline to the best response.

[Slide]

As shown in this slide, the same data are plotted to the end of treatment, a more conservative endpoint, and 17/21 responders, who are shown here, remained improved at the end of their treatment time point, a range of 17-34 weeks. The patients who worsened had relapsed with progressive disease prior to the end of treatment.

Not only can you see from these graphs that the

patients felt better, but there was a statistically significant change in their baseline by a signed rank comparison.

[Slide]

When we analyzed the weighted disease burden at the end of treatment for all patients in this study, who are individually plotted as vertical bars, two-thirds of the patients who received $DAB_{389}IL-2$ showed improvement in their disease burden, and this included objective responders, who are shown in pink, as well as other patients. Several patients who had remarkable responses dropped early, before they could be documented as responders. Several other patients who were graded as responders relapsed before the end of therapy.

[Slide]

Furthermore, treating physicians were asked to assess their patients CTCL severity, as well as erythroderma, that was present in 7 patients initially. Again, at best response, all responders showed improvement in global severity scores, shown on the left, and in erythroderma, shown on the right.

[Slide]

When the data are plotted from baseline to end of therapy, all except a few relapsing patients showed improvements. These changes were also statistically

significant.

[Slide]

One patient with facial plaques who achieved complete remission illustrates how symptomatic improvement mirrored the objective response.

[Slide]

The objective skin burden, plotted in blue, correlates exactly with her own improved global assessment, in red, and with pruritus, shown in orange, and with the physician CTCL severity score, shown in yellow.

[Slide]

Yet another way to look at the meaning of a physician-determined objective response is to evaluate the benefit to the patient as assessed by the FACT-G tool, filled out by each patient. This quality of life assessment has a total score of 112, and is composed of 5 sub-scores of well being. FACT-G data from all responding patients, shown on the left, others in the middle, and all patients plotted to the right, are shown. The baseline scores are shown in white and are compared to the end of treatment scores, shown in pink.

In the 21 responding patients in this study there was a statistically significant improvement in their FACT-G composite score at the end of treatment, as indicated by the asterisk. As expected, patients who did not respond had a

significant decrease in their scores, however, and importantly, the overall patient population receiving Dabble had maintained quality of life during their treatment.

[Slide]

In conclusion, $DAB_{389}IL-2$ is effective for CTCL in heavily pretreated CTCL patients and in patients with advanced disease. The overall objective response rate was 30% including a 10% complete response rate. There was a trend toward the higher dose being of more benefit for advanced patients.

In addition to the objective responses seen in these patients, responding patients derived benefit in symptoms of pruritus and in overall skin severity, and had significant improvement in their quality of life.

[Slide]

I would like to turn the podium over to Dr. Timothy Kuzel, who will now discuss the safety data.

Integrated Safety Data

DR. KUZEL: Thank you, Dr. Duvic. I would like to thank the Committee for permitting me to speak today regarding this new therapy for cutaneous T-cell lymphoma.

[Slide]

I will review the safety data from the 71 ps in the pivotal trial we have just discussed. I will then review the integrated safety data from an additional 73

patients, lymphoma patients in a completed Phase I trial and the pivotal trial. One ineligible patient from the pivotal trial has been deleted.

Although safety data will be presented in tabular format, the spectrum of adverse events experienced with this new drug can be more easily understood in the context of a number of clinically relevant syndromes, which I will present.

Finally, some pharmacodynamic information from a subset of patients is relevant to the toxicity, and an overall summary of integrated efficacy for the 106 CTCL patients will be presented at the conclusion.

[Slide]

Every patient experienced some adverse event in this pivotal trial. The majority were grade 1/2 and are inclusively listed in your briefing document. I will emphasize the grade 3/4 events. The grade 3/4 events are listed here by frequency greater than 5%. Less common events are listed in Table 20 of your briefing document.

When grade 3/4 toxicity us examined by treatment arm there are no differences between the 2 dosage levels. The most common adverse events in this trial, directly attributable to drug administration are infection, fever and chills and asthenia, the same side effects which determined the maximum tolerated dose in previous trials. Other

adverse events are less common.

Only the frequency of nausea or vomiting demonstrates a trend toward dose effect. Edema, dyspnea and hypotension will be addressed later.

[Slide]

This slide completes the list of grade 3/4 AEs. The secondary skin carcinomas are a common sequelae of the topical treatment many patients had experienced previously. Importantly, the side effects typically associated with cytotoxic agents, such as neutropenia, mucositis or alopecia are very uncommon.

Actually, DAB_{389}IL-2 behaves more as a biologic response modifier or recombinant protein product in the side effect profile despite its proven cytotoxic activity. These events typically occur at their worst during the first or second cycle of therapy. Some of the adverse events may even be preventable using standard medications commonly employed as premedications, which were prohibited due to the nature of this clinical trial, such as corticosteroids, 5HT3 antagonists and colony stimulating factors.

[Slide]

In addition to the trials discussed earlier, over 456 individuals have received DAB_{389}IL-2 and form the basis for a database which includes 216 patient with lymphoma, 195 patient with non-cancer indications and 45 normal

volunteers. These patient experiences have allowed characterization of the behavior of the drug in varied populations, identified pharmacodynamic issues of note, and have allowed the identification of clusters of adverse events into meaningful clinical syndromes.

The population of lymphoma patients treated in the Phase I trial described above and the pivotal trial form the basis of a combined population of 143 patients. These 143 patients exclude the 73 patients with lymphoma on ongoing blinded trials, the 93-04-11 and 93-04-14 trials, from these 216 patients with lymphoma shown above.

[Slide]

Trials with $DAB_{389}IL-2$ were initiated with protocol 92-04-01. This Phase I cohort, dose-escalation, open-label trial enrolled 73 patients with advanced, often refractory, cutaneous T-cell lymphomas, B-cell non-Hodgkin lymphomas or Hodgkin's disease.

The objectives included evaluating safety and tolerability, determining the maximum tolerated dose, and evaluating anti-tumor effects. All 73 patients will be included in a discussion of integrated safety and the 35 CTCL patients in support of efficacy.

[Slide]

Doses delivered ranted from 3-31 mcg/kg/day, administered daily for 5 consecutive days over 5-15 minutes

as an outpatient. Treatment could be repeated every 3 weeks to a maximum of 6 cycles in this trial.

[Slide]

The demographics of the 35 CTCL outpatients enrolled in the Phase I trial were similar to the patients enrolled in the Phase III pivotal trial you have just heard about. The median age in both trials was 64 years of age, and both trials included patients of both sexes. The median age of all 73 patients in the Phase I trial was only 52, reflecting the Hodgkin's disease patient population included in this Phase I trial.

[Slide]

For the entire Phase I population of 73 patients the characteristics were similar. However, a comparison of the 35 CTCL patient characteristics entered into the 2 trials demonstrates some differences. Although there were similar percentages of low and high stage disease patients as stratified by the stratification design in the Phase III trial, of note, CTCL patients in the Phase I trial had disease of shorter duration before study entry, 3 versus 5 years in the pivotal trial, and were less heavily pretreated in the Phase I trial, a median of 3 versus 5 prior therapies. These differences may be important when considering issues of response and toxicity.

[Slide]

This slide demonstrates grade 2/3 adverse events per patient in the 73 lymphoma patients in the Phase I trial compared to the pivotal trial population. There was a trend towards less toxicity in the Phase I trial, but no definite statistically significant differences exist. The spectrum of the toxicity remains similar, however, with infection and related symptoms and constitutional symptoms dominating, although the Phase I group had a slightly lesser frequency of most adverse events.

[Slide]

This slide completes the trial comparison of grade 3/4 toxicity. The difference in the CTCL populations and the younger age of the Hodgkin's disease patients likely explains the trend of somewhat less toxicity in the Phase I trial experience.

[Slide]

Discontinuations due to adverse events occurred in both patient populations in these 2 trials. And, 16/72 patients in the Phase I trial discontinued versus 26/71 in the pivotal trial. A variety of AEs, listed here, were identified by investigators as the reason for discontinuation. No single type of event or organ system afflicted appears to dominate the decision to withdraw, and the data would seem to suggest that patient and physician intolerance of toxicity varies and is not drug specific.

[Slide]

This slide shows the deaths in the pivotal trial and Phase I trial. Above the line on this chart are the events which occurred within 30 days of last drug administration, regardless of the study. Deaths within 30 days included 1 patient with progressive disease; 1 patient with Hodgkin's disease in the Phase I trial who died of respiratory failure after iatrogenic bilateral pneumothoraces, resulting in ARDS; and 2 patients with CTCL who died of cardiac events. One was a patient on day 30 of the 6th cycle whose cardiac arrest occurred in a hospice setting, and the other was a patient with extensive prior cardiac disease who died on day 31 of a cycle during an operative procedure to repair an iatrogenic pseudoaneurism from a previous cardiac catheterization.

Below the line are patients who died with unresolved AEs at any time subsequent to enrollment in the trial. One was a patient with CTCL who died of progressive disease, and 2 other deaths were identified in elderly patients, including 1 84-year old woman who was admitted to a local hospital with increasing skin pain and exfoliation, likely secondary to progressive disease, who was placed on escalating doses of narcotics infusion. She was found dead in her sleep in her bed on the 6th hospital day of that stay.

[Slide]

When adverse event frequency of events is broken down by patient, a decrease in frequency of adverse event is noted as progressive courses are administered. Although this may be a reflection of susceptible patients withdrawing from the treatment early after only 1 or 2 courses, the pattern also exists in patients who actually receive repetitive dosing. As shown in yellow by patients receiving 4 or more courses of therapy, a pattern of tachyphylaxis which is common to biologic response modifier therapy emerges.

[Slide]

The individual AEs in these studies are often clustered in clinical syndromes. For example, constitutional symptoms, such as fatigue, fever and chills, myalgias or arthralgias were noted in 91% of patients. These occurred most commonly after the first cycle of therapy and were often prevented on subsequent cycles by use of permitted premedications, usually Tylenol or antihistamines, in addition to the tachyphylaxis issues just mentioned.

[Slide]

As mentioned by Dr. Bunn, infections complications are common in the natural history of this disease and in the treatment course of these patients. Forty-eight percent of

the combined population experienced some infection, ranging from viral upper respiratory tract infection to frank bacteremia. Six patients discontinue treatment due to infectious issues, but investigators often considered the infection unrelated to the $DAB_{389}IL-2$ treatment. When individual characteristics were examined to identify factors associated with infection, only advanced disease stage correlated with the higher frequency and severity of infection, as it has in other series.

[Slide]

Ninety-seven, or 68%, of the combined population experienced acute drug administration-related adverse events. These events are similar to the type observed when administering other human protein products, such as gamma globulin or monoclonal antibodies, and include hypotension, back pain, dyspnea, rash, chest pain, tachycardia or flushing.

Three patients, or 2%, experience grade 3/4 events. The symptoms could be treated by interrupting infusion, administering antihistamines and then, once the reaction subsided, reinfusing the drug at a slower rate. Several patients were subsequently retreated without recurrence. Pretreatment levels of antibodies to $DAB_{389}IL-2$ did not correlate with the possibility of experiencing this side effect.

[Slide]

A vascular leak syndrome as identified retrospectively in 10% of treated lymphoma patients. The patients were identified by a common combination of any 2 of the individually coded adverse events of edema, hypotension and/or hypoalbuminemia. The event only occurred in patients with CTCL. The constellation evolves within 10 days of the treatment. Eight patients required hospitalization. Seven of the patients then discontinued because of these symptoms, but 7 others were retreated. No deaths were observed. Careful monitoring of the patients' fluid balances and judicious use of intravenous replacement will limit the consequences of this side effect.

[Slide]

Distinct cardiovascular AEs, characterized as thrombotic events, have been retrospectively analyzed as well. Eight percent of all lymphoma patients experienced an event, such as superficial or deep venous thrombosis, or arterial thrombotic events. The 5 patients with superficial thrombophlebitis resolved with simple conservative management. Two patients with a DVT were observed in the setting of prolonged hospitalization or other coexisting risks of DVT, and were successfully treated. Episodes of arterial thrombosis were less often observed, and included a peripheral lung occlusion in a patient with preexistent

symptomatic peripheral vascular occlusive disease, a single cerebral vascular accident which resolved, and the 2 myocardial infarctions I mentioned earlier during the discussions of the deaths.

[Slide]

Neurologic events have been observed, including CNS symptoms such as confusion or light-headedness, and peripheral nervous AEs such as paresthesias. Approximately two-thirds of the events were grade 1/2 in severity. Often they occurred concurrent with other metabolic disturbances such as the vascular leak syndrome.

One patient was identified as having aseptic meningitis in the setting of delirium, both of which resolve with time, and 1 patient has been diagnosed with Alzheimer's disease during the study.

[Slide]

Several laboratory abnormal results were identified during these trials. Hematologic toxicity was unusual and was represented only by mild anemia, thrombocytopenia or leukopenia. Neutropenia was unusual, and life-threatening neutropenia did not occur.

These events were noted, often occurred in the setting of progressive disease or infection. No patient required colony stimulating factors during the trial. Grade 3/4 lymphopenia, a common finding in patients with lymphoma,

was present in 15% of patients at baseline.

[Slide]

Because of recent recognition of prolonged lymphopenia associated with several newer therapies or lymphoproliferative disorders, such as the purine analogs, concern regarding the targeting of CD4 cells in these trials was appropriate even though the IL-2 receptor, as mentioned earlier, is present only on activated or malignant lymphocytes. Careful flow cytometric assessments of T-cell subsets has been a feature of the trials to date.

This slide demonstrates the transient increase in total lymphocyte count immediately following a week of therapy, likely related to distribution phenomena. But all patients had levels of normal lymphocytes return to baseline by the end of study. The mean levels remained above the lower limit of normal for lymphocytes at all times.

[Slide]

Clinical chemistry abnormalities occurred more frequently. Hypoalbuminemia developed in 83% of patients and was grade 3 or worse in 14%. There was a rapid fall in levels associated with $DAB_{389}IL\text{-}2$ administration, which resolved after the nadir on day 12.

An amendment limiting patients to treatment only when albumin was greater than 3.0 g/dL was felt appropriate to avoid prolonged hypoalbuminemia which might be associated

with a vascular leak.

Mild renal dysfunction occurred in 8% of patients. A single patient experienced a grade 3 rise in creatinine. The abnormality resolved and the patient was successfully retreated.

[Slide]

Elevations in transaminases occurred in 87/143, or 61% of patients but no evidence of chronic hepatic injury was observed, such as hyperbilirubinemia or prolonged coagulation profiles. This transaminitis is usually worst after the fist cycle of treatment, as with interferon and other biologics.

This chart demonstrates mean levels of ALT as a function of treatment course and the number of patients at risk. Tachyphylaxis develops with mean peak levels increasing with repetitive dosing.

[Slide]

Thankfully, I have now completed the presentation of integrated safety --

[Laughter]

-- and we will turn to issues of immunogenicity and pharmacokinetics and overall efficacy.

[Slide]

The combined cancer population has allowed confirmation of issues of immunogenicity and pharmacokinetic

profile. Antibody formation may have an impact on drug clearance and, therefore, on toxicity tachyphylaxis and response to therapy. Alternatively, antibody formation may put patients at risk for some side effects. Therefore, a few words regarding antibody formation are relevant.

DAB_{389}IL-2 contains sequences from diphtheria toxin, and vaccination to diphtheria toxoid results in antibody formation which potentially cross-reacts with DAB_{389}IL-2. Data is available on 114 patients from the Phase I and pivotal trials.

Interestingly, only 38% of patients had antibodies detectable prior to treatment. When responders are compared to all patients, 38% of both groups, using an ELISA, had antibodies at baseline. Some of the antibodies, however, bind to epitopes on the molecule which are effectively neutralizing.

Using a cell-based bioassay to detect any neutralizing antibody, which is slightly more sensitive compared to the ELISA, there were also no differences at baseline between responders and all patients, although the percentage of positive patients was slightly higher at approximately 50%. After treatment nearly all patients have antibodies detectable by ELISA or neutralizing assay.

The effect of the antibodies to IL-2 is unclear. A smaller percentage of patients had antibodies to the IL-2

portion of the molecule, both at baseline and the end of dosing, although not as high in titer as the other antibodies. Antibodies to IL-2 have also been observed after treatment with interleukin-2 and no deleterious effects have been noted.

[Slide]

As shown here, the ability to mount an immune response during treatment does not predict for response. Both responders and all patients have similar levels of antibodies present after 2 cycles of therapy, approximately 90% of patients. The favorable effect of antibodies may be to tachyphylaxis side effects concurrent with the development of antibodies but this is not definite. It does not appear that the presence of antibodies predisposes to side effects, especially the acute infusion-related events.

[Slide]

The combined population has also been studied to confirm pharmacokinetic consistency. The area under the curve is proportional to dose delivered across the dose-ranging study to date. There is no evidence of accumulation during the week of dosing. A half-life of approximately 70 minutes has been observed. Clearance of the $DAB_{389}IL-2$ is increased 2- to 3-fold after the development of antibodies.

[Slide]

This slide demonstrates the mean C_{max} and AUC during day 1 of course 1 and 3 respectively by dose group. There is clearly significant inter-patient variability in the pharmacokinetics of this drug, as demonstrated by the standard deviations. Despite the increased clearance rate associated with antibody formation resulting in lower overall mean values in course 3 from course 1 for both dose groups, the higher dose group retains increased values for the C_{max} and AUC in course 3. Importantly, peak serum concentrations exceed that required for in vitro cytotoxicity in courses 1 and 3.

[Slide]

Finally, I would like to show additional efficacy data which supports the pivotal trial data. Response definitions differed slightly between the 2 trials. The Phase I trial required minimum response duration to exceed 4 weeks compared to the 6-week requirement in the Phase III pivotal trial. The overall response rate in the 35 CTCL patients in the Phase I trial was 37% compared to 30% in the pivotal trial. The rates of complete remission were similar, 14% versus 10%, despite the more heavily pretreated population in the pivotal trial.

[Slide]

The duration of response curves in the 2 groups of

CTCL patients from the time of initiation of drug treatment, the most oncologists view the value of durable remissions, are overlapping during the early follow-up period. The difference which emerges in the tails of the curve result in a slight prolongation of the median response duration favoring the less heavily pretreated population in the Phase I trial, resulting in median duration of response from time of drug initiation of 9.1 months versus 6.9 months.

Importantly, prolonged remissions were observed in both trials. Durable remissions in advanced disease have occurred even with the early construct in clinical trials.

[Slide]

Adverse events are common but manageable in heavily pretreated CTCL patients. consistent objective responses have been observed in 2 separate clinical trials.

I would allow Dr. Jean Nichols to return to summarize the presentations. Thank you.

Summary

[Slide]

DR. NICHOLS: Overall, as we discussed today, T-cell lymphoma is a dramatically disabling and disfiguring disease, but it is ultimately fatal. $DAB_{389}IL-2$ represents a new class of receptor-active cytotoxic fusion proteins. We have demonstrated that $DAB_{389}IL-2$ can lead to reductions in tumor burden in heavily pretreated patients, and that those

reductions in tumor burden are paralleled by improvement in disease-specific symptoms. We have shown those improvement in rigorous clinical program that sets a new standard for the evaluation of CTCL patients.

Phase I/II data supports that data that we observed in pivotal studies. Toxicities are common but manageable and, interestingly, similar to some other approved biologics, and that includes the tachyphylaxis that is observed for many symptoms.

[Slide]

Importantly, toxicities do not appear to overlap with some other non-biologic therapies that are used in this disease, and that is particularly true for myelosuppression and immunosuppression.

[Slide]

We believe that $DAB_{389}IL-2$ offers a safe and efficacious new alternative for patients with cutaneous T-cell lymphoma who have recurrent or persistent disease despite prior therapy, and we are requesting approval for ONTAK or $DAB_{389}IL-2$ in this patient population.

We are now available to answer any questions that you might have. I just want to indicate that we have a few additional individuals available also to answer questions, Dr. Philip Lavin, our statistician for these studies who is with Boston Biostatistics; Dr. Patricia Bacha, from Seragen;

Dr. Francine Foss, an investigator in these studies; Dr. Fiona Craig, pathologist for these studies from University of Texas; Dr. James Rubin, FACT expert for these studies at MD Anderson; Dr. Seth Stevens, who originated the tool we used for assessing tumor burden; and Dr. Astra Liepa, our quality of life analysis expert from Eli Lilly, and I will be available to moderate questions as needed.

Questions from the Committee

DR. DUTCHER: Thank you very much. We are now going to address questions to the sponsor. Dr. Sausville?

DR. SAUSVILLE: Thank you. I also would like to extend my congratulations on a very rigorously conducted and clearly very pointed examination of several important issues in evaluating a new therapy in this disease.

I do have a number of questions though. First, one of the entry criteria for the pivotal trial was the expression of the IL-2 receptor on what were perceived to be malignant tumor cells. Yet, incorporation of this information into any potential labeling indication is conspicuously absent. Would you care to discuss that issue?

DR. NICHOLS: Well, as was described earlier, we did require assessment of samples for IL-2 receptor expression and set that cut-off. However, what we observed in the trials is that data could be quite variable, and I would like to ask Dr. Bacha, from Seragen, just to describe

what we did observe with the biopsy samples. Then I would like to ask Dr. Fiona Craig to comment on what the assay detects.

DR. BACHA: First of all, I would like to clarify that the entry criteria were set very low. It required only 20% of the cells in the biopsy to express the CD25 antigen. In addition, it also -- as Dr. Craig can probably comment on better, did not require, because of difficulties in detecting the malignant cells versus potentially reactive lymphocytes, that there be a distinction between those.

What we have done in terms of looking at the variability of those samples is to look at the population that were screened for these studies, and that included over 300-some biopsies. About 10% of those patients had multiple biopsies, either taken at different times or different sites on the body. Of those 10% of the biopsies, again, about 14/32 patients we looked at had a variable expression. One sample was positive by the assay, one sample was negative.

Seven of those patients actually were entered in the trial, and of those 7 patients 3 had documented responses. So, again, it is a question of what the assay is really telling us. We have felt for that reason that we would want further discussion around it. I think Dr. Craig can discuss the issues around the assay.

DR. NICHOLS: Just one other bit of information,

there were also 2 patients of a group who have relapsed and reentered into the rollover study that I mentioned, protocol 93-04-14. There are 2 patients who, at the time of rebiopsy for entry into that study, again did not score as detectable and did regain a response.

DR. CRAIG: I am Fiona Craig. I am the pathologist who performed these assay studies. This was a very difficult assay for us to perform. I was using frozen-section immunohistochemistry. This is an assay that is not commonly available in all pathology laboratories.

The assay was also really not at the sensitivity that we needed to detect the levels of receptors that are required to kill a cell, only 50-100 receptors being required. The assay really was not that sensitive by any means.

There was also a great deal of heterogeneity observed with this assay. Looking at an individual skin biopsy, there are not only tumor cells; there is an intimate mixture of reactive lymphocytes and tumor cells, and it was impossible for me, using frozen-section immunohistochemistry, to separate those 2 cell populations. That is one of the reasons why we had originally chosen the 20% cut-off because lower than that I felt that I really couldn't reliably say whether the interleukin-2 receptor was being expressed on the tumor cells. So, that was the

heterogeneity within an individual biopsy.

As has already been mentioned, there was also heterogeneity between biopsies in the same patient. So, if I received more than one biopsy from the same patient at the same time, one was often positive and the other negative. So, it was really quite variable.

I think this also reflects the fact that the assay was not sensitive enough to pick up the levels of receptors that we needed. So, there were certainly problems with using an assay to pick up the receptor at the level that we required, and considerable variability was identified with this assay.

DR. SAUSVILLE: Thank you. Again, recognizing that heterogeneity or variability is certain part of the pathologic features of the disease, it is fair to say though that if you did have a patient population that lacked the receptor, they would not be expected to respond. Is that correct?

DR. NICHOLS: Yes.

DR. SAUSVILLE: Thank you. Another question relates to the toxicity issues. There is characterization of vascular leak syndrome recognized retrospectively in 10%. But we hear that 83% of patients had hypoalbuminemia. Can I infer from that the reason for the hypoalbuminemia is different than vascular leak, or do you believe that it is

part of the spectrum?

DR. KUZEL: The way we retrospectively looked at that was we brought up hypoalbuminemia as a single event, but we also looked at edema and hypotension and then we pooled all of those patients and compared them to try to identify patients retrospectively that clinically appeared to have it. So, hypoalbuminemia was a common one of the events, but single isolated hypoalbuminemia didn't seem to predict for the vascular leak or indicate the presence of vascular leak when we reviewed case report forms.

DR. SAUSVILLE: So, then really your definition of vascular leak is not only hypoalbuminemia but would require some clinical perspective as well?

DR. KUZEL: Correct.

DR. SAUSVILLE: Could you elaborate on that?

DR. KUZEL: It was either significant edema in the presence of that hypoalbuminemia or a significant clinical event of marked hypotension in the presence of hypoalbuminemia.

DR. SAUSVILLE: Likewise, did patients who had neurological, shall we say, problems which, in your estimation, is 44% of patients, was this relatable to the incidence of hypoalbuminemia, stepping aside from whether it was related to the vascular leak syndrome?

DR. KUZEL: It didn't seem to track very well with

hypoalbuminemia. It seemed to occur more commonly with more serious combinations with hypoalbuminemia, like the vascular leak syndrome, where there were multiple other metabolic issues, hypoxemia occasionally manifesting as well.

In addition, it is important to remember that many of these patients are on significant doses of antihistamines. The patient with delirium, for example, was my own patient and actually was overdosing on antihistamines, and that was actually felt to be contributing to his mental status changes at the time of his hospital administration.

DR. SAUSVILLE: So, to summarize, if you would include, just for the sake of discussion, hypoalbuminemia within the spectrum of changes that might be characterized as vascular leak, admittedly a very low grade, was there a dose-relatedness in this toxicity?

DR. KUZEL: We could not find a clear dose-related phenomenon with either hypoalbuminemia or vascular leak syndrome. The number of vascular leak patients, even retrospectively, was small and was actually in the 2 different studies and different dose groups. So, given those limitations, there was no clear dose relationship to the hypoalbuminemia.

DR. SAUSVILLE: So then, together with your response data, you would say that there is a dose-

relatedness to neither toxicity or efficacy here?

DR. KUZEL: Yes.

DR. SAUSVILLE: Nor to expression of the receptor?

DR. KUZEL: With regards to dose?

DR. SAUSVILLE: Right.

DR. KUZEL: I mean, that was determined before they were in a dose group.

DR. SAUSVILLE: Right, but I guess efficacy and receptor and dose. If you got a lower dose and had a higher receptor, did you have a higher chance of responding?

DR. KUZEL: We didn't really have a quantifiable method of receptor analysis. So, it is really a qualitative cut-off at 20%. So, that is difficult to analyze.

DR. SAUSVILLE: Thank you. Just as a point of curiosity, what were the units of your concentrations in pharmacokinetics?

DR. KUZEL: Nanograms.

DR. SAUSVILLE: Thank you.

DR. BERGFELD: I would also like to ask a question on the antibody response which appears to be ubiquitous between the responders and non-responders, and the fact that they do mount an antibody response, and the meaning of this, and then a statement on tachyphylaxis, which is a very old type of phenomenon that we see clinically as well as, I guess, histologically. I would like that explained. When

antibody response does not seem to be indicative of response of tumor, then what is this tachyphylaxis phenomenon that you are referring to that may explain the diminished averse effect but the continuation of some response?

DR. NICHOLS: I will answer part of that question and then ask Dr. Kuzel and also Dr. Bacha to respond to that also.

In terms of the antibody, I will just indicate that in terms of just clinical data there are 11 patients in the pivotal study who have relapsed and been retreated in the rollover study. Of those 11 patients, 5 have re-responded, and all of those patients had antibodies at the levels that you saw presented by Dr. Kuzel. So, that is just what we have seen in that way.

We have also seen that kind of data in rheumatoid arthritis patients. In terms of why that may be the case, what we know is that are not a large number of receptors have to be engaged on the surface of a cell in order to get productive entry and cell killing. So, it just may be that although clearance is affected there is still a possibility of getting enough material to a target cell to kill that cell and decrease tumor burden.

DR. BUNN: I have a different answer. Years ago we studied recombinant interferon. One of the products was said to have a higher rate of antibody response than the

other. Clinically this meant nothing. Every patient has tachyphylaxis whether they get antibody or they don't, and responses are totally independent of the antibody levels. That is the same thing we find here. My answer is we don't know. We don't know what these antibodies mean. Every patient gets tachyphylaxis whether they get an antibody or they don't. Okay? And, responses are independent of antibody or antibody levels. So, we have measured something interesting. Maybe somebody else is a genius but I don't know what it means.

[Laughter]

DR. BERGMAN: I am afraid that is what I also gathered from your information.

[Laughter]

DR. BERMAN: Dr. Nichols, could you clarify for me -- I was a little confused -- whether you will require patients going on this study to have the presence of the IL-2 receptor or not? The draft of your package insert suggests that this is not a requirement.

DR. NICHOLS: We did not include it in the recommended draft labeling for the reasons of heterogeneity that were indicated earlier, but that is obviously a negotiation that will occur with the Agency and, obviously, we will wait to hear input.

DR. BERMAN: So, what is your feeling about the

presence of the receptor and its relationship to response?

DR. NICHOLS: Well, as Dr. Sausville indicated, we do believe an IL-2 receptor has to be present in order to see specific cytotoxic action. So, we are not trying to say anything different from that. What I think we also feel from the data that we have is that we may miss patients who have sufficient receptor numbers to respond with the current assay. So, it just has to be placed in the context of what that piece of information means.

DR. BERMAN: The second question relates to toxicity and incidence of hypotension that you saw. Was this all within an hour of the infusion, or while receiving infusion, number one, and number two, would you make a recommendation that patients be observed for a set period of time after the infusion to prevent this?

DR. KUZEL: There were really two separate kinds of hypotension that we have seen. One was in the spectrum of the immediate infusion-related event, and would occur actually during the infusion. So, during that first 5-15 minutes during infusion. It is probably not unreasonable to have patients wait around some minutes after the infusion but generally it was during the infusion.

The second kind of hypotension was part of the vascular leak syndrome, and that actually developed usually late, usually after the week of treatment, usually into the

next week actually. That is a separate kind of hypotension that does require some contact with the patient on sort of an ongoing basis to make sure that they are doing okay and those events aren't happening. But, again, monitoring them for that prolonged period is really impractical in this day and age.

DR. BERMAN: So, somewhere in your package insert it should be stated that patients should be seen at least for the first and second infusion at least on a weekly basis to assess for second episodes of vascular leak.

DR. KUZEL: I mean, the incidence of vascular leak was relatively low so that to require all patients to come sort of during the first and second week afterwards is cumbersome, and I think that is, again, something that probably the FDA should negotiate in terms of the insert labeling language.

DR. DUTCHER: Another question related to the toxicity, Dr. Kuzel, in terms of the infections. Since these people often carry staph, and staph infections are common without any other type of treatment, was there any evidence of IL-2-related problems such as toxic shock or granulocyte immobility that we saw with IL-2 alone?

DR. KUZEL: Granulocyte mobility issues have not been studied with the drug. So, it is impossible really to comment on that. Catheters of any kind in these patients

are really difficult. We have learned that with every treatment we use. Indwelling catheters in particular are very problematic, simply because these patients are all carriers of staph; they all have disrupted skin barriers. So, we certainly expect staph infections. A number of the infections that were actually documented were cutaneous infections where the skin lesions were swabbed and that was the documentation of skin infection. So, you do need to be aware that these patients carry staph, and I think the doctors who take care of these patients are well aware that they are really infectious groups of patients, really culture dishes waiting to get into trouble and they need to be closely watched.

DR. DUTCHER: But you didn't see any of the infections that there was some sepsis that were staph sepsis?

DR. KUZEL: In general, most of them were staph bacteremias.

DR. DUTCHER: But it didn't seem out of the spectrum that one sees with this disease?

DR. KUZEL: No, not when you are putting catheters in these patients. It didn't seem out of the ordinary.

DR. NICHOLS: Dr. Foss is also going to add a comment.

DR. FOSS: I just wanted to go back to some of the

data that Dr. Bunn presented. In the randomized study at NCI we did see staph bacteremia, both in the conservative arm where there were no catheters in those patients by and large, and also in the arm where patients got chemotherapy. In a couple of studies that I have done, most recently a study with EPOC which does require indwelling catheters, there was a 60% incidence of bacteremia. Most of these patients had staph bacteremia or other gram-positives.

So, I think what we are seeing here certainly is not out of line with respect to what one can expect in these patients, particularly as they get further along in their disease, and one thing we see in patients with CTCL is that as their disease becomes more advanced and they get toward the end part of their disease, one way that we as clinicians can pick that up is that they start getting infected more often. So, in following patients for many, many years, as many of us have, we can see clearly a change in the course of their disease when they start getting bacteremic all the time. So, I think that is really a natural history issue as well, and when we use this drug in earlier stage patients, as we are in the 11 study, I anticipate that we will see a slightly lower incidence of infections.

DR. OZOLS: Your proposed indication is for treatment in patients with prior therapy. There isn't really any approved prior therapy, I guess other than the

photopheresis. I am trying to figure out what kind of context of patients you would want to use this in. Maybe Dr. Duvic would tell us what your standard approach right now is for advanced patients.

DR. DUVIC: My approach to advanced patients is to avoid any agent use that further immunosuppressed them because, in my experience, use of DCF and combined chemotherapy results in deterioration of their immune system and often death from sepsis.

I think that we have the best response in patients with tumor stage disease, in my hands. These are patients who might get a response from chemotherapy that lasts a month or two but it comes right back. We have written a paper that is in press, showing that patients with advanced tumor stage disease who had failed other therapies had significant NCRs and PRs with this agent. I feel that this agent offers a new way of treating CTCL patients that is not immunosuppressive, and I would use it in any patient I felt would benefit from it, whether it is early or advanced stage disease.

DR. OZOLS: The indication says prior therapy, so what prior therapy would you use first?

DR. DUVIC: What prior therapy? Well, for early stage patients it would be patients who had failed some sort of electron beam or PUVA and nitrogen mustard. In later

patients, they have usually gone through that if they have evolved from early state. But I think it could be an earlier treatment for advanced stage patients who have failed conservative treatments.

DR. OZOLS: Well, would you give them interferon first and chemotherapy first or not?

DR. DUVIC: Well, I think that the symptoms with interferon are very similar to the symptoms with $DAB_{389}IL-2$, and if they had a large tumor burden, I think that the $DAB_{389}IL-2$ -- it is my feeling that it would clear them more rapidly than, say, interferon but it is just a feeling or clinical impression at this point.

DR. SWAIN: I have another question regarding this. What about the stage IV patients? None of those responded.

DR. DUVIC: No, that is not correct. The lady that I showed you, the Hispanic woman had Stage IVa disease with huge lymph nodes, blood and skin involvement, and she had a 68% reduction in her tumor burden, and had a PR that would have been longer lasting, except that she was asthmatic and had shortness of breath in the last course that I gave her. If I could have used steroids she would have continued on therapy and I think would have gotten even a better improvement. So, my IVa patient responded beautifully.

DR. SWAIN: So, it is 1/10.

DR. DUVIC: No, there are other patients. We can show you response by stage, if you would like to see that. We have a response by stage slide.

[Slide]

Here is the response by stage at the 2 dose levels. You can see that we had PRs in both doses for the IVa patients, and a CCR, complete clinical response, in 1 IVa patient. This is really impressive. I mean, IVa patients are difficult patients.

[Slide]

Here are all of the responders by stage again, both dose levels.

DR. SWAIN: Thank you.

DR. MARGOLIN: I am impressed by the organ system toxicities and the resemblance of these syndromes to patients that some of us have seen receiving high doses of exogenous IL-2. I wonder about the other concomitants of the presence of IL-2, such as eosinophilia and whether you see that with the disease, or whether you can distinguish that and, as part of that question, whether these CTCL patients are endogenously producing a lot of IL-2 from their disease during the proliferative stage of their disease, and/or whether with cell death and tumor lysis during this therapy you see release of endogenous IL-2 in vastly greater

proportions than the exogenous IL-2 effect from the DAB_{389}IL-2.

Then the second part of that question is what effect would you expect from steroid in abrogating response and/or toxicities. Several of you have mentioned several times that if we could only give steroid, dot, dot, dot.

[Laughter]

DR. KUZEL: I will try to take those in order if I remember them. I mean, I think those of us who use high-dose IL-2 for renal cell melanoma, we don't do it as an outpatient and it is a huge difference. There is certainly some overlap in the types of side effects and adverse events that we are talking about today, but certainly in terms of the toxicity compared to high-dose IL-2 with inpatient administration and intensive care unit monitoring often, there really is a difference. So, I am not sure that it relates to the kind of things that you see going on with the secondary cytokine cascade associated with IL-2.

Eosinophilia is problematic in terms of trying to monitor for similarity with IL-2 simply because such a high proportion of these patients actually have eosinophilia as part of their disease process. So, that becomes difficult, unfortunately.

I am trying to remember some of the other --

DR. MARGOLIN: Just to clarify, I wasn't trying to

say that this is toxic like high-dose IL-2. It was more a question of mechanisms.

DR. KUZEL: Okay. In terms of mechanisms, I mean, I personally think that obviously secondary cytokine release and the proliferation of the lymphocytes results in some of the toxicity with high-dose IL-2 or IL-2 in general. The mechanism of this drug, although it targets the receptor, literally within half an hour to an hour results in inhibition of protein synthesis and cell death. So, secondary cytokine cascade issues really should not be operative in the setting of the patients' lymphocytes that we are targeting. Since so many fewer other cells have actually IL-2 receptors in the resting state, we really shouldn't be targeting those as well.

DR. DUTCHER: And the third part was whether you think steroids will have an effect on response.

DR. KUZEL: Thank you for reminding me of that part. Obviously, steroids are a very bad thing with IL-2 because they block the effect, but they block it probably by blocking the secondary cytokine cascade. Actually, as we have talked over the last few days, at least with Paul Bunn and Madeleine, the feeling is that steroids would probably actually block some of the side effects and make the drug a little easier to give, and there is really nothing that would lead us to think we would be inhibiting the effect of

the drug. But steroids have been prohibited because of the nature of these trials and the anti-lympholytic effect that steroids have. So, we don't have any data.

DR. KROOK: I would be interested whether there were patients who were excluded because their receptor CD25 was less than 20, and if you take people who clinically have CTCL how many people were excluded by the pathologist because it was lower? This becomes of some importance because as we see these people, the few that there are, how do you choose? Do you simply see the disease, or does the assay have to be done? So, if we have a count on people who were excluded -- were 50% of the people excluded because of the assay or a very small number?

DR. BACHA: Approximately between 50% and 60% of the samples that were assayed would have qualified by the assay. So, you are excluding 40% to 60% of the patients.

DR. SCHILSKY: I have two questions. Since there doesn't seem to be any clear dose-response relationship, could you just explain to us a little bit further how the doses of 9 and 18 were chosen for the pivotal trial, and which dose you would propose to use for the future?

DR. NICHOLS: In terms of choosing the doses for the pivotal trial, I would just remind you that in the 01 Phase I/II study we identified 27 mcg/kg/day as the MTD.

DR. SCHILSKY: What led you to define that dose at

The first one was a healthy volunteer, bioequivalence study that was done because the formulation was actually changed midway through the development of this product from a phosphate-buffered drug to a citrate-buffered drug. This study was a parallel group design where all volunteers received 6 mcg/kg/day on a day 1-5 course, and concentrations of $DAB_{389}IL-2$ were measured on days 1 and 5.

The second study, what you have heard already about from the sponsor, was a Phase I/II study in patients with CTCL or lymphoma who received dose escalation courses from 3031 mcg/kg daily on days 1-5, and courses given every 3 weeks for up to 8 courses. Concentrations of $DAB_{389}IL-2$ were measured again during course 1, on days 1 and 5, and also in 3 patients in the trial concentrations were determined on course 3, days 1 and 5.

The final study that we will talk about this morning is the data from the Phase II/III pivotal study which, again, was in all patients with CTCL and, as you know from this morning, the 2 doses studied were 9 mcg/kg/day or 18 mcg/kg/day, given days 1 through 5 every 3 weeks for up to 8 courses. Concentrations were measured in a subset of these patients during courses 1 and 3 on therapy days 1 and 5. So, we will discuss each in succession.

[Slide]

The first study I mentioned was the bioequivalence

the MTD since there doesn't seem to be any dose toxicity relationship?

DR. NICHOLS: I am going to ask Tim to answer that question and then we will move on to answer the rest of the question.

DR. KUZEL: At 31 mcg/kg fatigue was the maximum tolerated dose defining toxicity. So, it occurred so frequently, actually, at that level that the previous level was defined as the MTD.

DR. NICHOLS: Just one other quick comment and then I am going to pass it to Dr. Bunn also to respond to this question. In that dose escalation study, above 19 mcg/kg/day we saw some renal effects. So, that is how we set the upper dose.

Then, in discussions with the Agency, actually, there was a recommendation that we include a lower dose. Given the nature of this patient population, we felt it was ethical to pick a dose that we thought could have an impact, and our animal studies had suggested that you needed at least a 2-fold difference in order to see any kind of difference. So, that is how we bracketed the range for the pivotal. Dr. Bunn?

DR. BUNN: The study design actually was partly to show if there was a safety difference between the two, and there was no any safety difference between the two. So, the

question is what you would to in practice. You know, I am kind of practical. I would like to have the opportunity to have both dose levels available to me. If I had a patient who was young and had a high tumor burden where the response seems to be higher with the higher dose, I would certainly use the higher dose. If I had an 80-year old with not too much tumor burden, I would probably pick the lower dose. Since there are no statistically significant differences, my own belief is that we ought to have the option as physicians of picking both. It is kind of like, you know, for taxol, you use 135, 175, 250. You know, as physicians, fortunately, we have the option and I don't see any reason not to have the option here.

DR. SCHILSKY: There don't seem to be good dose-relationships there either. So.

[Laughter]

DR. BUNN: I would like to ask Dr. Simon a question because this is intriguing to me. Actually, we have three committees here, Dermatology, ODAC and Biologics. There is an interesting issue which hasn't come to the fore too much. That issue relates to accelerated approval or actual approval for the drug. That relates to whether there is any net clinical benefit to the patient from the response. These patients had objective responses. One of the questions is does it mean anything?

DR. DUTCHER: Paul, I think we just want to finish questions to the sponsor right now. We can save that for the discussion

DR. BUNN: Okay.

DR. SCHILSKY: Can I ask my second question? My second question was whether anyone could comment on the mechanism of the hypoalbuminemia.

DR. DUTCHER: Dr. Sausville wants to comment.

DR. SAUSVILLE: This is very typical. These phenomena are seen in ricin toxin trials, pseudomonas toxin trials, and I think the business of making the distinction between hypoalbuminemia and vascular leak syndrome is artificial. I think it is part of a continuum. With these concentrations of drug lysin would cause pretty much the same degree of hypoalbuminemia.

DR. SCHILSKY: Do you think the hypoalbuminemia results from a decrease in albumin synthesis, or do you think it results from a leakage of albumin into the circulation.

DR. SAUSVILLE: Leakage. And, it has been very clearly shown in endothelial cell cultures that there is a non-targeted phenomenon for many of these toxins, inducing transudation of macromolecules. So, I feel very comfortable that actually steroids will probably be not very useful in addressing that toxicity. They may be quite useful if there

are allergic phenomena related to the neutralizing antibodies.

DR. BERGFELD: I had a question way back, and my question was to define the infection rate. I heard two sides of this, and being a dermatologist, I personally am aware of the cutaneous lymphoma problems, but in the patch and plaque state infection is really not a problem for us. I would like to mention that anything with scales on the skin carries staph. So, it can be psoriasis, it can be anything. It doesn't have to be an alteration of the barrier. So, people with disseminated scaling diseases have a lot of staph on their skins. This can be removed by just washing, by the way.

[Laughter]

But I would like to you address is infection a true result and adverse reaction to this biological, active new drug?

DR. DUVIC: Absolutely not. I have done a study that was published in Blood in 1997 that catalogs the incidence of staph in virgin MF patients wo arrive in my clinic, and 75% of patients with CTCL have staph culturable from their skin or blood; 10/12 photopheresis patients got staph sepsis during one study.

When patients get redder with CTCL they are infected with staph, and I have put many patients who have

Sezary syndrome in the hospital for IV vancomycin and seen a reduction in their skin burden. They clear up. Staph is an integral part of this disease. There may be some host-related inability to handle staph or to react more violently to super-antigens. I don't think this drug has anything to do with staph infections. It is part of the disease.

DR. BERMAN: This is again, Dr. Nichols, a clarification again on the receptor antibody data and positive and negative patients. It seems that you excluded from this study about 50% of all patients because they are IL-2 receptor negative, and we all understand the limitations with the assay and recognize the variability in patients, even among one patient's different samples. The question is do you really have any data on the IL-2 receptor negative patients and their response, or is this addressed in what you were saying about your rollover studies? Are there patients actually entering the study who don't have receptor positivity based on your assay?

DR. NICHOLS: No, not at this point in time. We don't have any data in receptor-negative patients with this assay.

DR. SIMON: I have two questions. One, is there any possibility of looking, or have you looked at the relationship between quantitative receptor level as obtained from your assay and either clinical characteristics or

response to the drug? That is my first question.

The other question is could you clarify the objectives and status of study 11, which you have not described?

DR. NICHOLS: Dr. Bacha will answer the first part.

DR. BACHA: Patients were defined as whether they had 20-50% of their cells expressing CD25 or 50 or greater. So, that is as close as we do to an analysis. Over approximately 80% of the patients fit in the 20-50%. We did look at an analysis to see if patients who had greater than 50% expression had a higher response rate, and it did not correlate. We did not do further analysis in terms of any other characterization. So.

DR. NICHOLS: In terms of the ongoing study, patients have to have received three or fewer prior therapies, and their stage is 1-3. So, there is some overlap in stage, but the intent was actually to create mutually exclusive populations based on the number of prior therapies in the two studies.

DR. SIMON: And what is the status in terms of when you expect to complete that study?

DR. NICHOLS: There are 73 patients that have been enrolled. The design is 3 equally balanced arms, 40 patients per arm; low and high dose, the 9 mcg/kg/day and 18

mcg/kg/day, and a placebo arm. It is actually accruing quite slowly. There have been lots of concerns from investigators about placebo even in the earlier stage patients.

DR. SCHILSKY: I have one other question that came to mind. You showed us some slides in the sort of the quality of life portion of the presentation where patients were assessing their skin and extent of pruritus. You showed us slides for responders where all the lines were going down. Do you have some of those slides for the non-responders?

DR. NICHOLS: Dr. Lavin? I hoped someone would ask that question, I would add.

[Laughter]

[Slide]

DR. LAVIN: What we did, we created some box and whisker plots here to show the displays of the impact of the response from the patient's perception. Pruritus is on the top right. That was measured with a visual analog scale, and the units on that are basically going down. Minus 2 represents a 20 mm improvement. So, this line, across here, represents a target threshold of what represents clinically meaningful. A week ago we were on the phone with Pat Keegan, trying to define prospectively what represented a meaningful change.

So, here we have the progressive disease patients; here we have the stable; here we have the partial responders; the CCRs; and the CRs. These numbers, here, correspond to the best response that was obtained by the patient, and these values, here, represent the distribution of the outcomes for pruritus within each of those categories. So, we had 27 patients whose best response was a partial response, and this represents the pruritus distribution at that point in time.

Attention should be given to the blue squares here. So, it starts out with a 3-unit worsening for pruritus, going down to pretty much not much of a change for the stable patients, to a 20 mm improvement for the partial responders, to a 40 mm improvement for the CCRs, and back to a 30 mm improvement. So, I guess you will agree with me that there is a relationship, a positive benefit that is experienced by these patients with pruritus in terms of better outcomes for those who have the response.

The same story holds for the global skin measurement that represents the minus 2 being the worsening, much worse, zero being no difference, and 1 -- anything below that representing a meaningful gain.

So, from the patients' perception we have at least half of the population, mainly the responders in particular, experiencing a nice gain, a nice benefit from the therapy.

DR. VOSE: In many of the other biologics we see interesting effects where there are some delayed responses to the therapies. Could you tell me what percentage of patients had an early response versus a delayed response that may have an effect for subsequent therapies?

DR. DUVIC: We have a slide of that, and we were quite interested to see that a number of our patients had responses out at 5, 6 7 and 8 courses. So, even though the majority of the responses occur during the first 2 courses, there are patients who have a slower response.

I would also like to say that 2 patients who had early withdrawal for acute adverse events when on to have 70% and 100% reduction in their tumor burden. Although they had an undocumented response, it was a clinically significant response, nonetheless.

[Slide]

So, this is the time to first response by course, and the first 2 courses have the majority, but there are responses that go all the way out. So, this would argue for prolonged dosing in some patients.

DR. SANTANA: So, how do you decide that because in the pivotal trial the intent was to give 8 cycles but the majority of patients did not get 8 cycles. So, how do you make that distinction? What is the recommendation? That you should at least give 2 courses and if there is no

response those patients should be treated with alternate therapy?

DR. DUVIC: No, I think that to know whether or not a patient is going to benefit you have to be out at 6 or 8 courses to know for sure, based on what we saw in this pivotal trial.

DR. BUNN: Can I say one thing? I mean, I think that's time to first response; it is not time to best response. Some of the patients, as you saw earlier, who had a PR on the first or second course became CRs in subsequent courses. It is like interferon, the patients that I showed you earlier. There may be a PR earlier but they are going to continue to respond over time, and I don't think we know the optimal duration but certainly there are people who respond early who keep getting better over time.

DR. VOSE: Just as a slight addition to that, it patients had other therapy after this, if they had a delayed response maybe it was a synergistic effect?

DR. NICHOLS: I can tell you that this is not all patients but of the 21 responders, 19 patients had 8 or more courses -- a couple of extra courses were allowed if they were continuing to evolve responses, and 2 had 6 courses. So, that gives you a sense at least in those patients.

DR. KUZEL: I think I would like to address both the questions. I mean, response was really sort of a

spectrum. Patients don't get 2 cycles with no change whatsoever and then spontaneously, instantly turn to a PR. Obviously, just like with other cancers, there is a gradual shrinkage until we get to that magical 50% that we like to call a PR.

So, I think with the question of how do you know whom to keep treating, I think you know whom to keep treating because those are patients who are evolving a response as you are watching.

The second question as to longer-term follow-up, actually, follow-up wasn't mandated once patients had their exit visit from the study, and there was no particular mandated subsequent therapy since many of these patients had such heavy pretreatment already. So, it is really a wide mixture of patients going into either literally the spectrum of hospice to probably a half dozen other kinds of therapies. So, there are no data in terms of synergistic benefits after treatment that can really be pulled out.

DR. VOSE: Thank you.

DR. DUTCHER: Dr. Sausville? And, this will be the last question.

DR. SAUSVILLE: Dr. Kuzel, that issue of response, in that figure that was shown on the people who got out to 8 course, am I to understand that getting out to 8 courses there was some sense of clinical benefit; they just didn't

formally meet the response criteria?

DR. KUZEL: Yes.

DR. SAUSVILLE: So, really you are saying that you treated somebody with what we might call a minor response or a biological effect.

DR. KUZEL: Right, and minor response is a term we don't use but biologic effect or anti-neoplastic effect was probably evident in those patients.

DR. SAUSVILLE: Right, and as real final question, to follow-up on --

[Laughter]

-- on what I think is a very important issue that was raised by Dr. Ozols, your proposed package indication says "persistent or recurrent despite prior therapy." I ask the clinicians in the room who are working with this, do we feel comfortable with an early stage patient who has a projected survival of, say, maybe 10, 12 years after even failing their first trial, putting them on this mediation that might have a notable incidence of things like vascular leak and neurologic findings? How do we feel we should qualify the issue of prior therapy here?

DR. NICHOLS: We will have Dr. Kuzel, Dr. Duvic and Dr. Bunn answer.

DR. KUZEL: The ongoing placebo-controlled trial allows no prior therapy for early stage patients, and

includes patients with Ia disease with no prior therapy being treated, and institutional review boards have routinely accepted it and the investigators have accepted it. Accrual is slow, as was noted. I think probably more so because of the placebo arm rather than because of the active treatment arms. So, I think it is acceptable to both investigators and patients. Do I think that patients routinely are going to go to systemic therapy with this drug for routine early stage disease? No, and the reason isn't necessarily the toxicity issue, it is more of a convenience issue. I think it is easier to do topical nitrogen mustard at home or PUVA periodically for early stage patients. I think patients will get previous therapy, whether it is in the package insert or not, before they get exposure to this drug in most cases, and especially with early stage disease.

DR. BUNN: It is the same for early stage patients. I have used topical therapies first. The question is when you need systemic treatment, what would you do? I certainly would use this ahead of combination chemotherapy. The question is would I use it before or after interferon. Probably in the beginning after interferon because I have a lot of experience with interferon, but I would certainly use it before chemotherapy.

It is a difficult labeling issue because, you

know, how many is enough? And, that is a tough issue. Certainly more than some; certainly less than what was required for this trial.

DR. DUVIC: I agree.

DR. DUTCHER: All right, thank you. We are going to take a 15-minute break. We are a little behind but that is okay. Be back here at 10:45.

[Brief recess]

DR. DUTCHER: If everyone will take their seats, we are going to get started. We are going to proceed with the FDA presentation. Dr. Trapnell?

FDA Presentation

DR. TRAPNELL: Thank you, Dr. Dutcher.

[Slide]

Members of the Advisory Committee, I am Dr. Carol Trapnell. I am a clinical pharmacologist in the Division of Clinical Trial Design and Analysis, in CBER, and I am going to give you just a few minutes of a perspective from the clinical pharmacology side on the application being considered this morning.

[Slide]

First of all, the company submitted actually several clinical pharmacology studies but I am only going to focus this morning on three of them.

[Slide]

study in healthy volunteers and, as I mentioned, the study was done to assess whether the 2 buffered products were bioequivalent. Just to make note, the citrate-buffered product is the one that is being considered for approval today.

In a nutshell, the results of this study really do not need to be considered for this indication because the pivotal study treated all patients at all times with the citrate-buffered product. But I just wanted to note, because this will be something that we will talk about later, that in this study with 1 course of therapy no patients developed antibodies to the drug that were measured.

[Slide]

This is data from the next study that I mentioned in my introductory slide, which is from the Phase I dose-ranging study in patients with CTCL or lymphoma and, as you can see from the course 1, day 1 data on this plot, the plot is the dosing cohort on the X axis versus the $DAB_{389}IL-2$ AUC measurements on the Y axis. A nice dose concentration response that seemed to be proportional to dose was observed.

It is important to note that the measurements on day 5 of course 1 were essentially identical to these numbers. So, there was really no change in the

pharmacokinetics from day 1 to day 5 of course 1 of therapy.

[Slide]

This is data from one of the patients of the three who had pharmacokinetic assessments done during both course 1 and course 3. As I mentioned, only three of these patients in the Phase I study had this kind of assessment done. The solid circles are from course 1, day 1 assessments, and the dotted lines with the open circles are from the course 3, day 1 assessments.

What we are plotting here on the X axis is time, on the Y axis is $DAB_{389}IL-2$ concentration. As you can see from this plot, I think it is pretty clear that after the first course, which gets a nice kind of elimination curve, compared to course 3 there is a significant change in the exposure of $DAB_{389}IL-2$ that is seen by course 3. Again these patients had concentrations measured at day 5 of both courses. If you put those curves on top of each other they look identical. So, by course 3 the pharmacokinetic profile, at least in this one patient, has changed compared to course 1.

[Slide]

Despite these finding, and again it was in a very preliminary number of patients, the company proceeded to do a Phase II/III trial looking at 2 comparative doses in patients with CTCL. I am going to focus my discussion now

on the findings from that study from a pharmacokinetic perspective because I think it will answer some of the questions that were raised by the Committee in the earlier question and answer session.

[Slide]

This slide represents the data from course 1, essentially day 1 and day 5 because, again, when you look at the 2 separately they really were identical. The open circle curve represents the data from the 18 mcg/kg cohort and the closed circle curve represents the data from the 9 mcg/kg cohort, and what we are plotting here again is time on the X axis and $DAB_{389}IL-2$ concentration on the Y axis.

As you can see on this particular slide from course 1 of therapy, there really is what I would say a nice dose concentration response that is linear, so that the higher dose clearly gets a higher response that really is probably pretty dose proportional. So, at this point I think we can be confident that with course 1 we really are administering 2 different doses that give 2 different exposures to the drug.

[Slide]

However, by course 3 of the therapy we have a whole different pharmacokinetic picture. Again, we have time on the X axis and $DAB_{389}IL-2$ concentration on the Y axis. This is the same scale as the previous scale to try

and draw the comparison on the differences.

I think it is safe to say that by course 3 the dose concentration proportionality has been lost, and the concentrations that have been achieved by the doses being given are markedly decreased compared to the first course.

[Slide]

This shows the same data in numeric form. I did not, on purpose, put in the standard deviations because it would have made the slide too busy, but I think the company showed that in their presentation and, as you saw earlier, there was a significant inter-individual variability for reasons that aren't really clear and were not really investigated.

But, again, in a numeric sense, looking at course 1, day 1 and the 2 dosing cohorts, there was a significant dose response, as the graphic data showed, that was essentially lost in the course 3, day 1 data which, again, is representative of the course 3, day 5 data.

The half-life, which is about 80 minutes with the first course, drops to about 40 minutes with the third course, and that is because the clearance essentially doubled. It went from about 2 mL/kg/minute to about 4 mL/kg/minute.

[Slide]

Now, the question, of course, is what is happening

here? Why is this changing and what can we understand about this? It turns out, as has already been mentioned, that there is significant and essentially consistent antibody formation against the $DAB_{389}IL-2$ therapy. Most of the patients at course 1, which is really their baseline assessment, had a low level of anti-$DAB_{389}IL-2$ antibodies, a titer of about 1:5, and this shows with this antibody titer at the 9 mcg/kg/day cohort and the 18 mcg/kg/day cohort, again, the AUC that is plotted on the Y axis is different and proportional to this. However, by the third course the antibody titer averaged about 1 to 3000 and, again the AUCs were markedly lower and the dose response has essentially been lost.

[Slide]

So, in conclusion, I would like to say that it appears that the pharmacokinetics or this product are significantly altered by the formation of anti-$DAB_{389}IL-2$ antibodies, which seem to be formed pretty uniformly after the first course of treatment. The course 1 pharmacokinetics, as I said, are dose proportional. The course 3 pharmacokinetics have lost their dose proportionality, and we do not have any data from subsequent courses of this therapy to understand if there are further alterations in the pharmacokinetics of this product.

There were no data submitted that assessed what

concentrations of $DAB_{389}IL-2$ are actually necessary for clinical effectiveness. It is very possible that the hypothesis could be that the lower levels that are seen with the subsequent courses are, in fact, sufficient to get a clinical response. It is also possible that, another hypothesis, that the high levels that were obtained with the first course combined with the lower levels seen with subsequent courses are also what is necessary for a clinical response. There are all sorts of other possibilities you could think of to try to understand how this drug is actually working to cause a clinical effect.

I think it remains uncertain, at least in my mind, what does and/or drug exposure should be recommended for the effective treatment of CTCL. I think there are certainly possibilities for further study. There could be some very nice information, I think, that could be got perhaps on computer modeling of the pharmacokinetic-pharmacodynamic information that is obtained and present in the Phase III trial to try and better understand what actually may be the effective regimen. We could also recommend some other therapies, or other models, or other doses for future study based on this information.

With that, I would like to introduce Dr. Bernard Parker to present the clinical overview and then we will both take questions after his presentation is finished.

Thank you.

Clinical Overview

[Slide]

DR. PARKER: These are the 4 trials that were performed to evaluate $DAB_{389}IL-2$ efficacy. The 2 completed studies that we reviewed are shown here, first the Phase I study, 92-04-01, which is a dose-escalation study and 73 patients had been entered. These patients had to have recurrent stage I-IV lymphomas which included Hodgkin's disease, non-Hodgkin's disease, and CTCL. Finally, the Phase III study, 93-04-10, which is a randomized, double-blind study. There are 71 patients that were enrolled in it. These patients had recurrent stage Ib through IVa CTCL. The safety data for these 2 ongoing studies have been sent for us to review, but as far as efficacy, we are reviewing these 2 studies, first starting with the Phase I.

[Slide]

The Phase I study design was a multicenter, open-label Phase I dose escalation. Eligibility, again, lymphoma patients of non-Hodgkin's type, Hodgkin's disease and CTCL. These patients had to express p55 or the p75 IL-2 receptor subunit. They had to have failed standard therapies and the Karnofsky performance status had to be greater than or equal to 70%.

[Slide]

The treatment was consisting of being randomized with one of the doses between a range of 3 mcg/kg to 31 mcg/kg of the citrate equivalent doses. At least 3 patients were in each cohort, and there were 9 dose levels. This was given as an IV infusion over 15-60 minutes daily for 5 days, with a 2-week observation, for a maximum of 6 cycles. The endpoints for the study were the maximum tolerated dose and the response rate.

[Slide]

There were 73 patients that were enrolled in this study, 38 of which were non-CTCL and 35 of which were CTCL patients. There were 20 patients that completed the study, or 27% completed the treatment. The major reasons for study discontinuation were disease progression at 51% and for adverse events at 16%.

[Slide]

There were 21 patients enrolled with Hodgkin's disease, 35 with CTCL and 17 patients with non-Hodgkin's lymphoma. The CTCL patients were well distributed by stage when compared with those patients with Hodgkin's disease and non-Hodgkin's lymphoma. Those patients, as you see, had more advanced stage upon enrollment. Additionally, these same patients, as noted down here, were more heavily pretreated when compared with the CTCL patients. The mean age for CTCL was 61 years of age, and most patients were

male.

[Slide]

The CTCL patients were well represented also for the dosing, as you can see. The citrate equivalent doses are emphasized here for consistency, although two-thirds of the patients were treated with the phosphate-buffered therapy also.

[Slide]

The maximum tolerated dosage was 27 mcg/kg/day for 5 days. Four of the five patients in the 31 mcg dose group withdrew due to adverse events. The dose-limiting toxicities in this Phase I study were nausea, vomiting, fever, chills and asthenia. Doses that were greater than 19 mcg were not well tolerated. This was reflected in the doses that were used in the major protocol that will be discussed later, as well as in the subsequent Phase III ongoing studies.

[Slide]

There was a 37% overall response rate. When looking at response rates by the stage of CTCL there appears to be a trend towards an improved response rate for those patients that had earlier stage diseases, as you can see here. The percentage of patients with the complete responses was 14% for the complete response rate. The complete response rate consisted of those patients that had

CRs and CCRs which were clinical complete responders. We will discuss those later.

[Slide]

The safety data -- 100% of the patients had at least one adverse event. Treatment had been discontinued in 12 patients and the doses had been modified in 12 patients due to adverse events. Twenty-four patients were reported to have serious adverse events and 2 patients died within 30 days of the study drug.

[Slide]

For the Phase III study the design was as follows: It was a multicenter, blinded, randomized 2-arm study that was stratified by stage. They were less than or equal to IIa versus those that were greater than or equal to stage IIb.

For eligibility, those pats with stages Ib through III for CTCL had to have at least 4 previous therapies. For those patients with stage IVa, those patients had to have at least 1 previous therapy. These patients had to have progressive disease. Their disease had to be evaluable in skin, blood and/or lymph nodes, and those patients that had been treated with previous $DAB_{389}IL\text{-}2$ therapy were not eligible.

[Slide]

The IL-2 expression was measured in the following

way, the skin and peripheral blood had been screened for the CD25, which is the interleukin-2 receptor alpha subunit. So, when this was screened, in the end there were 345 skin biopsies screened from 310 patients, with 32 patients actually having multiple specimens. And, 210 of the biopsies had greater than 20% CD25 positive cells; 30% had less than 20% CD25 positive cells expressed; and only 7 % of the samples were CD7 positive. This was measured because activated T cells also see to have expression for the CD25. The assay was insensitive to the level of receptor expression.

[Slide]

All patients were required to have pretreatment medicines. The $DAB_{389}IL-2$ was given at either 9 or 18 mcg/kg intravenously over 15-60 minutes per day for 5 days, with a cycle length of 21 days, and the planned course was 8 cycles.

[Slide]

The endpoints were as follows: The primary endpoint was overall response rate, specifically pooled but also within specific dose groups. Secondary endpoints included response duration; complete response rate which, again, was complete response plus complete clinical complete responders; time to treatment failure; symptom improvement; quality of life and pharmacokinetics .

[Slide]

The prespecified supopulations were as follows: They had an intent-to-treat population which were registered and randomized patients. There was an efficacy subpopulation. Those patients had to have had at least 1 dosage of the $DAB_{389}IL-2$. Finally, the evaluable efficacy population, which was patients that had at least 8 cycles of the $DAB_{389}IL-2$, that met all eligibility criteria. They had no concomitant anti-neoplastic therapy and they were assessable for tumor response.

[Slide]

The primary endpoint was overall response rate, and the response rate was stringently addressed by this independent committee, called DERC committee, the Data Endpoint Review Committee. The DERC consisted of 5 physicians, divided into 2 teams, each team having 1 oncologist and 1 dermatologist. There was also 1 referee who was a dermatologist. The data for all patients were reviewed by the DERC, and the primary endpoint was based upon the tumor response assessment by DERC.

[Slide]

The response definitions are as follows: Complete response are those patients that had no clinical evidence of disease and no tumor on biopsy. Those patients with complete clinical response had no clinical evidence of

disease but had tumor present on biopsy. Finally, partial responders were those patients that had at least a 50% reduction in tumor burden. All responses had to be durable for greater than or equal to 6 weeks.

[Slide]

The tumor response assessment for CTCL was as follows: The percent change of the tumor burden was to equal the average of the percent change of skin, plus percent change of nodes, plus the percent change of blood.

I just want to mention that this is expressed as a percent change from the baseline. For those patients that had nodal involvement, those patients that had this measurement done had to have at least an LN3 stage for the lymph node, which means that they had to have the enlarged nodes with large clusters of convoluted cells, greater than or equal to 6 clusters. For the blood involvement, for those patients with blood involvement, those patients had to have greater than 20% circulating abnormal lymphocytes present. This was evaluated by 2 assessors per study site, and subsequent assessments were performed 3-6 weeks apart.

[Slide]

Among the supportive measurements we focused on the following: The patient's pruritus visual analog scale. We also focused on rescue medication usage. There are 4 medicines that were looked at, Aveeno oatmeal bath; the

Atarax, hydroxyzine at 25 mg tablets, Eucerin cream and Aquaphor cream.

[Slide]

There were 30 patients that completed this study, or 42% of the patients completed. The major reasons for study discontinuation in this Phase III study were as follows: Adverse events at 37% and disease progression at 11%.

[Slide]

There were 71 patients enrolled, and these patients were randomized evenly among the 2 dose groups. This was already discussed by the sponsor, and the racial distribution in this study is consistent with the racial incidence in the general population with this disease.

[Slide]

There was a predominance of patients with skin only disease, as mentioned here. We have 78% with skin only disease. These patients were also evenly distributed within both dosing groups. Approximately 82% of these patients with skin only disease had less than 10% body surface area involved versus 18% for those with greater than 10% body surface area involvement.

The median duration across all groups is 4.7 years, and I also need to mention that the number of prior treatments for both treatment groups was heavily noted

within the greater than or equal to 4 prior treatments.

[Slide]

There were 21 responders out of the 71 patients enrolled, which led to an overall response rate based on DERC assessment at 30%. The median response duration was 4 months, and within this group there was a 10% complete response rate noticed, with a median duration of 9 months.

[Slide]

This slide shows that the responses were seen at every stage. There was no clear dose-response rate relationship. There is a trend toward higher responses in patients that have less diseases, as noted here, with Ib having 44% and IIa having 30%.

[Slide]

Unlike the response by the dose slide that you saw previously, this response by stage demonstrates that 35% of the patients with skin only disease were responders, that is 19/55 patients. There is some suggestion of a dose-response relationship between 9 and 18 but the numbers are too small. Additionally, there were response within the high-dose group noted with patients that had lymph node and blood involvement but, again, the numbers are very small.

[Slide]

This slide shows the DERC response rate by study sites. I just want to mention that at every site listed

there was at least 1 response noted in each. These are the study sites that had at least 5 patients enrolled. So, there was at least 1 response noted in each.

[Slide]

The populations analyzed -- for the intent-to-treat population the number was 71, and all of these patients had ultimately received at least 1 cycle of $DAB_{389}IL-2$. So, they were all in the efficacy population. Finally, for the evaluable efficacy population -- well, 30 patients completed 8 cycles of therapy.

[Slide]

Within the evaluable subset there was a 63% response rate, or 19 patients out of the 30, with 7 patients having CRs and 12 patients having PRs. Additionally, there were 11 patients with Sezary syndrome, and the overall response rate here was 9%, with 2 responses.

[Slide]

The baseline values for the secondary efficacy measures are as follows: For the PVAS, or the pruritus visual analog scale, we have the scale score being from zero, which is no itch, to 10, which is the worst imaginable itch. Also, for the rescue medicines, hydroxyzine, Agaphor, Eucerin and Aveeno, these were the baseline median values for the medicines and for the visual analog scale for pruritus.

[Slide]

For the pruritus visual analog score at cycle 3 when compared with baseline there appears to be no difference between the dose groups. The responders, however, tended to have improvement at cycle 3 and at the last visit. With regards to hydroxyzine use at cycle 3 and at baseline, 24 patients were listed to have 9 mcg; 21 were listed at the 18 mcg dosage level. Of the 11 patients who received the 9 mcg dosage that were not treated with hydroxyzine at baseline, 1 ultimately required hydroxyzine therapy at cycle 3 and, likewise, for the patients treated in the 18 mcg dose group, of the 9, 2 ultimately needed to have hydroxyzine therapy.

On the other hand, the 13 patients treated in the 9 mcg group that did require hydroxyzine for treatment, 3 ultimately stopped usage of hydroxyzine. The same was noted with those patients treated at 18 mcg that we have listed here. Again, for responders it seems that there was also somewhat of a trend of a better response or an improvement in terms of decreasing the amount of hydroxyzine needed.

[Slide]

For the safety analysis in this Phase III study, 100% of the patients experienced at least 1 adverse event; 55% of the patients experienced at least 1 serious adverse event. When we say serious adverse event, this means those

patients that required or that had prolonged hospitalization; those patients that developed secondary malignancies; patients that also died. So, this is the serious adverse event group. And, 37% of the patients withdrew from the study due to adverse events.

[Slide]

For the integrated summary of efficacy, we wanted to evaluate the results across both Phase III and Phase I studies. Because the DERC assessment was used in the Phase III study, the investigator data that was collected in both studies was pooled in order to evaluate the response rates for early versus late disease. Therefore, because we used the investigator response data in this case, our overall response rate was slightly higher, as Dr. Bunn observed and as he mentioned. So, here the overall response rate was at 44%, with the 93-10 Phase III study having an investigator-assessed response rate of 48%.

These data suggest a trend -- sort of a high likelihood actually of response with earlier stage disease when compared with the later stage disease, 59% in early disease and 36% in late stage.

[Slide]

The investigator-assessed response rates by dose range -- these were also pooled to evaluate the dose range to determine this and, again, there was no clear dose-

response relationship for those patients that had CRs versus PRs.

[Slide]

For the integrated summary of safety, 100% of the patients had experienced at least 1 adverse event. For the Phase III study the number was 70, 1 patient was excluded. For the Phase I study there were 73 patients. At the time of the submission of the original BLA, the safety data for ongoing studies, that is 93-04-11 and 93-04-14, had not been completed. Therefore, most of the safety data that will be presented next will be derived from the completed studies. Let me just add that 39% of the patients experienced grade 3 adverse events and 30% experienced grade 4 adverse events.

[Slide]

The major events that occurred will be discussed in the following order: Constitutional symptoms, gastrointestinal events, infections, hypersensitivity reactions, vascular leak syndrome, cardiovascular events and rash.

[Slide]

I need to mention that the Phase III study specified the use of premedications in order to try to avoid many of the constitutional or flu-like symptoms, and 91% of the patients reported having these flu-like syndromes and they consisted of one or more of the following, chills/

fever, asthenia, headaches, myalgias and arthralgias. Fever/chills and anorexia occurred -- there were 10-15% that had at least grade 3 toxicity, and the use of anti-pyretics and anti-emetics did not really help to resolve this problem in which the constitutional symptoms occurred.

[Slide]

Eighty-three percent of the patients reported having gastrointestinal symptoms, 55% having nausea, 36% having anorexia, 34% having vomiting and 29% having diarrhea. A smaller proportion ended up having at least grade 3 toxicities from each of these 4 groups. Onset was early in the treatment, and 2 patients were hospitalized for gastrointestinal symptoms; 5 patients ultimately discontinued treatment.

[Slide]

The incidence of this specific syndrome, allergic, hypersensitivity-like reactions, is not known. But it is characterized by the following constellation of symptoms: dyspnea, back pain, chest pain, chest tightness, hypotension, rash and tachycardia. This occurred during or within hours of the infusion. It was more common during the earlier cycles but was also reported during cycle 6 and 8. This was treated by either decreasing the infusion rate and/or use of antihistamines, corticosteroids and epinephrine. Five patients were reported to have at least a

grade 3 toxicity, and 4 of those 5 patients had ultimately withdrawn from treatment.

[Slide]

There were 3 major cardiovascular events that were reported in this integrated safety summary. Vasodilation was one that was reported in 22% of patients; 1% of the patients had grade 3 toxicity; tachycardia was also reported in 12% of the patients, with 1% having grade 3 and 1% having grade 4 toxicities. Actually, 1 patient discontinued treatment with tachycardia present.

[Slide]

Hypotension was reported in 32% of the patients, of 143 patients, with 4% having grade 3 toxicity, and 1% having grade 4 toxicity. One patient had to discontinue therapy and this hypotension was a manifestation, actually, noted in 2 syndromes. What we noticed was the hypersensitivity-like or the allergic reaction, and the second being the vascular leak syndrome.

[Slide]

Infections were reported in 48% of patients. There were different types of infections, and 21% of the patients had unspecified infections, and within that unspecified group 10% had at least a grade 3 toxicity. Other infections noted were urinary tract infections, sepsis, herpetic infections, pneumonia and cellulitis.

There are 6 patients that discontinued therapy due to the infections.

[Slide]

For the skin adverse events, 60% of patients reported cutaneous events, with rash being reported in multiple categories. These were characterized as either unspecified, 24%, maculopapular, 14\3%, petechial, vesicular or urticarial type. Symptomatic treatments included the use of topical agents, antihistamines and corticosteroids. Additionally, 20% of patients reported pruritus.

[Slide]

The vascular leak syndrome was defined as at least 2/3 symptoms in the triad of hypotension, edema and hypoalbuminemia. The vascular leak syndrome was reported in 24% of patients, with 8% of patients reporting with the complete triad of symptoms. Six percent of the patients were hospitalized, and 7 patients actually discontinued treatment due to VLS.

[Slide]

This is hypoalbuminemia that is being mentioned because it was one of the symptoms as part of the VLS, and 31% of all patients reported hypoalbuminemia, with 2% having grade 3 toxicity, 4% having grade 4 toxicity, 1 patient being hospitalized, 5 patients discontinuing treatment, and the onset of hypoalbuminemia was within days 2 through 5,

with an average time to recovery by day 18.

[Slide]

Continuing on with clinical adverse events, there were 11 patients that had thromboembolic events, with 6 patients having superficial thrombophlebitis and 3 patients having deep venous thrombosis. One particular patient had a complication of pulmonary embolism.

[Slide]

Other clinical adverse events noted were altered mental status in 8% of patients, and there was also one episode of pancreatitis.

[Slide]

For common laboratory abnormalities outside of hypoalbuminemia, we also noted that 34% of patients were observed to have elevated transaminase levels; 11% of those patients had grade 3 toxicity; 3 patients had to discontinue treatment. There was a greater frequency of this problem occurring during the first course of therapy, and elevated bilirubin levels were observed in only one patient.

[Slide]

Anemia of the hypochromic type was reported in 15% of patients, with 6% having grade 3 and 1% having grade 4. Three patients were hospitalized for this, and 1 patient discontinued treatment.

Thrombocytopenia had 8% of patients presenting,

with 1% having grade 3 and 1% having grade 4. One patient discontinued treatment. That particular patient was noted to have low white cell counts along with that.

Finally, leukopenia was noted in 6% of patients, with 2% having grade 3 and 1% having grade 4.

[Slide]

Lymphopenia was noted in 34% of patients. That is, this was grade 3-4 lymphopenia that was noticed. The onset was early in the cycle, from days 1-5, and there was a return to baseline noted by day 15. There was no change in percentage of T or B cells, although there was an absolute decrease in cell count. This was done by FACS analysis in patients on the study. There was a transient decrease in T cells which occurred within an hour of the first transfusion, and this returned to baseline by day 8 in normal volunteers.

[Slide]

The immunologic responses that Dr. Trapnell mentioned earlier, this occurred in 90% of patients after the first 2 cycles, and this was associated with a rapid clearance of drug product, as Dr. Trapnell mentioned.

[Slide]

The incidence of fever, chills, nausea and vomiting, as well as asthenia decreased in later cycles. The incidence of hypotension, infection, pain, and rash were

similar in the early and the late cycles. The assessment for toxicity, when comparing with toxicity and cycle number, was confounded by the following things, the high dropout rate, which was particularly noticed in the Phase I study, 92-04-01; the frequent use of premedications; and the immunologic response that was noted.

[Slide]

Fifty-vive percent of the patients in the Phase III study had at least 1 serious adverse event, and 32% in the Phase I study had at least 1 serious adverse event. Twenty percent of the patients were noticed in the 93-04-11 study, which is the ongoing study, and the same percentage was noticed in this particular study, ongoing.

The incidence of serious adverse events and a proportion of patients who discontinued for adverse events was similar for the 2 dose groups, 9 mcg and 18 mcg.

[Slide]

Infections are the most serious adverse event reported, and infections were reported in 17% of patients. Six patients had to discontinue treatment, and these patients had sepsis, pneumonia, endocarditis, staphylococcal infection, sinusitis, urinary tract infection and Herpes zoster infection. Ten of those 25 patients that had serious infections events had multiple episodes of infection noticed.

[Slide]

There were 17 second malignancies that have been reported in 8 patients, or 5% of the patients. Fifteen reports were of squamous cell carcinoma and basal cell carcinoma of the skin, and one report of prostate cancer in a patient that actually had skin cancer along with the prostate cancer and, finally, one other report of a patient with anaplastic astrocytoma.

[Slide]

Other serious adverse events noted were drug-induced fever at 4%, hypotension at 3%, rash at 3%, pulmonary edema at 1%, and dehydration at 1%.

[Slide]

There were 11 deaths in the 4 lymphoma trials that I have listed here. The same 7 patients that were mentioned by Dr. Kuzel will be discussed here as the deaths where the treatment may be considered as the contributing factor to the deaths.

[Slide]

First, patient coded 319, this patient was treated at 18 mcg. This was a 76-year old female who had stage IIb disease. This patient ultimately died from bacterial infection on cycle 2, day 65. This patient's treatment course was complicated by a myocardial infarction, pulmonary embolism I believe, and by vascular leak syndrome. This

patient ultimately discontinued treatment due to the vascular leak syndrome.

Patient 1102 had been treated at 9 mcg. This was an 84-year old female with stage IIa disease. This patient died from unknown causes on cycle 1, day 71. This patient's course had been complicated by bacteremia, and this patient ultimately discontinued due to hypoalbuminemia.

[Slide]

Patient 2301 was treated at 18 mcg. This was a 71-year old male with stage Ib disease, who died with coronary-artery disease in a nursing home. He died at cycle 6, day 30. This patient's course was complicated by dehydration and altered mental status. This patient also was known to have weight loss of 25 lbs.

[Slide]

Patient 2601 was treated at 18 mcg/kg. This was a 68-year old male with stage IIa disease. He ultimately died from myocardial infarction on cycle 1, day 31. This patient's course was complicated by angina, day 15 of treatment.

[Slide]

Within protocol 92-04-01 we had patient 402 who was treated at 9 mcg. This patient was a 27-year old male. That, again, was mentioned by Dr. Kuzel. He had Hodgkin's disease, who was also status post autologous bone marrow

transplant. This patient ultimately died from ARDS, acute respiratory distress syndrome, on cycle 2, day 22. This patient had an onset of dyspnea on study day 9, during cycle 2, and this patient ultimately progressed to having diffuse alveolitis and inflammatory infiltlrate. There was no indication of the infectious organism or malignancy on autopsy.

[Slide]

Patient 103, treated at 9 mcg, was a 44-year old male with stage IVa disease, had progressive disease at death at cycle 1, day 15. This patient's course was complicated by catheter-related Staph. aureus infection, by cytomegaloviral infection on day 7, disseminated intravascular coagulopathy, hyperbilirubinemia and hypoalbuminemia.

Patient 102 was treated at 6 mcg. This patient also died from progressive disease, noted at cycle 1, day 45. This was a 60-year old made with stage III disease. This patient discontinued on cycle 1, day 12 due to unresolved deep venous thrombosis.

[Slide]

So, accelerated approval will be hinging upon the following: The presence of severe or life-threatening disease, with no acceptable alternative therapy; the effect on the surrogate, as shown in adequate controlled trials,

and the endpoint must be reasonably likely to predict the clinical benefit. Finally, the approval that is contingent on additional studies which validate the surrogate endpoints is correlated with clinical benefit.

[Slide]

The ongoing study, protocol 93-04-11, has the following design: It is a randomized double-blinded study, 3-arm trial with a placebo arm, 9 mcg or 18 mcg arm. The patients with CTCL have to have stages Ia to III, with less than or equal to 3 prior therapies. The endpoints for this study include overall response rate, the complete response rate and response duration, as well as the relief of symptoms or pruritus, and time to treatment failure.

[Slide]

For the analytic plan for this study, the assumptions are of an overall response rate of 40% in the 9 mcg and 19 mcg dose groups versus 10% overall response rate in the placebo group. The sample size of 120 patients with 40 patients per arm is adequate to detect this difference at 90%, with an alpha of 0.05. Comparison of the overall response rate between the placebo and the 9 mcg and 18 mcg groups can serve as the secondary endpoint.

I would like to open this discussion now for questions.

Questions from the Committee

DR. DUTCHER: Thank you. Are there questions for the FDA from the Committee? Dr. Sausville?

DR. SAUSVILLE: This is in reference to the pharmacokinetics analysis, Dr. Trapnell. The data that you presented which demonstrated an increase in the peak concentration at the 9 mcg/kg as opposed to the 18 mcg/kg is intriguing in that it may correlate with the trend that was previously noted to a higher response rate in tumor stage disease, because with the nature of these lesions one would expect the higher penetration to be necessary. Have you or anybody else analyzed the pharmacology in relation to the responses seen in the different subgroups?

DR. TRAPNELL: No, we did not analyze that data. But I certainly agree that that is a very key analysis that we will be pursuing.

DR. BERMAN: Another pharmacokinetic question, how sure are you that the decrease in the area under the curve is directly related to the increasing level of the antibody? Did you look at urinary excretion of these? Because we have seen that the response doesn't correlate with the antibody titer. So, is it completely clear that the AUC drop is related?

DR. TRAPNELL: That is a good question. The urine was not collected for analysis. But, again, I think it is important to remember that we really do not understand what

concentrations or exposures are really necessary for any kind of clinical benefit, and even though the concentrations significantly change with the antibodies, that still may be enough to cause some response. It is just not known.

Again, I really think that this data is ripe for some really sophisticated computer modeling where you can actually enter as covariates antibody levels, clinical response values, pharmacokinetic exposure values, and then make some assumptions to see if there is any way to try and get a better handle on whether these relationships are relevant and then take that data from there for further evaluation.

DR. SAUSVILLE: Although I would point out, just as a comment, that the levels that are being achieved here are well in excess of what could cause responses in in vitro types of experiments with different cells with IL-2 receptors.

DR. TRAPNELL: Right, I agree with that, and I thin the question is are we really overdosing significantly in the first course, and could that be causing more of the toxicities? It just wasn't really well researched or well evaluated, and I think it could definitely be looked at again. I think to start off with some PK/PD modeling and then better understand what the data is trying to tell us.

DR. SEIGEL: Dr. Bergman, I would note that Dr.

Trapnell's slide suggests not only the AUC change but that the peak levels are significantly lower on the third course, including even those measured within several minutes, suggesting that it is improbable that that would be entirely due to accelerated urinary excretion or metabolism.

DR. OZOLS: Dr. Parker, in the same way that we think that many of the infections are related to the natural history of this disease, in the deaths that you reported, I mean, how many do you think adverse event really sort of drug related or actually induced by the drug, or how much are we really seeing from some very sick patients, some of them who died two months after treatment and so forth? What is your sense the relationship between treatment and deaths?

DR. PARKER: Yes, that is sort of hard for us to assess; hard for us to determine whether the drug actually in itself is responsible, but we do feel that it may contribute somehow to the death perhaps. Perhaps Dr. Keegan could --

[Laughter]

DR. SEIGEL: You need a controlled trial, I think, to know the answer to that.

DR. KEEGAN: Yes. I think it was very difficult to determine. There was also a lot of missing information. It was very difficult to assess whether or not some of these adverse events had actually resolved at any point prior to

the patient's death. The extent to which some of these deaths due to progressive disease -- some were better documented than others. I think the most disconcerting death to us was the patient with Hodgkin's disease who was status post transplant, who had clear onset of symptoms and progression of pulmonary symptoms, and while his death may have been complicated by some procedures that were performed, the onset of this toxicity preceded all of that and was progressive, you know, prior to those procedures. At the time of autopsy there wasn't an infectious organism, nor was there evidence of Hodgkin's disease in the lungs, as it was reported to us, and the temporal relationship and the progression, I think, were two of the things that made us most concerned about that patient in particular. For the rest of them there is inadequate information to tell really.

DR. MARGOLIN: I have two related questions for Dr. Parker about your choice of data to present, both of which would appear to make the drug more active and more safe than the sponsor's, in fact.

One is that you used all the patients in the Phase I study in your integrated summary of toxicities, I believe, and that would include patients at lower doses which, presumably, would mean less toxicity. You also used investigator assessments rather than the DERC assessments for your responses. So I am just curious how you would

justify those choices.

DR. PARKER: This was done just because for the Phase III the DERC assessment, the way they assessed was a lot more stringent, and there had to be a certain number of consecutive visits in order for one to call a response a response versus that of the Phase I study where the best response was listed as the response. For the DERC, we had some responses that -- you know, there were some patients that had, say, one complete response noted on a visit, but then that patient could have been lost to follow-up or any other reason. So, ultimately if that patient had three previous PRs, previous partial responses, then that patient was called a partial responder. The DERC assessment was very stringent, and the way of measuring response was not consistent with that of the Phase I. So, we just chose to take investigator responses which at least chose the best response noted, and add that in with the Phase I study responses.

DR. SEIGEL: Let me just further clarify that. We don't believe that the investigator responses are a more accurate or appropriate measure, quite to the contrary. But I think what is being said is that for the purpose of pooling the two studies to get additional power to investigate the question of response rates in early disease versus late disease, we though it was difficult to pool two

different measures of response rates, particularly for that comparison.

DR. KEEGAN: I think the other comment about safety has to do with the fact that, if anything, as you look across these data there doesn't appear to be a particularly good dose-response relationship in many events with regards to toxicity, and I think we wanted to be able to represent that, that there was really toxicity observed across virtually every dose level that was tested. While there may have been some events that were common at the higher dose levels, clearly there is toxicity well distributed across the range and, again, it gave us more information in terms of numbers.

DR. SIMON: I wish I had the same question because one thing that impressed me was that for the Phase II study there were substantial discrepancies between the DERC assessment of response and the investigators' assessment of response. So, I was also wondering why -- unless you had judged that the DERC assessment was in some way not consistent with the protocol definition, why you would have used the investigators' assessment for the Phase I trial.

The other question I have is did the FDA attempt to do any kind of statistical analysis of the relationship between partial response and symptomatic benefit?

DR. KEEGAN: We actually did responses looking at

the pooled data set because really the numbers are kind of small. So, it might have been enriched just by including the complete responders. The one thing I want to make clear about our assessment of the relationship of symptoms to response is that we could not find clear evidence that there was, in fact, an association of decreased symptoms, particularly pruritus, and of medication to use for treatment of pruritus in responders. There may have been a suggestion, some hints, but clearly there was no clear evidence that patients who responded as a group had relief of symptoms, the major one of which was pruritus.

DR. SIMON: The reason why I asked about partial responders is that for the Phase II trial, except for the stage Ib patients, for all patients other than Ib, there were 55 such patients and there were only 2 CRs. So, that is a CR rate of less than 4%. So, most of the responders, outside of stage Ib, were partial responders. So, the issue was, was there any relationship between partial response and symptomatic benefit?

DR. SEIGEL: To further expound on that, there are about 8 or 10 different measures of symptomatic benefit here -- the visual analog scale, the use of 5 different medications, and patients' and physicians' global assessment. There is not a clear, well-defined way to make that comparison and, certainly the responder-non-responder

comparison for any of them. We looked at several, obviously. The sponsor has shown you some other ones. Our bottom line I think was correctly stated by Dr. Keegan, that by including all responders, partial and complete, there is an occasional trend but we don't find anything very convincing or compelling suggesting better symptomatic response.

There are a number of problems. Some of the data you saw compared baseline to best symptomatic score on study. That, obviously, has its significant biases. There are significant problems with multiplicity. Some of the scales used had some problems, including asking people basically to compare how they were to their memories rather than contemporaneous scores of how they had been at baseline. So, it is a difficult database to make a lot of, but our conclusion at this point is that we are not persuaded that there is solid evidence.

DR. SCHILSKY: I guess I have two questions for Dr. Parker. I was a little confused by this subset analysis that you showed us where you took out the 30 patients who completed all 8 cycles of therapy, and then told us that 63% of them responded. Now, to some extent you might expect that responding patients would have a greater likelihood of completing all 8 cycles of therapy. So, I am not sure what information that provides us that is particularly useful.

It was of some interest that in the sponsor's presentation it seemed like most of the responses actually occurred after the second cycle of therapy, or by the time of the second cycle of therapy.

So, I suppose what I am asking you is since you culled out this subset, do you want to tell us anything about what the response rate was in the patients who did not complete all cycles of therapy? Presumably, you looked at that as well.

DR. PARKER: Yes, actually that is a good point that you bring up with regards to the fact that one would expect to see a greater response rate among those patients that had completed 8 cycles, and usually when looking at that particular subsets of patients, you will find that those patients may have had better performance statuses. They may have had less tumor involvement. Perhaps they were treated less than the patients that could not complete 8 cycles. So, you would expect a somewhat healthier population to have a better response rate. I did not follow-up to look into those patients that did not complete 8 cycles.

DR. SCHILSKY: I guess I am trying to get a sense from you what you consider to be the risk/benefit ratio in the sense that, yes, you might expect the patients who were not responding but were having adverse events to be

withdrawn from the study before completing the full 8 courses of therapy, whereas those patients who were responding and having the same adverse events might be continued on the study because it was felt to be more advantageous to them to continue than to withdraw despite the adverse events. So, what is your assessment, I guess, of the risk/benefit ratio?

DR. PARKER: Well, you are asking me if those patients that, say, had been responders that had less treatment or that did not complete therapy --

DR. SCHILSKY: It would be helpful to know whether the patients who were withdrawn early had a similar likelihood of response as those who completed the 8 cycles. Or, conversely, whether the ones who completed the 8 cycles had a similar incidence of adverse events compared to those who were withdrawn prematurely.

DR. KEEGAN: We didn't analyze to look whether or not there were differences in adverse events. I think what you have hypothesized is something that we have also considered. We don't want to overplay this analysis. We only put it in because it was one of the prespecified analyses that the sponsor said that they were going to look at, and we just included it for completeness. We, by any means, don't mean to suggest anything more than that.

DR. SEIGEL: Indeed, it would be quite erroneous

to try to conclude any causal relationship between completion and response rate. Most of those responders, as you just saw on the sponsor's slide, had responded by the time they showed up for their third cycle, and almost all by the time that they showed up for their fourth cycle. So, the fact that they got the fourth to the eighth cycles, in most cases, did not cause them to be responder.

DR. TRAPNELL: I just want to comment too that I think this difference in the response -- you know, one of the things in the differential diagnosis, if you will, of that reason is that perhaps it is pharmacologic. You know, perhaps this high exposure that you get early is what is causing the response early, and the fact that you are getting a relatively low exposure later, and in fact we don't even know what the exposures were after the third cause. It was not looked at. It is conceivable that by course 5 the levels are even lower and the clearance is even higher. We just don't know the answer.

DR. SCHILSKY: Can I infer from your comments then that you believe that the higher dose is the more appropriate dose?

[Laughter]

DR. KEEGAN: Well, you know, again I think it depends on what your theory is on how this is working. If you think the way to do this is to treat patients with the

highest possible exposure as long as you can, i.e., until antibody formation essentially negates, if you will, your therapy, then perhaps the dosing strategy would be to give the MTD, if you will, as long as you can until the concentrations start falling due to antibody response, and maybe that is the end of your ability to use this. Again, that is just one of my hypotheses. There is no data to support that. But, I think certainly the fact that you get much higher exposures early and see response rates so quickly relatively to later, you certainly have to start wondering what is going on pharmacologically.

DR. OZOLS: I want to get back to this issue of benefit for the responding patients. I mean, that is one of the key issues, to see what kind of clinical benefit there was for the responding patients. It seems to me the sponsor presented some data that strongly suggested that the pruritus and patient assessment really correlated better with the responders. Do you disagree with that interpretation?

DR. KEEGAN: Yes, we do. The analysis that they presented was really a time to best response. At least one of them was time to best response, actually probably more than one of these analyses were at best response as defined by the actual score obtained. When you look at the individual data, there is a lot of noise in the data. You

can look at that and see that really if you went to just one cycle before or after, you know, the difference has gone.

The other is that the changes themselves, while they may numerically be different but we focused -- what we tried to do is look at changes that were clinically important on those scales. You had to get at least a 2 cm change. We looked at several points in time, not just the individual best responses but patients over time, which was a little difficult because even in the Phase III study there were dropouts, but looking at comparing baseline to how patients were at cycle 2, baseline to cycle 3 which is the one that we presented because that was the median time when the majority of patients had already demonstrated the initiation of their response, or baseline versus the last treatment visit, we really couldn't find significant differences between baselines and those scores for the pruritus visual analog scale or the overall responders. Individual patients perhaps did appear to have had some symptom improvement, but for the group of responders the median was not even to a significant change, had not changed by a significant amount.

DR. DUTCHER: Would you like to make a comment?

DR. LAVIN: Yes. Phil Lavin. I did a calculation of Dr. Parker's slide 20, which is the percentage of patients with clinically significant changes on the PVAS

score at cycle 3. I just multiplied out and I calculated the number on the 9 dose level and the 18 dose level that improved, and I got 9 in the 9 dose and 9 in the 18 dose. That is a total of 18 subjects. I calculated the number of worsenings, and there were 3 in the 9 group and 1 in the other group, for a total of 5. So, the statistical comparison of 18 against 5, just by doing a calculation of the number improved versus number worsened, that is significant at a p value of less than 0.01. That is point one.

Point number two, I would like to draw your attention to some of the other items that are in your briefing document. Specifically -- I don't know if we are able to put slides up here, but these would be slides 13 and 14R, if those are available.

DR. SEIGEL: I believe the question was not whether we found more people improved than worsened. This is, of course, an uncontrolled, unblinded trial. I don't know what to make of that. I believe the question was about whether there was a difference between the proportions that improved or worsened in responders versus non-responders, and that is also in that.

DR. LAVIN: That is also significant as well.

DR. SEIGEL: That is not correct. There were 10/21 responders; 6/8 improved. At dose 18 we are talking

about one-third or maybe 9/28 --

DR. LAVIN: Ten versus two. So, if you were to flip a coin and get "heads" --

DR. SEIGEL: I am sorry, 33% improved on dose 18, 36% improved on dose 9. You are comparing improved to worsened. The question is did improved differ in responders versus non-responders, symptomatic improvement.

DR. LAVIN: Right. I am calculating here 10/21, which would be the 48%; and I am calculating 2/21, which would be 9%.

DR. SEIGEL: The 9% is worsened. You want to look at the 33% on dose 18 and the 36% on dose 9 and compare it to 47%.

DR. LAVIN: Right -- well, no, that is not a fair comparison because --

DR. SEIGEL: Well, if you are interested in did more people improve than worsened, I think we are in agreement. More people improved than worsened. If you are comparing the percent improved in responders to non-responders, that is a different comparison.

DR. LAVIN: And that is 10 versus 2, from Dr. Parker's data.

DR. SEIGEL: It is 10 versus 8.

DR. LAVIN: Ten versus two. But I just want to make the point here that from the data provided you in the

briefing document, not to mention Dr. Parker's data plus the data that we presented earlier, we show major improvements for the responders, the PRs, further improvements for the CCRs, and further improvement for the CRs. It is unmistakable for the pruritus. It is unmistakable for the perception of the patients. It is unmistakable from the perception of the physicians. So, we basically have a solid story here whether we look at it from time to best response, or the way that you would prefer, time to the end of treatment. So, we have it in both situations.

DR. SEIGEL: Let me go back to that table because I think there is an important misstatement of fact here.

DR. DUTCHER: Page 20 in the handout.

DR. SEIGEL: Page 20. We are looking at the number who improved in each group, 48% of 21 is 10 out of those 21.

DR. LAVIN: Right.

DR. SEIGEL: And, 33% of the 28 in the 18 dose is 9/28; 36% of the 24 at the 9 dose is 9/24. That is 18 out of those 52 total.

DR. LAVIN: Right.

DR. SEIGEL: So, you have 10/21 versus not 2 but 8 out of the other 31. So, 10/21 responders improved, 8/31 non-responders improved. That, as I noted, is a minor trend in favor of responders.

DR. LAVIN: Right. I am comparing horizontally across.

DR. SEIGEL: Yes, that is what I tried to say.

DR. DUTCHER: Can Dr. Simon make a comment?

DR. SIMON: I have two comments. One, the table we are looking at on page 20 is cycle 3 compared to baseline. So, I am not sure, was everybody still on study at cycle 3? If not, this is really a biased comparison because you can't just drop out the patients that went off study because of adverse events or progressive disease, and then talk about improved versus worsening of the remainder.

The other point I guess I would like to make, Dr. Lavin, is that the thing that prompted my question was slide 20 which you put up, which to me was very unimpressive in terms of making the case that there was a symptomatic improvement for the partial responders. I saw it for the complete responders; I didn't see it for the partial responders. And, there was no statistically significant claimed for it in your slide and, frankly, it didn't look like there was much difference between the PRs and the stable disease patients.

DR. LAVIN: Yes, I would submit that the data are strongest from what we presented, both in terms of the charts, that 19R, as well as the data that Dr. Duvic displayed.

DR. SEIGEL: We looked at those analyses using end of treatment as well. They are very similar to Phase III. That also introduces biases because there is no fixed time point. The only other data available are at last visit, which in some patients is early and in some is late. It depends in part on degree of toxicity and dropouts which may reflect symptoms.

DR. DUTCHER: So, your conclusion is that there is no relationship to response?

DR. SEIGEL: No, absolutely not. I don't think we can conclude that there is no relationship. I think we have a study from which we cannot conclude whether there is or there isn't one, but we don't find any evidence of that.

DR. MARGOLIN: I was also concerned about the same point that Dr. Schilsky made, which is what exactly is the meaning or the significance of the analysis of patients who made it trough to 8 cycles. I guess the difference that the sponsor is trying to point out here is that, unlike with chemotherapy, these patients are presumably arbitrarily expected to get an 8-cycle treatment because you can't analyze these patients very well the way we do with chemotherapy, after every one or two cycles and decide whether they go on if they are responding or they don't go on if they are not.

But that brings to mind the question of how do we

decide about stopping therapy in patients, other than by toxicities, and whether I have interpreted correctly the issue about 8 planned cycles. I don't know whether that should be answered by the sponsor or whether you guys can tackle that.

DR. DUTCHER: I think that is one of the questions the Agency has put to us.

DR. KEEGAN: I think the one issue, Dr. Margolin, is that clearly people do assess whether patients are responding because they have assessed that time to response is after two cycles. So, clearly there is a way to assess whether or not the patients are responding.

DR. MARGOLIN: But to progression is different because, you know, meeting an objective response in order to continue therapy is different than just having absence of progression or undue toxicity in order to continue therapy.

Committee Discussion and Vote

DR. DUTCHER: Thank you. I think we should entertain discussion. We have six questions from the Agency to go through, and Dr. Sausville has a few questions. Are we going to have time for all of this? Will it be faster to use the overheads?

DR. SAUSVILLE: Yes, the overheads that I made were merely to structure the discussion. I didn't mean it to be separate from the ongoing discussion. We can either

have them or not have them, as the case may be.

So, I want to thank Dr. Dutcher and the Committee for inviting me to serve as an ad hoc member of this group as it considers what I think is a real challenge, as well as an opportunity.

It is a challenge because, as we have heard, this drug offers a number of differences in comparison to the usual type of agent we consider. On the other hand, from both a scientific and practical perspective, one might consider it to represent an opportunity because it is among the first of what many of us hope will be therapies that are directed at the underlying biology of the neoplasm rather than just, shall we say, less specific targets.

[Slide]

I have structured a few overheads to go along with the questions that were put to the Committee. Question one, is response rate and duration meaningful? I think everybody would agree and no one can deny that responses clearly have been documented. But the magnitude and duration of these responses are clearly the same, and perhaps worse, than with the variety of the approved agents.

I guess I would be interested in hearing from fellow Committee members. Clearly, many of these patients are treated with chemotherapeutic agents that no one would agree represent ultimately useful or long-term therapies. I

think that the ability to use an agent that, despite the difficulties that we have heard, has been associated in at least a subset of patients with very prolonged, admittedly in a tail of the curve type of way, response is notable.

Response did occur in some very heavily pretreated patients but the pivotal study did not control for refractoriness to a particular treatment. I think that if this is used, some better sense of when to use it is going to really have to be introduced certainly into the package labeling and, hopefully, emerge from prior treatment.

The clinical value was perceived by some responders that the median duration of response is about as long as the treatment course, and more patients were removed from the study owing to adverse events rather than disease worsening. On the other hand, as was suggested, patients with this problem often have a variety of other concomitant conditions and it is not clear that certainly these would have entered into the consideration.

[Slide]

I have changed the order somewhat. I would submit that in heavily pretreated, so-called refractory patients, the toxicity that we see here is well within the spectrum that one could see with a variety of standard approaches, and that the toxicity per se, therefore, while it is a matter for consideration and better management, by itself

should not be a factor arguing against favorable consideration.

However, I do emphasize that in early stage untreated patients the toxicity is probably what is beyond what we could expect from a variety of approaches, including topical ointment of nitrogen mustard, retinoids, as well as particularly low-dose interferon.

Also, I would point out that vascular phenomena, and I would wrap this all with the myocardial infarctions, the capillary leak, perhaps some of the neurologic phenomena, need better definition and follow-up. I would point out that from my experience, the infection rate encountered here is not clearly increased beyond what might occur in heavily pretreated patients with this problem.

[Slide]

With respect to the issue of dose, responses have been seen at both doses in the current study, 9 mcg/kg/day and 18 mcg/kg/day. I emphasize the suggestion and the intriguing correlation with pharmacology that we heard of better efficacy at higher dose in the T3 tumor stage patients. But I would point out that responses have also been seen in the prior study at a wide range of doses. Therefore, I don't really think we know what the effective dose is for those earlier stage patients.

Therefore, the dose-response relation for either

efficacy or toxicity, unfortunately, is not at this point established and, if approved in one way or another, the package label might consider lower doses for earlier stage patients, and future studies might compare doses and, as we heard, pharmacology by T stage.

[Slide]

The majority of these responses occurred by course number 4 on the pivotal study. High levels of neutralizing antibodies are detected by courses number 2 and number 3, and those correlated with the decrease in constitutional signs in transaminitis and increased clearance. Thus, to me, the value of treatment beyond 3 courses is not apparent from the available data. However, I see the point that in responding or benefiting or non-responding, etc. patients one might make the case for further courses.

[Slide]

The final issue is that the pivotal study demanded that one biopsy have at least 20% positive cells for CD25. Only 58% of patients met this criterion. While heterogeneity in IL-2 receptor expression is certainly known, to ignore the fact that this is the only database that we have addressing efficacy is in this IL-2 receptor expressing population would not be justified. I think a further follow-up study to address the response rate in IL-2 receptor negative patients would be necessary.

Arguments in the briefing document related to non-predictive value, non-prognostic factor, invasive procedure for skin biopsy, in my opinion are not relevant as certainly any number of courses of a not useful medicine is also an invasive procedure of sorts.

Finally, with respect to the issue of measure of efficacy, and I didn't make a slide of this but to respond to the prior discussion, everybody agrees that more patients itched less than those who did not, at least in those who finished treatment. To those of you who have dealt with this disease, this disease is almost biblical in its disfigurement and its disability. So, I think that issue needs some consideration with respect to assessing the potential benefit even of this symptomatic relief. Thank you.

DR. DUTCHER: Thank you. We are running a little behind. Dr. Bergfeld has a few general comments to make because she may have to run out on us before we finish the questions.

DR. BERGFELD: Well, thank you very much. As a dermatologist, I would like to respond that we are in need of another drug for the treatment of Mycosis fungoides and other related T-cell lymphomas, and I feel that this is a very interesting therapy that has been proposed and is being contemplated by the FDA and the submitter.

I too believe that the efficacy of this particular biological response modifier shows efficacy. I think that the toxicity information is profound, certainly not unlike other chemotherapeutic agents, and appears to be self-controlling in the fact that those who have profound side effects drop out of study and those who don't continue. So, there is a safety valve there just by the toxicity.

If the toxicity is managed, that is provocative for thought because one could manage that and in long-term studies or follow-up studies one might see a different outcome than we are appreciating in this particular report.

I believe also the pharmacokinetics are very interesting because what you see is a low dose in the beginning with a dose response which then tapers off as the antibodies go up and stabilize, suggesting perhaps, as has been stated by others, that perhaps the first two doses may be the most important dosing that is therapeutic.

I believe that the proposed mechanism is nice on paper; that it is a hypothesis and perhaps in the long-run we may see that this particular agent works differently and in many different cells and tissues, and this would be studied also in the long-term situation to review and follow.

I believe that in my setting this would be a very interesting therapy, and I would suggest that it be

supported in a restricted manner, and that if it is approved that it be approved with restriction for this disease and that there be some monitoring put in place as to the screening of those who enter, as well as the screening of those who continue therapy, and long-term screening to figure out what happens to these patients many years later off drug or even on drug.

So, with that, I will just close and say that I am for approval of this drug with restrictions, enhancement of the package insert documentation that we see here, this is a little bit weak, going back to the conversations that have gone around the table from all the participants, to see if we can't make this a more meaningful document. Thank you.

DR. DUTCHER: Thank you. I think we should proceed to the questions at hand. Thank you both for your insights into this disease and the issues related to its treatment.

I am going to let you read the preface paragraphs. Question number one is, does the Committee believe that an overall response rate of 30% and a complete response rate of 10% is reasonably likely to predict clinical benefit in patients with CTCL who have failed one or more systemic therapies, based on the data presented?

What we usually do is ask for comments from the discussants, if they wish to comment, and then we will have

a vote.

DR. BERGMAN: I have already made my opinion clear, I believe, and I would say that yes is my answer.

DR. SAUSVILLE: And my answer is yes.

DR. DUTCHER: Dr. Vose?

DR. VOSE: I just want to agree that for anyone who has taken care of these patients, it is a miserable disease and any drug that can give us some symptomatic relief, maybe not complete response, but it can help some patients and some, for an extended period of time, have truly great benefit so that I think it is a useful agent.

DR. DUTCHER: Dr. Berman?

DR. BERMAN: Yes, just to add to that, if you look at the slide that showed all of the prior treatments and the response rates, some of these had five, eight and ten patients. So, this is one of the larger studies. So, I think this response rate falls well within prior reports.

DR. DUTCHER: All right, all those who would vote yes as an answer to question number one, raise your hand.

[Show of hands]

Fourteen. Fourteen "yes." No "noes."

The second question is discussing the toxicity of this molecule. Thirty-nine percent of patients experienced grade 3 and 30% experienced grade 4 adverse events. Is the incidence and severity of toxicity associated with $DAB_{389}IL\text{-}2$

treatment acceptable given the response rates and durations of responses observed in the data presented?

Comments? Dr. Simon?

DR. SIMON: The only comment I would have is just really advice to the FDA. I think this was a heterogeneous set of patients. Once you get beyond the stage Ib patients, the CR rate was 2/55; the total response rate was 25%, and the duration of the PRs was, I think, 4 months. So, you are getting different results in terms of response from the Ib than you are from all of the other stages.

DR. DUTCHER: Dr. Sausville?

DR. SAUSVILLE: Yes, I would echo the notion of heterogeneity, but perhaps emphasize a somewhat different aspect. I believe that the severity of the toxicity is well within what might be acceptable for the advanced stage, so-called refractory population. I believe that if it is approved, the labeling must clearly make a distinction between those patients and the earlier stage patients. But within that circumscribed language I definitely believe that the toxicity would be acceptable.

DR. SEIGEL: Just for clarity, I think Dr. Simon is pointing out that the response rates are lower in more advanced patients but you are suggesting, nonetheless, given the nature of the toxicity, that would be appropriate?

DR. SAUSVILLE: I think Dr. Simon is appropriately

focusing on the complete response rate which is unquestioned. On the other hand, if you recall the data presented, there was evidence that PRs, as one could define them, did occur at a notable incidence in the more advanced stage patients. As was emphasized by Dr. Vose, a good PR is not a bad thing in this situation.

DR. VOSE: I just want to agree with that. I think that the toxicities, as we are noting here, are very acceptable for this type of patient population in advanced stage. For early stage disease, I agree, it may be that they may want to wait until a little bit later to use it. So, I think that should be taken into consideration.

DR. BERMAN: I would just like to reemphasize the point that we are looking at monoclonal antibodies and they have a whole different set of safety and efficacy. Having, you know, just sat on the committee that licensed rituximab, I think that this falls not only within, but I would urge for earlier treatment of patients just because we don't know their response and maybe we can build on it by using this in combination with interferon or the most acceptable treatment. So, I would definitely say --

DR. DUTCHER: That falls into question number three, which is what additional studies would you like to see.

DR. BERMAN: I am just trying to move on to lunch!

[Laughter]

DR. DUTCHER: With respect to toxicity for the advanced patients, you want to urge that as a recommendation to FDA?

DR. SAUSVILLE: Yes.

DR. DUTCHER: So, those who feel that the toxicity is acceptable, please raise your hand.

[Show of hands]

Fourteen "yes." No "no."

DR. DUTCHER: So, to go back to Dr. Berman with question number three -- put you on the spot a little bit -- this is a discussion of no differences in overall response rate, secondary efficacy measures, or the toxicity profile between the two dose levels. Furthermore, due to the immunogenicity, there was no difference in measured circulating drug levels beyond the first cycle. Does the Committee feel that there is sufficient information to recommend a dose? Please discuss dose or dosage range which is appropriate for labeling or future study. What additional studies are recommended to further explore dose and dose range?

That is not exactly what you were getting to but it might be a place to start. Do you want to comment?

DR. BERMAN: Well, I kind of like what Dr. Bunn said earlier about having the ability to use different doses

in different settings. Are we restricted to providing -- we are not? So, we can say that the dose can be given -- like any other medicine --

DR. SEIGEL: Many medications are indicated over a range of doses.

DR. BERMAN: So, I would aim for providing some laterality here for the clinician.

DR. MARGOLIN: I would like to take an opposing view on that. I know we are not supposed to discuss economics but it seems to me we have spent a few hours seeing that there is absolutely no detectable difference in any parameter with respect to dose, except perhaps some early exposure, and that may be important but we haven 't seen proof of it. So, I am not sure if one were to release now the availability of more than one dose how a treating physician could have any way to select the dose based on any parameter for their patient.

DR. SAUSVILLE: I certainly recognize that as a very important issue, however, from a scientific point of view I really am persuaded by the difference in pharmacology that was obtained with the higher dose. Ultimately, this is a matter of affinity constants and equilibrium constants, and you need to get as much drug as possible to a point where it can bind to a high-affinity receptor. If you don't do that, you won't get a response. So, I would rather limit

the number of courses in terms of economics than eliminate the ability to choose the higher dose, particularly for the II stage patients.

DR. BERGFELD: I concur with that.

DR. DUTCHER: All right. What additional studies would be recommended to further explore dose and dose range issues? You are suggesting pharmacology for one?

DR. SAUSVILLE: Yes, as well as follow-up and some type of trial of what T stage responds to what dose because I really don't feel that that has been fleshed out here. There is a hint of important differences and it clearly needs to be addressed.

DR. SEIGEL: Dr. Sausville, a question for clarification, when you look at cytokine studies in vivo and in vitro, but more readily in vitro where it is easier to control, of course, the issues are affinity and concentration and the comparison of the concentration to the KA and KD. But typically what you find when you look at a dose-response curve is an S-shape curve that plateaus after a certain level because of adequate saturation to maximally trigger the target cell. Why then would you assume that in those circumstances a higher dose is better, absent clinical data suggesting that?

DR. SAUSVILLE: The principal reason derives from the consideration of, as it were, the tumor architecture of

the T3 lesion, which is a lump, a large lump. It is not an in vitro situation where all cells are exposed equally. A higher concentration may directly promote better diffusion into large tumor masses. So, I think that is one issue. I do emphasize, however, that would be among the issues that would need to be followed up.

DR. BERMAN: I think that the next study, the 93-11 study, which is the blinded, 3-arm between the placebo, the 9 and the 18 study, will help answer the dose. But the other is that I would urge that that study be opened up to the IL-2 receptor negative patients so the company can develop a base to know whether it works in people whose tumors don't express IL-2 receptors.

DR. SAUSVILLE: That is in essence question six, or something like question six. The "nouvelle" question six.

DR. DUTCHER: So, in terms of recommending a dose, does the Committee feel that a dose range is more appropriate at this point in time? All those who would say yes, raise your hand.

[Show of hands]

Twelve. All those who do not?

[Show of hands]

Two.

Talking about durability of treatment in question

number four, given that the drug exposure beyond the first one or two cycles is markedly decreased due to the immunogenicity of the molecule and the median time of onset of response is 2 cycles, does the Committee feel that there is sufficient information to recommend a specific duration of therapy? Please discuss the recommended duration of treatment and the information from the baseline studies which should be available to physicians for guidance regarding the duration of therapy. What additional studies should be considered to evaluate the appropriate duration of treatment?

DR. VOSE: I feel that there really is not adequate information to justify how many cycles is appropriate. Probably the best thing to do would be to put the graphic in the table that we looked at as far as the number of cycles and patients that respond. I think it is not clear at all that you really need to go out to 8 cycles to get adequate response. So, we definitely need further studies in that area.

DR. SAUSVILLE: One way to do that would be to say less than X number of percent of responses were documented to occur, say, after 3 courses of treatment. That pretty much says it.

DR. VOSE: Right.

DR. BERMAN: I would recommend putting in the

pamphlet the chart that just shows the responses -- the bar graph that shows the responses.

DR. VOSE: Right, because I think that tells the story really.

DR. KROOK: I guess I personally feel that both the patients which we have seen here either are going to discontinue or their physician is going to discontinue for one reason or the other, and following up on Dr. Margolin's comment, cost is an issue. At least in my office, a lot of people quit simply because they can't afford it. Now, that is a different issue but I think patients and physicians will say how many courses. I don't think it matters what we do here. I really don't.

[Laughter]

DR. VOSE: That is a little disheartening!

DR. KROOK: It is nice to put it there but it gets into other problems, like HMOs.

DR. SAUSVILLE: That is actually a good point. We might want to say at least 3 are associated with a fair --

DR. KROOK: Right.

DR. SEIGEL: I think I hear you saying we need to look a little more closely at, you know, what is the conditional probability after 2 courses, you have had no response or maybe a minor response, or after 3 courses. We will provide some appropriate data to allow physicians and

patients to decide.

DR. DUTCHER: I think what Dr. Krook is saying is you don't want to put people in a position where they suddenly are cut off from the drug.

Question number five is regarding the ongoing 3-arm trial in stage Ia to III, utilizing the 2 dose levels plus a placebo control as a potentially confirmatory trial to validate clinical benefit of objective tumor responses. The endpoints of this trial are overall and complete responses rate, response duration, relief of symptoms, time to treatment failure and overall quality of life. Which of these endpoints does the Committee feel would be acceptable for confirming clinical benefit: durable responses with definitive evidence of relief or pruritus, decrease in other tumor-related morbidity, i.e., infections, significant improvement in disease-free survival, significant improvement in overall survival? The current study may not contain adequate power to detect significant differences in disease-free and overall survival Should the study be modified to allow assessment of the effects on these outcomes?

DR. VOSE: I think in this patient population really the most important endpoint is symptom relief because response is very difficult to adjust or to really evaluate in these patients because it is skin-based disease usually.

It is just very difficult to really do that, and I think what we are trying to get at is does the patient get better, and that is really the best endpoint.

DR. SCHILSKY: I don't actually have a problem with any of those endpoints, but I am very concerned that if the drug receives accelerated approval following this meeting that it will be impossible to complete the ongoing trial because I don't believe that any patient or physician will be willing to accept randomization to placebo. So, I think that both the FDA and the sponsor need to be thinking about alternative study designs.

DR. DUTCHER: I think that is a major point.

DR. SAUSVILLE: I guess in follow-up to that, I would argue against the business of disease-free survival and overall survival, because I think that is introducing a set of concerns that is very difficult to address because of the many confounding issues we heard described by both the sponsor and Dr. Parker. I think emphasizing I guess I would say a previously agreed upon symptom assessment or score plus, obviously, consideration of durable responses would be the way to go.

DR. SEIGEL: Let me get clarification. Is it the sense of the Committee that with this approval, as recommended -- if we went ahead with this approval as recommended with the restrictions regarding refractory and

severe disease, as well as the notations regarding known and unknown toxicities, is it in fact the feeling of the Committee that it is inappropriate or perhaps just impractical to do further placebo-controlled studies? Because at this point, with the baseline toxicities in this disease, like infections or whatever, absent a placebo-controlled study it is going to be pretty hard to get answers to a lot of the questions raised without it. I think it is an important position for this Committee, either to say forget it or to take the position that, no, those studies are important and there are settings in which they still can be done.

DR. DUTCHER: Well, you have two kinds of patients. If you are going to have symptomatic patients, you are going to want to see symptom relief. Those patients are going to want to be treated with something.

DR. VOSE: I think it would be better to have the other arm as a treatment. Interferon probably would be a possible choice.

DR. MARGOLIN: I think you can say whatever you want about whether the trial should be done but people and docs are going to vote with their feet. However, one group you may still be able to do, which Dr. Berman suggested and which is an excellent idea, is the patients with negative CD25, and you may still be able to find enough of those

patients where the drug hasn't been proven or even tested to justify the placebo-controlled assignment and to actually get some accrual.

DR. KEEGAN: The problem with that being, of course, if the study is negative would we have to withdraw approval? I don't think we would want to be in that position, as a confirmatory trial. So, you would recommend that we should consider as first-line systemic therapy interferon versus this drug in another population?

DR. DUTCHER: Dr. Bunn, do you want to make a comment?

DR. BUNN: This was actually discussed at length with the FDA in the design of this trial, and since half of the patients have already received interferon, you know, you would be excluding perhaps more than of the patients. So, that would be most difficult. As I mentioned, many physicians will, you know, give interferon first in their practice before this drug, which is probably reasonable.

DR. SEIGEL: I guess I would have another question about that. If this is an accelerated approval, typically, as required by regulation, a confirmatory study is one which is required to verify baseline benefit. Would you be suggesting we require this drug to be better than interferon to demonstrate clinical benefit? Or, if we are simply requiring it to be similar, then that is not a heck of a lot

different from doing an uncontrolled study in terms of what we will be able to tell about it and we might just as well do the uncontrolled study.

DR. SAUSVILLE: I mean, from a biologic perspective, there is no reason to expect that the same subset of patients that are going to respond to interferon are necessarily those that are going to respond to this therapy. So, in my mind, to require it to be better -- I mean comparability is certainly reasonable.

I guess I would put for discussion the notion that we are, as I recall the vote, approving for advanced refractory patients as initial therapy or treatment of early stage patients that have clearly failed prior therapies. So, in my view, although I agree with Rich that depending on the language that is ultimately adopted there may be greater or lesser enthusiasm for the randomized study, I still think it is possible to construct language that would really encourage the importance of the placebo group in those earlier stage patients. Because I think it is a very important study if we can try and promote it.

DR. VOSE: But from the point of view of the symptomatic patients, I think it is just not possible to have a placebo.

DR. BUNN: One of the questions is for those less advanced patients. You know, that study, hopefully, is

going to get done. But the patients in this study are different. They are more advanced and more refractory. I don't know whether there are data anyone is ever going to generate to show patient benefit. These patients had objective responses and have benefited. For these patients, I just think it is full approval. I don't understand.

DR. SEIGEL: Well, I guess what I would ask of the Committee in that regard is are objective responses enough? If not, one of the things that is in this question is are durable responses with definitive evidence of relief of pruritus enough? That could be obtained from non-controlled studies. I guess the company thinks they have demonstrated that and we can re-review other analyses, many of which are, you know, relatively recently done and not yet reviewed. But if those data are not there, the question would be -- you know, if we determine, as we think now, that those data are not there, should we, one, simply say responses alone are directly indicative of benefit? Or, two, in whatever studies are done look for better evidence that responses are associated with clinical improvement. Or, do we need to look for something else more definitive?

DR. SIMON: Well, as a non-clinician I will give you my opinion.

[Laughter]

My opinion is that a CR in this disease is self-

evident and clinically beneficial, and that for a PR, what I have seen is that it is more questionable, and I would personally think that that is associated with symptom relief, like reduced amount of itching.

DR. MARGOLIN: Just to go back for a second to the issue about placebo control, and it also gets back to the issue of deciding when a patient is clearly not responding to this therapy, the ones on the placebo arm, those patients I guess have the rollover trial to go right into. So, you are not really asking them not to take treatment, but to be willing to wait until it is just obvious and clear that their disease is progressing and then they have treatment available to them.

DR. SIMON: Really, I don't think we should say anything to discourage that randomization. For the more advanced patients that is mostly PRs that we are getting, with a duration median of 4 months.

DR. DUTCHER: So, it sounds like there is a sentiment that the placebo-controlled trial for the earlier patients should continue with the ability to rollover into the other trial. So, then the question is are we looking at, for the advanced patients, accelerated approval or approval?

DR. KEEGAN: Actually, the ongoing study does allow for rollover for placebo-control patients already into

that study.

DR. SCHILSKY: I just wanted to make the comment that I don't want my comments to be misinterpreted to say that the ongoing study shouldn't be completed, if possible, but I do think that if the drug is approved, that would require modification of the consent form of the ongoing trial, to make it known to patients and institutional review boards that the drug is now approved. I think, in so doing, there may be some IRBs that would raise a question about the appropriateness of continuing a placebo-controlled trial, and there may be patients and doctors who would have concerns about enrolling on a placebo-controlled trial.

I think the option of having patients get the drug in an open-label fashion at the time of progression on the placebo is an excellent option and, hopefully, that would not significantly impact on the accrual to the study. But, you know, my point is that we can't not let the world know that the drug is approved, if that is the case, and it will have an impact on the ongoing trial.

DR. SEIGEL: I missed the start of what you said, but the gist of your comment, as I understand it, is to modify that protocol to allow early escape of progression?

DR. MARGOLIN: As Dr. Keegan pointed out, it already says that. But I fully agree with Dr. Schilsky. I am on an IRB, doing a lot of regulatory stuff besides this,

and there is no question, you would have to put something --

DR. SEIGEL: Of course --

DR. MARGOLIN: -- but also to point out that the group for whom this approval is presumably going to occur is not exactly the group in this study.

DR. DUTCHER: Dr. Kuzel?

DR. KUZEL: There are a couple of problems with that placebo-controlled trial that the rollover doesn't directly necessary achieve. First of all, patients have to have progressive disease to rollover. So patients who are symptomatic and enrolled on placebo who are stable and do not meet the criteria for progressive disease continue to get saline infusions every 3 weeks for 5 consecutive days until they achieve that. So, you know, there is a significant number of patients that are clearly going to -- you know, are they going to be life-threatened? No, but they are certainly going to be greatly inconvenienced for a prolonged period, waiting to perhaps progress. And, the ability to give patients perhaps open-label drug, I agree, will probably hurt that.

You know, the original genesis of the placebo trial was not a toxicity comparison. It was an issue that there was a sense evidently in the early discussions that at least 10% of patients with significant disease burden would respond to spontaneous remission saline. I mean, that

certainly isn't my experience in patients with anything but the most fleeting MF, and those are not patients who are going to be treated on this anyway.

So, it would seem to me that another logical option would be to freeze the placebo arm and close it. We will have 20-some patients who have been now treated with a long natural history of placebo, and we can look at that data and it will give you a little more toxicity information, as well as response information, if the group feels that it is needed.

DR. DUTCHER: Go ahead. We are not going to try to rewrite the study for you right now --

DR. SAUSVILLE: Yes, I would strongly emphasize trying not to rewrite the study. I think it is an extremely important opportunity. I think if the language that ultimately is used conveys the difference between the patient population that it is approved, it would preserve what I think is an important opportunity. With all due respect to the practicalities, I don't believe that that would deny anybody -- there is the rollover into active drug -- the opportunity for ultimately getting a response. So.

DR. OZOLS: I disagree. I don't think it will happen. I think once this drug is approved -- the patients and the doctors already have been by their feet; they are not putting patients on these trials because their community

already knew that this was an active agent, and I think you are going to see more of that the moment this gets approved, and I don't think patients are going to be willing to take placebo. If you have early stage disease and you the potential not only of making it better but perhaps a longer duration of remission, and the earlier the better, I think people are going to opt --

DR. SAUSVILLE: I must say, it is not clear the earlier the better. It is one of the issues that needs to be looked at. I would hope this Committee's role is to argue from the science, and if doctors and patients choose to vote with their feet that is a societal issue rather than a scientific issue.

DR. OZOLS: But it is going to happen.

DR. DUTCHER: I guess the question that we don't know yet in the design of this study, that hasn't really been discussed here, is what are the questions being asked that you are going to get the placebo? Toxicity? Dose? Durability of response in these diverse patients? I mean, there are so many questions that were presented in the studies that were completed that I think it would not hurt to re-look at the design of that study with the questions in mind and see how much you do or do not need the placebo arm.

DR. SEIGEL: There are also issues of disease course, of time to natural progression of disease. I am

told that some therapies with this disease are thought by some perhaps to hasten the development of visceral disease. Is this a therapy which theoretically could eliminate lymphocytes that are tumor specific and that might play some roll in controlling the disease? I didn't want to raise that as a likely possibility but I am suggesting that to the extent that one can do a placebo control, one can look at -- you know, even in a placebo control where the endpoint is progression one can gather data as to the efficacy of the drug, not simply on remission but on disease course.

DR. VOSE: And, I think scientifically, all of us would really like to have a placebo-controlled trial. I just think it is not practical. I mean, already the are having trouble getting accrual into the trial. It is just not going to happen.

DR. DUTCHER: Well, the other possibility is changing the time point at which rollover occurs, rather than requiring progressive disease, perhaps a certain period of courses, period of observation.

DR. SAUSVILLE: That is a good suggestion because from the data that we heard today, 3 courses would pretty much allow you to have some number for some people who have not derived a response but who are clearly not harmed in terms of toxicity, they would get a chance to go on the active therapy. Actually, all you could do is assay for

diphtheria IL-2 antibodies --

[Laughter]

DR. DUTCHER: Did we answer number six? This is the issue of having evidence on biopsy specimens of IL-2 receptor. Should the indication be limited to patients in whom expression of CD25 can be demonstrated for more than 20% of the cells? We have all heard the inherent problems with the assay on tissue. There is also the issue of looking at peripheral blood. Comments? Dr. Ozols?

DR. OZOLS: I am puzzled by this. We are hearing that this assay may not be able to have any reproducibility, and heterogeneity. I mean, it is not like doing an estrogen-receptor assay where we know whether the assay works or not. I mean, if we were strict as to patients who don't have the receptor, is that because they don't have the receptor or because the assay didn't pick it up?

DR. SAUSVILLE: There are various levels of stringency that one could imagine bringing to bear on this issue, including such techniques as PCR, and RNAase protection, etc., etc.

DR. OZOLS: But who is going to do those?

DR. SAUSVILLE: Well, all right. I think the practicality -- and, again, the data set we were presented departs from the population that had the features indicated. That is the best I can do. To make the leap, and I would

call it a leap at this point, that those patients in whom biopsy after biopsy they are negative are going to have the same response, or whatever -- it is not in the data. So, again, while I accept the issue of difficulties in terms of heterogeneity in patients, it is the perfect question to be asked in a further study. And, that is as far as I think the data permits us to go.

DR. SIMON: I agree with that. I don't understand the logic actually of the sponsor's presentation about the assay. Unless you believe that the assay was totally random and that the people who got into this study were just as likely to be IL-2 negative as positive, and that the assay was totally irrelevant, the fact that you see some heterogeneity among tumor nodules with regard to the assay doesn't mean that your results are applicable to the patients who didn't get into the study. So, I see no basis for having the indication include people who -- I think it should be restricted to people who have the eligibility with regard to IL-2 receptors as to what was used in the study.

DR. NICHOLS: And I think we were clear earlier but I will just repeat it. I think our concern is was a fairly large patient population being eliminated who might have the possibility of responding if they were treated for a time period for their physician to establish whether or not they were responding. It might allow them that

opportunity that won't exist with the restriction.

DR. DUTCHER: I think we have two studies suggested that weren't on the list of questions. One was an earlier stage patient study, and a second was in the IL-2-receptor negative patients as a formal study to really test the hypothesis that there is something else going on and that it is too insensitive to detect it.

But I think the sense of the Committee is that we would like to have formal knowledge that you do benefit people that are negative. Correct?

Have we any other pressing issues? No? All right, we are going to have to have a short lunch because we are getting behind and we have another drug this afternoon. Thank you all for your attention. Thank you to our consultants and other Committee members. And, we will start at 1:40.

[Whereupon, at 1:0 p.m., the proceedings were recessed, to be resumed at 1:40 p.m.]

AFTERNOON SESSION

DR. DUTCHER: Before we get started, I think Dr. Justice would like to say a few words and then we will introduce the Committee.

DR. JUSTICE: It is my privilege to thank Dr. Swain for all of her efforts over the last four years. As a member of ODAC, we very much appreciate all the help you have given us and the excellent advice that you have provided us, and we are all kind of sad because this is your last meeting as an official member of the Committee, but we look forward to having you back on occasion as a consultant. In recognition of your service to FDA and the public, we have a plaque from the Center for Drug Evaluation and Research in recognition of your distinguished service, and a letter of gratitude from Dr. Woodcock and a certificate and letter from Dr. Friedman. Thank you very much.

[Applause]

DR. SWAIN: Thank you.

DR. DUTCHER: Thank you. We second that. We have a few new members t the table so I think we will just quickly go around the table once more and introduce the people here.

MR. GIDDES: Ken Giddes, patient representative.

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

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

MS. BEAMAN: Carolyn Beaman, Sisters Network, and consumer rep. to the Committee.

DR. DUTCHER: Janice Dutcher, Albert Einstein, New York.

DR. SOMERS: Karen Somers, the Executive Secretary to the Committee, FDA.

DR. OZOLS: Bob Ozols, Fox Chase, in Philadelphia.

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

DR. SANTANA: Victor Santana, St. Jude's Children's Research Hospital, in Memphis, Tennessee.

DR. WILLIAMS: Grant Williams, FDA.

DR. HIRSCHFELD: Steven Hirschfield, FDA.

DR. JUSTICE: Bob Justice, Acting Director, Division of Oncology, FDA.

DR. SIMON: Richard Simon, National Cancer Institute.

DR. DUTCHER: Somers will now read the conflict of interest statement.

Conflict of Interest

DR. SOMERS: One more time, 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 interest 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:

Full waivers have been granted to Dr. Victor Santana, Dr. Robert Ozols and Dr. Kim Margolin. In addition, Dr. James Krook has been granted a limited waiver that permits him to participate in the discussions concerning Hycamtin, however, he will be excluded from voting on this product.

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

In addition, we would like to disclose for the record that Dr. Robert Ozols and Dr. Richard Schilsky have interests which do not constitute a financial interest in the particular matter within the meaning of the 18 USC 208, but which could create the appearance of a conflict. The Agency has determined, not withstanding these interests, that the interest in the government and Dr. Ozols' and Dr. Schilsky's participation outweighs the concern that the integrity of the Agency's programs and operations may be

questioned. Therefore, Drs. Ozols and Schilsky may participate fully in today's discussion and vote concerning Hycamtin.

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

DR. DUTCHER: All right, then we are going to begin with the sponsor's presentation. Dr. Fields?

Sponsor Presentation, Introduction

DR. FIELDS: Chair Dutcher, members of the Oncology Drug Advisory Committee, FDA review team and ladies and gentlemen, good afternoon.

[Slide]

My name is Scott Fields and I am currently the group director for oncology clinical development, SmithKline Beecham Pharmaceuticals. SmithKline Beecham are pleased to bring to this Committee Hycamtin, a topoisomerase inhibitor which is currently approved for the treatment of patients

with metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy.

Today, we will present to you information on the safety and efficacy of Hycamtin in the treatment of small cell lung cancer after failure of first-line chemotherapy.

We believe this is the largest randomization trial in second-line small cell lung cancer, and we compare Hycamtin to the 3-drug regimen of cytoxin, Adriamycin and vincristine.

Before we begin the program today, on behalf of SmithKline Beecham, I would like to express our appreciation to the FDA for the advice and cooperation they have provided throughout the drug development, sNDA preparation and the review process. We are grateful to Drs. Hirschfeld, Justice and Williams, as well as Debbie Patterson, and the entire NDA review of the Oncology Division. I would also like to thank the ODAC members for taking the time to consider this application.

[Slide]

Small cell lung cancer is most common among current or past smokers. Compared to other types of lung cancer, small cell has a greater tendency to metastasize to other parts of the body by the time the patient is diagnosed. Two-thirds of all small cell lung cancer patients have extensive metastasis at the time of diagnosis.

Patients with advanced stage disease have a median survival of only 9 months.

There are currently only limited options for treating small cell lung cancer, one of the most deadly malignancies among both men and women. Since most small cell lung cancer patients will eventually relapse and become difficult to treat, there is a need for new agents that can be used to treat patients, particularly those who progress following first-line chemotherapy.

We believe the data we present today will demonstrate that Hycamtin represents an important therapeutic option in the treatment of small cell lung cancer, particularly given the fact that no agent is approved specifically for second-line small cell lung cancer.

[Slide]

For the presentation today we propose to follow the agenda shown on this slide. Dr. Richard Gralla, of the Ochsner Cancer Institute, will present an overview of small cell lung cancer chemotherapy. Dr. Joan Schiller, of the University of Wisconsin Comprehensive Cancer Center, will then discuss the pivotal Phase III study. I will then return to describe the supportive studies, give the safety summary and then make some concluding remarks prior to answering the questions.

[Slide]

In addition to these presenters, we also have with us today Dr. Roman Perez-Soler, from MD Anderson, who has considerable experience with small cell lung cancer as well as in the use of Hycamtin. Also, Dr. Andres Shaer, who is a radiologist from Fox Chase Cancer Center and has done the independent radiologic review for us for patients in the United States. We are grateful for their participation to day.

[Slide]

I am now pleased to introduce Dr. Richard Gralla, Director of the Ochsner Cancer Institute.

Overview of Chemotherapy in SCLC

DR. GRALLA: Good afternoon.

[Slide]

As presented by Dr. Fields, small cell lung cancer represents one-quarter of all the lung cancer, and is the most common cause of cancer-related death among both women and men in the United States. At presentation, about two-thirds of people with small cell will present with extensive disease. That is, cancer metastatic outside of the hemithorax with the primary tumor. This is relevant to our discussion today in that we will mainly be discussing patients with extensive disease.

This is the malignancy most associated with

tobacco use. This fact is important not only because of its terrible public health impact, but also because of its implication for the treatment of individual patients. Tobacco use is also the major risk factor for emphysema and heart disease. Most of these patients have important co-morbid conditions, making treatment for them even more difficult.

[Slide]

It is a paradox that there are many drugs with demonstrated activity in first-line use, as shown on this slide, but few that have been shown to be active in previously treated patients. This slide lists the most commonly used agents in first-line therapy, and their activity, in a comprehensive review that we published just a few years ago. Typically, a useful single-agent response rate would be considered to be more than 15% or 20% major response rate.

[Slide]

The role of chemotherapy and of combination chemotherapy has been clearly established in small cell lung cancer in older randomized trials, where we can see that it was actually, 30 years ago, compared with placebo with a single agent and that combinations were found to be more active than single agents. These slides also illustrate the very poor prognosis associated in first-line therapy with no

treatment or inactive treatment in these older trials.

[Slide]

Many combination regimens are currently used, but these two, etoposide and cisplatin, and cyclophosphamide, doxorubicin, Adriamycin and vincristine, are two of the most popular and have emerged as the most used first-line regimens. Now, there are some oncologists who prefer one or the other or alternations of these but, overall, these are very commonly used regimens in the treatment of non-small cell lung cancer.

For first-line treatment, you can see that the response rates are fairly high and the survivals are reasonable considering the very poor prognosis for untreated or poorly treated patients. It can also be seen that for either etoposide-cisplatinum or cytoxin-Adriamycin-vincristine patients with limited disease do substantially better in terms of both response rates and survival than those with extensive disease. I will be using the abbreviations EP for etoposide-platinum and CAV for cyclophosphamide-Adriamycin-vincristine.

[Slide]

These two regimens, EP and CAV, have been tested against each other, as is illustrated in this large U.S. multi-institutional trial, reported by Roth and his colleagues from the Southeast Oncology Group in over 400

previously untreated patients with extensive disease. Results have actually differed very little in other trials in extensive disease, and I believe that this study is representative and reflects the views of most oncologists. That is, EP or CAV or both given in an alternating fashion yield similar results in terms of partial and complete response, that is, about 50% or 60% overall major response rate in extensive disease, and in survival, with medians around 8 to 8.5 months for either regimen, EP or CAV or for both regimens in alternation. Thus, CAV or EP at present are the best regimens available and results are similar for their outcomes in most parameters, if not all parameters.

[Slide]

It must be realized that while these regimens are quite active, these combination regimens also can have safety and efficacy, especially in this group of patients with previous smoking histories and with co-morbid conditions. Mortality rates in the 4-7% are common in both combination and single-agent chemotherapy regimens even in first-line patients with extensive small cell lung cancer, as was seen in the SEOG trial.

Similar regimens used in ovarian cancer or in breast cancer or lymphoma where co-morbidity is less common have lower treatment-associated death rates.

[Slide]

We must also realize that patients with lung cancer, both small cell and non-small cell, are highly symptomatic with their cancer, as is seen in the results of this prospective patient-reported survey. Both pulmonary symptoms including cough, pain, dyspnea, and general symptoms such as fatigue and anorexia are extremely common in this patient population, as was shown by using the validated LCSS quality of life and symptom scale instrument. The average number of cancer-related symptoms per patient is 3, and palliation must remain a major goal for any treatment of small cell lung cancer, especially in extensive disease which represents the majority of patients and for whom long-term survival is uncommon.

[Slide]

It is useful to examine the context of current treatment. There is definitely and clearly survival advantage for first-line chemotherapy, but this benefit is modest for most patients. While long-term survival is possible, it occurs primarily in patients with limited disease and in fewer than 20% of those patients as well. Nearly all patients with extensive disease relapse, and long-term survival is essentially anecdotal in this population group.

Most chemotherapeutic agents are mutually cross-resistant. So, there are very few good strategies for

second-line chemotherapy and, therefore, there is no consensus on which second-line regimen should be used. Few agents are active in second-line use but, nonetheless, there is a strong need for better therapy for patients in second-line who have relapsed because these patients are highly symptomatic and response is generally associated with both survival and palliative benefits. So, if we could have more agents that would have some degree of activity in this disease, we could expect to improve the outlook for our patients.

[Slide]

In the study that I mentioned before where we reviewed single agents for first-line activity, we also looked at second-line activity. There, we looked at 57 different agents, which were what we could find in the literature, 141 papers and over 3000 patients.

If you look at the first-line activity, in the middle of the slide, you can see that if you draw the bar of activity at 20% or greater major response rate 11 out of the 57, or about 20% of the agents had that degree of activity. Unfortunately, you have to draw the line of activity a little lower for second line, at 15% activity, because we could find that only 5 out of 57, or 9% of the agents had 15% or greater activity when used as second-line chemotherapy in small cell.

[Slide]

Now, how do patients do in terms of survival after relapse from modern first-line chemotherapy if no further treatment, or if an ineffective agent is given? It is difficult to find data in the literature on this, but there are two studies that I think are illustrative. First is the Italian study in which patients had prior treatment with EP and CAV in alternation, published in 1990, and for second-line treatment the patients were followed and not given further treatment. From the time of progression in the small number of patients, 27, the median survival was only a month and a half.

There was also a SWOG study, published by Dr. Albain and her colleagues, in Cancer, just a few years ago. There, again, the patients received EP or CAV or both in alternation, and the second-line treatment was a low-dose cyclophosphamide followed by ARAC protocol that, unfortunately, was not very active, with less than 5% response rate. In those 67 patients the median survival, in these carefully followed patients, was only 2.5 months.

So, we can see that overall the median survival in these studies, which are about the best that we can find, is about 2 months, plus/minus a couple of weeks, if patients received no further treatment or if the treatment is ineffective.

[Slide]

With no consensus on a choice of second-line regimens, several possibilities could be considered, and one of these recently has been oral etoposide. That is the lower arm of this trial. But this recent British trial, published in Lancet by the MRC, helps to clarify the choice. It randomly assigned nearly 340 patients to receive either oral etoposide daily versus intravenous CAV. About a third of those patients assigned to the intravenous arm received etoposide plus vincristine intravenously instead of CAV.

Now, this is a first-line study, a first-line palliative study, meaning that the patients were felt to have much poorer prognostic factors, meaning largely in an extensive disease group or performance status and an older population. The results were disappointing, showing inferior results with oral etoposide, with a significant difference in survival favoring the CAV arm, and no toxicity advantage for the oral etoposide when compared with the CAV group. This led the investigators to conclude, as I have on the bottom of the slide, that oral etoposide should not be used alone in a palliative setting in small cell lung cancer.

In addition to demonstrating that oral etoposide did not perform well, this trial illustrates the difficulty that even a highly active single agent, such as etoposide,

has in competing with an active combination, such as CAV, in small cell lung cancer.

[Slide]

There is a fairly good second-line study comparing the active first-line combinations of CAV and EP when they are used in second line. This comes from the previously discussed Southeast Oncology study by Roth and colleagues. Here, in this trial, they crossed over 100 patients who had received either CAV or EP as their initial treatment. They were crossed over to the opposite regimen.

So, in the first column, those patients who received CAV as second line had all received EP as the initial therapy, and those who received EP as a second-line regimen had all received CAV, and after progression were crossed over to those regimens. No significant differences were seen in response or survival, although there is somewhat of a trend for a difference in response rate with EP. Clearly, no differences were seen in survival, whether survival is measured from the start of treatment with the initial primary regimen or whether survival is measured from the start of second-line treatment with either CAV or EP. Thus, CAV or EP in second line are very similar, with the survival in the second-line treatment being in the 4-5 month range.

Now, response rates can be affected also by

whether or not patients respond to the initial treatment, and this gave a slight benefit to each one of those regimens, in the 2% to 6% range, if they looked only at those who were sensitive to the first-line chemotherapy, but made no differences in terms of significance between the two regimens.

[Slide]

How has CAV done in other second-line trials? This slide lists the trial that I just mentioned, the USA SCG trial, the Roth et al. study. That is on the top row, and three other trials that have reported on results of CAV as second line.

It is difficult to find formal reports of well-conducted second-line trials, but I think that these are reasonably well studied trials that give some insight. As can be seen, the major response rates vary from about 12% to over 30% with CAV given in second line. These variations in response rates could be influenced by several factors: performance status of patients; extent of disease, as indicated in the Canadian trial where extensive disease patients did not do as well as limited disease patients; methods of response assessment; patient selection; patient response to initial therapy; and other factors as well.

The two trials reporting survival from the start of second-line CAV indicate a 3.5- to 4.5-month median

survival, which appears to be about the best results that are reported in repeated studies with any regimen that has been subjected to this kind of review. I think this is as good as any multiply tested regimens are in terms of response and survival in small cell lung cancer.

[Slide]

Well, there are two different ways that people have proposed for testing new agents in small cell lung cancer. Dr. David Etinger and I were here at ODAC a few years ago to discuss these and, basically, they fall in the first and the second way.

The first, on the left-hand side of the slide -- it says, in this patient generally with extensive disease, with no prior chemotherapy, and this approach does have some advantages. Higher response rates with such a new agent or new method are likely, and there would likely be fewer early disease complications allowing, the study to be easily completed. But there are disadvantages, and one of the major disadvantages is that standard chemotherapy regimens such as CAV or EP have high response and palliation rates and patients would not be receiving these initially.

Then, another approach is to look at only previously treated patients, perhaps those again with extensive disease who have good performance status after initial therapy or who have been sensitive to their initial

therapy. This would be an important approach because good second-line treatment is a major unmet need for many thousands of patients with small cell lung cancer, and this approach may identify new agents that are not wholly cross-resistant with the initial chemotherapy that had been used, allowing different possibilities for further treatment. But there are disadvantages, especially since it would be more difficult to demonstrate useful activity in this previously treated group.

[Slide]

There certainly are many new methods and new agents that are available to us to look at, and that are under study in lung cancer today, and we are all very excited about these approaches and look forward to their results.

If we look at the new agents, this list that I have put here is a small one but these are interesting agents. Topoisomerase I inhibitors are particularly interesting not only because of their activity in other tumors but --

[Slide]

-- with the activity that was seen in this fairly large Phase II trial of 48 patients receiving topotecan as initial treatment. Again, these are patients with extensive disease. The 5-day intravenous topotecan treatment yielded

a major response rate of nearly 40% as a single agent, and the median survival was 10 months. Now, the response rate is due entirely to the topotecan but the survival rate is due to both the topotecan and whatever chemotherapy was given thereafter.

[Slide]

So to conclude, there are few agents with demonstrated second-line activity in small cell lung cancer. There is no agent that is currently approved specifically for this indication.

This is a common clinical problem, relapse in small cell lung cancer, and it is a major unmet need. CAV appears to be as effective a combination as is available in this setting with reports in several second-line trials. After relapse, without effective treatment we have patients who are highly symptomatic and survival is very short, at 1.5 to 2.5 months in the trials that give us results of survival in that setting without effective treatment.

It is possible that if we had active single agents after relapse that they would have the potential to provide palliation, give a modest survival benefit and offer a rational approach for use in future combinations.

I look forward to Dr. Schiller's presentation concerning the further randomized trial with topotecan. Dr. Schiller?

Pivotal Phase III Study

DR. SCHILLER: Thank you very much.

[Slide]

090 was a randomized Phase III study of Hycamtin versus CAV as second-line therapy in small cell lung cancer patients who had relapsed at least 60 days after completion of their first-line therapy.

[Slide]

Patients were stratified on the basis of performance status and extent of disease at relapse. They were than randomized to receive either Hycamtin at a dose of 1.5 mg/m^2/day as a 30-minute IV infusion for 5 consecutive days, or to receive CAV, cyclophosphamide 1000 mg/m^2 on day 1, doxorubicin 45 mg/m^2 on day 1 and vincristine 2 malignant. Cycles were repeated every 21 days for 4-6 cycles for stable or responding disease respectively. Patients were allowed to receive additional cycles at the discretion of the investigator if thought to be clinically indicated.

[Slide]

The primary endpoint of this study was to evaluate response rate and duration of response. The secondary endpoints include time to response, time to progression, survival improvement of symptoms and toxicities.

[Slide]

Standard response criteria were used for the definition of response. All responses had to be confirmed 4 weeks later and all responses underwent independent radiological review. The target accrual was 200 evaluable patients, 100 in each arm. The study had a 90% power to rule out a 14% difference in response rate between Hycamtin and CAV in favor of CAV.

[Slide]

The eligibility criteria are summarized on this slide. All patients were required to have progressive or recurrent limited or extensive stage small cell lung cancer. Patients must have had one, and only one prior first-line regimen. They must have had a documented partial or complete response to their first-line chemotherapy. The recurrence must have been 60 days or more after completing their first-line chemotherapy, and patients were required to have bidimensionally measurable disease.

[Slide]

Patients were required to have adequate renal, hepatic and bone marrow function. They must have had a performance status of 0, 1 or 2. Asymptomatic brain metastases were allowed, and prior therapy with doxorubicin or epirubicin was also permitted providing it did not exceed 270 mg/m^2 or 540 mg/m^2 respectively. At least 24 hours must have lapsed since the last radiotherapy treatment.

[Slide]

Patients were entered on the trial between June of 1995 and March of 1997 from 45 institutions, including institutions in the U.S., Canada, Europe, U.K. and South Africa.

[Slide]

And, 223 patients were entered on the trial; 207 patients were eligible; 12 patients were cancelled before receiving any therapy. The data I will be showing you today will be on the 211 patients who received any therapy on the study. However, a response analysis was also done on all 223 registered patients in an intent-to-treat analysis. Response and survival analyses were also done on the subgroup of 195 eligible and treated patients.

[Slide]

Five patients on the Hycamtin arm and 7 on the CAV arm were cancelled. The reasons for not receiving therapy included withdrawal of consent and progression of disease.

[Slide]

The mean age in both groups was 61 years old, and 77% of the Hycamtin patients and 78% of the CAV patients had a performance status of 0 or 1. There were more women entered on the Hycamtin arm than the CAV arm, although this was not statistically significant.

[Slide]

The arms were well balanced in terms of extent of disease, patients with bulky disease and patients with liver metastases. However, more patients with brain metastases were entered on the CAV arm. A subgroup analysis was done in patients without brain metastases and the survival, res rates and time to progression results do not differ from the 211 patients I will be presenting.

[Slide]

The study was well balanced in terms of best response to prior first-line chemotherapy, as well as time to progression from prior first-line chemotherapy.

[Slide]

This slide shows the prior chemotherapy regimens that patients received, and 97% of patients in both arms received an etoposide-containing regimen at some point in their first-line therapy; 26% of patients on the Hycamtin and 22% of patients on the CAV arm had received anthracycline as part of their first-line therapy.

[Slide]

The patients on the Hycamtin arm received a total of 446 courses, while patients on the CAV received 3559 courses. The median number of courses on the Hycamtin arm was 4 and on the CAV arm was 3. There was no difference in the percentage of courses that were delayed over 7 days between the 2 arms, or the percentage of courses requiring

dose reductions.

[Slide]

Twenty-four percent of patients receiving Hycamtin had partial response to therapy. One patient on the CAV arm had a complete response and 17% had a partial response, for an overall response rate of 18%. The difference between the overall response of 24% on the Hycamtin arm and 18% on the CAV arm was not statistically different.

[Slide]

Although response rates did not differ between the two arms, this result did achieve the protocol's primary objective by establishing that Hycamtin is at least as effective as CAV in this patient population.

[Slide]

Response analysis was also done on all 223 registered patients in an intent-to-treat analysis. Again, response rates did not differ statistically between the two arms.

[Slide]

The duration of response, time to progression and time to response between Hycamtin and CAV was not statistically significant different. The median survival on the Hycamtin arm was 25 weeks compared to 24.7 weeks on the CAV arm. Forty-seven percent of patients receiving Hycamtin were alive at 6 months compared to 45% receiving CAV; 14% of

patients in both arms were alive at 12 months. Needless to say, these differences were not statistically significant different. Response and survival analyses were also done on the subgroup of eligible and treated patients. No differences in response rate, time to progression and median survival were observed between the 2 arms in this subgroup of patients.

[Slide]

Shown on this slide is the time to progression curve of the patients on the Hycamtin and CAV arms.

[Slide]

This slide shows the survival curve of patients on the Hycamtin and CAV. Again, these were not statistically significant different based upon the log rank analysis.

[Slide]

Nine symptoms were also assessed on this study using a disease-specific symptom questionnaire to evaluate symptom palliation. Seven symptoms had been part of a previous validated instrument. Patients assessed their symptoms on a scale of 1-4.

[Slide]

Symptoms were assessed pretreatment and prior to each cycle by the patient. Improvement was defined as a positive change sustained for 2 consecutive assessments.

[Slide]

Nine symptoms were evaluated. The disease-specific pulmonary symptoms included cough, dyspnea, chest pain, hoarseness and hemoptysis. The general constitutional symptoms included fatigue, activity level, anorexia and insomnia.

[Slide]

This slide shows the percentage of patients that had an improvement in constitutional symptoms. More patients receiving Hycamtin had an improvement in fatigue, activity level, anorexia and insomnia than patients receiving CAV. This was statistically significant for the first 3, fatigue, anorexia and daily activity.

[Slide]

Lung cancer symptoms that were assessed are shown in this slide in the order of frequency. More patients on the Hycamtin arm had an improvement in 4 of these, shortness of breath, cough, chest pain and hoarseness, than on the CAV arm. This was statistically significant for shortness of breath and hoarseness.

Note that although Hycamtin did not improve hemoptysis more than CAV, the number of observations in both arms was small.

[Slide]

I will now turn my attention to the safety data, including hematological and non-hematological toxicities,

serious adverse experiences and deaths.

[Slide]

The median neutrophil count was slightly lower on the CAV arm compared to the Hycamtin arm. Approximately 70% of the patients on both arms developed grade 4 neutropenia at some point in their course. However, there was a higher incidence of grade 4 neutropenia on the CAV arm in course 1, and overall more CAV courses were associated with grade 4 neutropenia than Hycamtin courses.

[Slide]

There was no difference in the number of patients experiencing febrile neutropenia or sepsis between the 2 arms, although more CAV courses were associated with febrile neutropenia and grade 2 or worse infection than Hycamtin courses. And, 2.8% of patients on the Hycamtin arm died due to infection or sepsis compared to 1.9% on the CAV arm. This was not statistically significant.

[Slide]

More thrombocytopenia was seen with Hycamtin than with CAV, although the median nadir platelet count with Hycamtin was only 81,000. There was no difference in bleeding complications between the 2 arms. Six percent of Hycamtin courses required platelet transfusions compared to 1% of CAV courses.

[Slide]

Hycamtin was also associated with more anemia and red blood cell transfusions compared to CAV.

[Slide]

Other toxicities occurring in 5% or more of patients are shown on this slide. They include nausea and vomiting, shortness of breath, asthenia, fatigue, abdominal pain and neurotoxicity. However, there was no difference between these 2 arms with the exception of neurotoxicity, and 5.7% of patients on the CAV arm experienced grade 3 neurotoxicity while no patients on the Hycamtin arm experienced grade 3 neurotoxicity.

[Slide]

There was no statistically significant difference in the number of dose reductions for hematological toxicities between the 2 arms. There were more dose reductions for non-hematological toxicity on the CAV arm, and 10.5% of patients receiving CAV had a dose reduction for non-hematological toxicity. This was due primarily to neurotoxicity. No patients on the Hycamtin arm had a dose reduction for neurotoxicity.

[Slide]

This slide shows the most frequently reported serious adverse events. They included febrile neutropenia, granulocytopenia, thrombocytopenia, pneumonia, sepsis and fever. There was no difference in any of these between the

Hycamtin arm and CAV, with the exception of thrombocytopenia.

[Slide]

The percentage of patients withdrawing for related adverse experiences was 9.3% on the Hycamtin arm and 9.6% on the CAN arm.

[Slide]

Fifteen patients on the Hycamtin arm and 8 patients on the CAV arm died within 30 days of their last dose. Four of these on the Hycamtin arm were thought to be drug related compared to 3 on the CAV arm. There was no statistically significant difference between the number of unrelated deaths on the 2 arms, which was primarily due to progressive disease.

[Slide]

In conclusion, Hycamtin was associated with more thrombocytopenia and anemia, while CAV was associated with more dose reductions for non-hematological toxicity including neurotoxicity.

[Slide]

Hycamtin provides greater symptom relief than CAV and yields response rates and survival similar to the 3-drug combination of cytoxin, Adriamycin and vincristine.

We conclude that Hycamtin is comparable to CAV in terms of response rates and survival, and is an active and

well tolerated drug.

Thank you. Dr. Fields will now be concluding our presentation.

Supportive Studies, Summary and Conclusions

[Slide]

DR. FIELDS: You have just heard Dr. Schiller present the results of our randomized Phase III study. What I would like to do is present an overview of our Phase II program.

There were 3 Phase II non-comparative studies in this program. All patients received 1 prior chemotherapy regimen. Patients were stratified for sensitivity to first-line chemotherapy using greater than 90 days from the time of last treatment to the time of documented relapse as criteria for sensitivity. Other eligibility criteria were essentially the same as for our Phase III study.

[Slide]

As you can see, these were large Phase II studies. They were multi-institutional studies. One was done in North America, one was done in Europe and one other was done in Europe under the auspices of the EORTC.

[Slide]

If we look at response rates, and I have put up 090 for comparison, you can see that their response rates in the Phase II program ranged from 11% to 31% in the sensitive

patients, which is comparable to the results of the 090 study. However, in the refractory populations the response rates only ranged from 2% to 7%, lower than the sensitive patients as one would expect.

If we look at response duration, again, the Phase II studies had response duration of about 20-23 weeks, which is somewhat higher than our Phase III randomized study for Hycamtin at 14 weeks. The refractory population had even longer response durations, although I will point out that there were few responders so it is difficult to compare.

[Slide]

If we look at time to progression, the overall time to progression in the Phase II studies was approximately 13 weeks, which is similar to our Phase III study which also had a time to progression of 13 weeks. Time to progression for the refractory patients in the Phase II program was approximately 8 weeks, which is lower than the sensitive patients.

[Slide]

Finally, if we look at survival, we see that the overall survival in the sensitive group ranges from 26 to 36 weeks, a little bit higher than in our Phase III program where it was 25 weeks.

[Slide]

However, this population did have a definition of

sensitivity that was somewhat more restrictive, using 60 instead of 90 days, and perhaps that explains the small difference. In the refractory patients the overall survival rates were less, being under 20 weeks.

[Slide]

In one of our Phase II studies we did have a disease-specific symptom questionnaire. I have listed the 7 symptoms that we had in this questionnaire on the left. Two symptoms were not included in study 053 but were later added in our randomized study. Under the percents I show the number of patients who improved, the specific symptoms in both 053 and 090, and you can see that the results are comparable. In the denominators of these fractions I have put the number of people who had these symptoms at baseline and, once again, you can see that there is a considerable number of patients in both 053 and 090 with these symptoms, except for hemoptysis where only 9/15 patients had these symptoms to begin with.

[Slide]

If we look at the integrated overview of efficacy, the 4 studies, the 1 Phase III study and the 3 Phase II studies, had similar designs to be able to combine these studies to do an efficacy analysis. These were analyzed using criteria of sensitive versus refractory patients.

[Slide]

For the sensitive patients, the overall complete response rate was 3.6% and the partial response rate was 16%, for an overall response rate of approximately 20%. In the refractory patients the overall response rate was only 4%, and I will point out that there were a number of patients with stable disease in both groups.

[Slide]

Looking at the median time to events, the response duration in the refractory group of patients was a little bit longer than the sensitive at 25 versus 18 weeks, although there were few patients in the refractory group. The time to progression, survival and 1-year survival were all greater in the sensitive patients, as expected, with approximately 20% 1-year survival for the sensitive patients.

[Slide]

In conclusion, the Phase II data that we presented are consistent with the efficacy data Dr. Schiller presented for the randomized Phase III study.

[Slide]

I would now like to review the safety of Hycamtin in small cell lung cancer, and I am going to contrast that to the ovarian cancer population for which the drug has already been approved. I will do this for hematologic toxicity, non-hematologic toxicity, serious adverse

experiences, deaths and withdrawals.

[Slide]

This overview will include the 426 small cell lung cancer patients and the 453 ovarian cancer patients who received Hycamtin for 5 days every 3 weeks at a dose of 1.4 mg/m^2.

[Slide]

As you can see, the target dose was similar in both groups, about 75% or 80%. The median courses were greater for ovarian than small cell, although in the 090 study, using sensitive patients, the median courses were 4 instead of 3. Dose delays and reductions were more common in the small cell lung cancer population, but this was due to the use of G-CSF, which I will show you on the next slide.

[Slide]

If we look at the neutrophil toxicity, we can see it is very similar in both groups of patients. However, G-CSF was used considerably more frequently in the group of ovarian cancer patients, and the reason for this is that in the ovarian studies it was mandated that in order to maintain dose intensity G-CSF was to be used but that was not the case in the small cell pp.

[Slide]

Infectious complications were similar in both

groups, including febrile neutropenia, sepsis, grade 2 infections and deaths due to sepsis.

[Slide]

Platelet nadir was a bit lower with the small cell population, 76,000 versus 92,000. There was a modest increase in transfusions in the small cell population. However, severe bleeding was infrequent in both populations with less than 1% of courses complicated by severe bleeding.

[Slide]

The red blood cell toxicity was similar for both groups. There were a number of transfusions for both groups, and this may be due in part to the fact that we had mandated transfusions for anyone whose hemoglobin fell below 9, regardless of whether or not they were symptomatic.

[Slide]

Severe, that is grade 3-4, toxicity was infrequent for GI symptoms. It was more frequent in the ovarian population, as one might expect from the nature of the disease. However, with routine anti-emetics it was not difficult to prevent the nausea and vomiting but since the agent is not extremely anti-emetic medications are not routinely used. The other complications, again, were fairly infrequent in both groups.

[Slide]

If we look at the other non-hem/tox, you can see that, again, there were not very many patients who had grade 3-4 toxicity. Dyspnea was mainly due to the underlying disease in small cell lung cancer. Again, otherwise these toxicities were fairly infrequent.

[Slide]

Serious adverse events were similar in both groups, approximately 27% to 30% were related.

[Slide]

Withdrawals for adverse experiences were not common, 5% to 8% of the patients.

[Slide]

Deaths were more frequent in the patients with small cell lung cancer. Deaths within 30 days were mainly due to progressive disease. However, related deaths occurred in about 5% versus 1% with ovarian cancer. This result is consistent with what Dr. Gralla had presented to you of the results in first-line small cell lung cancer regimens and death rates.

[Slide]

Therefore, in summary, we can say that toxicities in the small cell lung cancer population are similar to the ovarian population. The predominant toxicity is clearly hematologic. Grade 3-4 non-hematologic toxicity is not frequent, and there is no evidence for significant organ

toxicity.

[Slide]

Before concluding, I would like to review a few of the cases that Dr. Gralla discussed in his opening presentation. First, over 90% of all patients with small cell lung cancer will relapse after first-line chemotherapy. Survival after relapse will be approximately 2 months if patients are not given effective treatment. This group of patients is high symptomatic. The treatment options are limited for this group of patients. Right now, no agents are specifically approved for second-line small cell lung cancer.

[Slide]

We have shown that single-agent Hycamtin is active in small cell lung cancer, as demonstrated in this large randomized second-line study; that the single-agent Hycamtin is as active, or is comparable to the CAV combination in the randomized study. We have shown evidence for symptom palliation. And, we feel that Hycamtin represents a new therapeutic option for the treatment of second-line small cell patients.

[Slide]

Therefore, we would like you to consider the use of Hycamtin as indicated for the treatment of small cell lung cancer after failure of first-line chemotherapy.

Let me close by saying that we appreciate this opportunity to present our data on Hycamtin, and at this time we would be pleased to try and answer your questions. Thank you.

Questions from the Committee

DR. DUTCHER: Thank you. The meeting is open for questions for the sponsor. Dr. Krook?

DR. KROOK: Just a couple of things that I thought of. One, in the patients who were placed on the randomization, I note that 22% of the people who had CAV had prior anthracycline exposure. Was that Adriamycin or was that commonly another one?

DR. FIELDS: Yes, in the vast majority it was Adriamycin.

DR. KROOK: I take it for granted that they had not reached 450 mg/m^2.

DR. FIELDS: Right. As we have shown, you could only have half of that so that you could have at least 4 courses.

DR. KROOK: The second question, I noted on slide 23 that there was a study that the dose was different at 2 mg/m^2 and that the response rate there was 39%, with a 10-month survival. I think the note was made by Dr. Gralla that other drugs are given afterwards. The choice of 15 chosen to correspond with the ovarian dose, a similar dose,

or was there excess of toxicity in that group that apparently had a higher response rate? I realize they are all extensive patients but we had a somewhat higher response rate and a longer survival rate.

DR. FIELDS: Yes, that was a study that was done in first-line small cell and Dr. Schiller was the first author, so I will let her comment on that study.

DR. SCHILLER: That study was originally designed when the maximum tolerated dose of topotecan was not known, and at that point we thought it was going to be 2.0. It did also require growth factor support. I think if we were to do it again we would not choose that dose.

DR. KROOK: Would I also say that all patients who were entered on this study, or at least the majority had had radiotherapy perhaps to the chest lesion at least? I mean, some of these were extensive disease perhaps that had had a response and went on but a certain majority would have had radiotherapy to the chest.

DR. FIELDS: Yes, the number of patients in both the CAV and Hycamtin group had prior radiotherapy. It was about 56% for the CAV group and just over 60% for Hycamtin, very similar in both.

DR. OZOLS: Getting back to the question about doses and dose schedule of Hycamtin, I mean, the biggest toxicity in that trial was related to the myelosuppression.

In the randomized trial about 14% of the patients had G-CSF and about 20% required platelets. Some of the asthenia certainly could have been related to the anemia that these patients experienced. Do you think you need this kind of a dose intensity that you are using in this group of patients? Any correlation between both the randomized trial and any other Phase II trial about dose reductions and response? I mean, do you think this is the appropriate dose to use in this group of patients?

DR. FIELDS: Unlike the ovarian patients who were allowed to be dose reduced, so if we looked at the toxicity by course, it can decrease if the patient's dose goes down. We didn't formally analyze it. We know that if we were to look by course for platelet toxicity, it goes down from about 21% in the first course to less than 5% when you get to about course 3 or 4. That is probably just due to dose reduction, but we did not study that formally. That is not as true for transfusions or white cells. But we have not done a formal study that we could present that shows a dose-response curve. I can't give you an exact answer as to whether this is the best dose but it seems to be an effective dose with acceptable toxicity.

DR. OZOLS: And, your last slide about the indication for second-line treatment, even for refractory patients or just for sensitive patients?

DR. FIELDS: Well, the indication was a general indication but the company feels that the activity has been demonstrated in patients who are at least 60 days from the time of their last chemotherapy to the time that they got treated.

DR. SIMON: A couple of questions. A couple of times you mentioned median survival of 1.5 to 2.5, or something like that, months for patients for second-line treatment, and you quoted a couple of studies, an Italian study and a SWOG study with low-dose cyclophosphamide. Have you done any sort of analysis to see whether there was comparability of patients in those studies to your Phase III trial, whether they would have satisfied your eligibility criteria, for example for performance status?

DR. FIELDS: Dr. Gralla, who reviewed the study, maybe could answer that question.

DR. GRALLA: yes, I believe they would for performance status. They are also largely an extensive disease population and that was true here as well. As far as you can tell from those reports, they do appear to be relatively similar. In terms of the time after last treatment for progression of disease, that cannot be discerned from those reports.

DR. SIMON: The other question I had, when you presented the tables of symptomatic improvement by symptoms,

you had less than the full battery of patients included in those analyses. What determines whether the patient got into those analyses? You had about 100 patients per arm but nowhere does it approach 100 patients in those analyses.

DR. FIELDS: In those tables, what we looked at is all the patients that had that symptom to see if they improved.

DR. SIMON: Well, even like fatigue.

DR. FIELDS: Yes, so if somebody never had fatigue, they would never make it into the denominator of that particular analysis.

DR. SCHILSKY: I wanted to explore this issue a bit further of sensitive versus refractory. Could you just briefly review what the definition of sensitive was as it was applied in these analyses?

DR. FIELDS: The difference between Phase II and the Phase III was just the 60 or 90 days, and that represented the time from the last dose a patient would have received the prior therapy to the time the patient had a relapse.

DR. SCHILSKY: So, if they relapsed -- if we take 60 days, if they relapsed at less than 60 days they were considered refractory; if they relapsed more than 60 days they were considered sensitive?

DR. FIELDS: But that would be the case in the

Phase III study that used that where there were no refractory patients but, yes, that would be how we defined it.

DR. SCHILSKY: So, do we have a way of estimating in the universe of small cell patients what proportion of patients might meet the criteria for sensitive versus refractory at the time of their initial relapse?

DR. FIELDS: I mean, we can't, of course, have an answer from our studies because we enrolled about half and half. So, that wouldn't be an accurate answer but maybe Dr. Gralla or Dr. Schiller could comment on that. They may have a better answer.

DR. GRALLA: The answer is no.

[Laughter]

I think it is difficult to say really what the percentage of patients would be. If you look back at that Southeast Oncology Group study though, Rich, about a third of those patients went on to receive further therapy later who might otherwise have been eligible, but you can't tell what percentage didn't want to be crossed over. So, I think it would be difficult to say. Certainly, as we all know, the overwhelming majority of limited disease patients and a small majority of extensive disease patients do respond. So, the majority would theoretically be eligible. Since most of those went to 3-4 treatments and then stopped, I

would think that it would be the majority of patients who would be "sensitive" and would not relapse for 60 days after their last treatment.

DR. SCHILSKY: Just so I am clear, the pivotal trial, the randomized trial did not discriminate between sensitive or refractory. This whole analysis is based on patients in the Phase II studies? I am sorry, they were all sensitive?

DR. FIELDS: They were all sensitive using the 60-day criteria.

DR. KROOK: Actually, it is almost the same question. It appears to me that all people on 90 either had to have their response and had to have 60 days of drug-free time, but my question was going to be, obviously, some people relapse on day 61 and some relapse a year later. Is there any difference in response between the relapse time? We have a population in 090 that is sensitive, defined by response. There are obviously a few people who relapsed shortly after 60 days, and I believe that the longer the disease-free interval, the better the response.

DR. FIELDS: Yes, we looked at that in a couple of different ways, although I am not sure it will completely answer your question. First, we looked at patients who relapsed 90 days or less to see if that would make any difference. I think we should have a slide on that.

[Slide]

Of the 22 and 21 patients on CAV, and I will point out that a couple in each arm actually had less than 60 days for this, about 13.6%, 4.8% of patients responded on Hycamtin versus CAV respectively. It is a small number but, certainly, there were some responders.

We also looked at prognostic factors to see if that would make a difference in terms of whether or not a patient was longer off therapy. From the literature you would expect that there would be some difference. I will point out that in the two groups, CAV and Hycamtin, they were equal. We showed that there was no difference between the two groups there.

[Slide]

But in terms of prognostic factors, for response rate what you see is that the only prognostic factor that we had is liver metastasis. I am sorry, gender also was a prognostic factor for response rate.

DR. MARGOLIN: Just a couple of comments or questions to clarify about the claims and who the population of patients were. First of all, I think it is good that there isn't a claim for survival because I think that even though Dr. Gralla's answer to whether these patients were comparable that are claimed to have a 1.5- to 2.5-month survival sort of in the community at large are comparable, I

don't think we can agree since these patients' clocks didn't start until 2 months after their last exposure to chemotherapy. So, they already look like a somewhat more favorable group.

Also, did you say that approximately 60% of the patients in both arms had had their radiation, suggesting that a number similar to that was represented by patients who started out with limited stage disease. Is that not correct?

DR. FIELDS: I can't tell you if that is correct. It is probably a fair comment. I could ask again if maybe Dr. Gralla could comment on how many patients might get radiotherapy that had limited versus extensive disease because some will have palliation, I suppose. But I would guess that you are right, that the majority would have had limited disease to begin with.

DR. DUTCHER: Do you have that information?

[Slide]

DR. FIELDS: So, you can see the prior chest radiotherapy is about 62% and 56% for CAV.

DR. SCHILLER: I was also going to add that only about 15% of patients had limited stage disease; about 85% had extensive stage disease.

DR. GRALLA: I think your point is well taken. It is not clear how many had limited disease at the first time,

but any patient who had probably had an excellent response with extensive disease might have received whole brain RT, and certainly a number of patients would have received palliative RT thereafter. But it is difficult from those community reports, as you mentioned, to know what percentage of those people present with limited and extensive disease. Those studies are only as good as far as they go. There are really not a lot of studies that help us there.

DR. DUTCHER: I would like to get back to Dr. Ozols' point about the dose in this population because they have been heavily treated with previous chemotherapy, perhaps some of them have had carboplatin, which we couldn't tell from the listing, although they had all had etoposide. Do you have any sense of the time to response, the dose at which people responded after dose reductions and whether, in fact, there is a lot more leeway than the 1.5 because certainly I think the practice with this drug in previously treated patients is a lot of dose reduction.

DR. FIELDS: Yes, there may be a couple of answers. We do have time to response. I believe it was approximately 6 weeks. Dr. Perez-Solar did a study in refractory patients using the 1.25 dose and he might comment on that.

DR. PEREZ-SOLAR: Yes, we did a study in the refractory population and we used 1.25. Certainly, I think

the proportion of patients with grade 4 myelosuppression was the same but in that study there were no tox deaths. So it may have been that our population of patients was more selected. So, it may be that the lower dose obviously is going to be less toxic. However, we cannot tell if the activity in the sensitive population will be the same because that was only refractory patients. So, it has not been done. We don't know if 1.25 would be as effective as 1.5.

DR. SWAIN: I wanted to get back to Dr. Simon's question about symptom improvements since one of the claims that you are making is that there is symptom improvement. As you said, you don't include all the patients in those charts. Do you have data looking at the responders and if they had symptom improvement, and then all patients rather than just putting in the patients who had the symptom to begin with?

DR. FIELDS: Yes. I will ask Dr. Gralla to answer the question about responders and symptom improvement, and then we can also look at all the patients in the denominator. I think that is what you would like to see in the symptoms improvement. So, we can show that after Dr. Gralla responds.

DR. GRALLA: Of course, it is difficult for a patient who doesn't have pain to improvement on pain. So,

the percentage of patients who had the symptoms were very similar to prior studies looking at people with small cell and non-small cell with these symptoms.

DR. SWAIN: I guess the converse would be did people decrease their performance or get pain?

DR. GRALLA: I think that is certainly worth looking at. But if we look at did the people who responded have better symptom control than those that did not, again, symptom control was a secondary endpoint for this trial and the subset analysis of looking at responders versus non-responders was not part of the power of the study or the size of the study.

Nonetheless, it is an excellent point that we are all curious about. If we simply look at numerical differences, if you take the 9 symptoms, in 7/9 symptoms there was greater improvement for those who responded to topotecan, and the same is true for CAV. If you look at the responders to CAV, 7/9 of the symptoms were more likely to be improved, or were improved for those responders. So, overall there was this trend towards improvement with response, albeit with the caveat that that was not the original design and some of those are very small numbers. For instance, there were only 6 patients who responded who had hemoptysis. So, you know, I would take that with a bit of a grain of salt.

DR. SANTANA: I want to get back to the issue of dose and toxicity. Knowing that many of these patients had had a prior platinum-containing regimen, if I remember the data correctly, do you have any data on pharmacodynamic relationships between renal function and the degree of myelosuppression that these patients suffered?

DR. FIELDS: We know that there was some relationship between creatinine clearance and the degree of neutropenia, but in a study done at Johns Hopkins where they looked at this in a group of patients with renal dysfunction, until the creatinine clearance got below 40 there really was not a great effect. We have seen that, you know, some patients with renal dysfunction might have a little bit more toxicity but not in a formal way. So, that is probably the best answer I can give you on that.

I did want to go back though to a question Dr. Swain had asked, and if we could just show a slide that puts all the patients in the denominator.

[Slide]

Basically, if we looked at all the patients in the denominator, obviously, the percent drops but, again, you see that the statistical significance remains for dyspnea, hoarseness, fatigue and activities of daily life. So, it doesn't really change the results but it does change the proportions.

The other question that I think you asked was did we look at how the symptoms got worse if you looked at all the patients. We did look at that and, just in summary, two of the symptoms were statistically significant in terms of time to worsening. If it would be helpful, I could show you the Kaplan-Meier plots of those symptoms.

[Slide]

If you looked at dyspnea and anorexia in terms of time to patients getting worse, those two were statistically better on Hycamtin and the rest came out equal.

[Slide]

And, I just want to show you one of the Kaplan-Meier curves to give you an idea of what we did. This would be dyspnea, and the line in black at the top would be Hycamtin and the dashed line would be CAV. If you just draw a Kaplan-Meier curve till symptoms worsen, which is all that we did here, we found that for the two symptoms I showed you there wasn't a more rapid worsening in two of the symptoms. The rest, again, showed a numerical trend for Hycamtin but not significant.

MR. GIDDES: In trial 90, patients taking the Hycamtin had a higher death rate than the patients taking the CAV drugs. Do you have any idea why the death rate was higher, and how do you think this can be controlled?

DR. FIELDS: As was shown, the overall death rate

was higher but most of the patients had progressive disease, and most of that was in the first cycle. So, while it is difficult to prove, certainly for early progressive disease rate, I think that is just one of the things that you get in the study. The actual related deaths, again, were 4 related deaths on Hycamtin and 3 related deaths on CAV. In both of those groups there was a death or two that was kind of equivocal. So, it is, again, well within the numbers that Dr. Gralla had stated of about 5% typical. These were actually a little bit less. So, I think the early death was not that high for this population.

DR. MARGOLIN: I am sorry but we may have to go back to that symptom slide. I am really bothered by the claim that there is statistically significant improvement in some of those selected disease-related symptoms in the absence of any real difference in response rate, unless you say that somehow responses were of greater quality with the Hycamtin; they are certainly not greater in duration.

And, the two questions I want to pose for consideration are whether since these are patient-reported symptoms the concept of an IND drug bias could have been introduced into the patient-reported symptom list, and also whether you looked at whether there was a difference in steroid use as an anti-emetic for these patients because some of those symptoms could have been relieved, at least

transiently, by the use of steroids.

DR. FIELDS: Yes, what we have done, and I can go through those, to answer the second question first, we did look at medications in terms of whether the medications, like bronchodilators etc. -- we went through them to see if there was any obvious benefit. We weren't able to find any benefit. We could not explain it by medications.

I am sorry, I have forgotten the first part of the question.

DR. MARGOLIN: Well, the concept of the IND drug bias, which we have discussed in this Committee before. Patient-reported symptoms may be influenced by the fact that the patient knows that he is on a drug which is not investigational but for this purpose it is a new drug.

DR. FIELDS: Yes, Dr. Gralla has had a lot of experience in these quality of life issues. Perhaps you have a thought on that?

DR. GRALLA: I guess there are probably two ways to look at it. One is your question about the steroids which could have made a difference, but typically, such as the ASCO guideline committee, has recommended for CAV steroids would be recommended for anti-emetics but not for topotecan. So, it would be more likely to be on the combination regimen than on the topotecan.

Secondly, your point about an open study, not a

blinded study, could be real for a bias for a study drug versus a combination regimen. However, we do know from the COATS study that looks at symptoms or complaints and concerns that patients have getting chemotherapy that time at the clinic is one of the top ten complaints that patients have, and being there five days in a row every three weeks versus one day might really have a negative bias towards a new drug. So, these are all things that I think could be considered but, again, these are patient reports and I think they report how they feel.

DR. OZOLS: I think in general too, there has been the observation that patients with lung cancer who get chemotherapy frequently will get symptom relief that is not correlated with their "objective" response. So, I am not sure that is really -- I mean, sometimes you see that, you see symptom relief first not just for this drug but a lot of chemotherapy trials in the past have shown that.

DR. GRALLA: And, I think, as you bring up, Bob, it is possible that a smaller response, not an objective partial response, could have symptom relief as well, which I think illustrates your point.

DR. SCHILSKY: As long as Dr. Gralla has the microphone, I wanted to ask this question of an experienced lung cancer doctor. If I were a patient with extensive small cell who had progressed after my front-line

chemotherapy, what criteria would you use to recommend to me that I receive topotecan as opposed to CAV as my next course of treatment?

DR. GRALLA: This is a question for me? Okay. Well, I think, first of all, the most important thing is to discuss with the patient whether or not they want further therapy. I think certainly that reasonable performance status patients would. I think that either one would be among my top choices. Clearly, if patients had had neurotoxicity in the past I would not want them to be on CAV. If they had any cardiovascular disease I would prefer that they not be on Adriamycin, especially the combination of cytoxan and Adria. And, I think for simplicity of use, the lack of hair loss if that is a problem for the patient, and for the slightly greater difficulty in use of anti-emetics, whatever, I generally would prefer the single agent, given similar results. And, I do have some confidence, having been one of the investigators on this study, in the symptom relief being greater. So, in our clinic, as we have done, we would prefer the topotecan.

DR. KROOK: A question which usually asked at this Committee, and here we have chosen the best of the worst, that people who have responded, and then we have retreated following the protocol treatment. Can you tell me what percentage got "best" supportive care versus crossover?

And, again, here CAV probably would be more likely to go to the topotecan only because topotecan is not usually used. So, I anticipate there is a group that got best supportive care, some that got CAV, and that is one of the reasons, as Dr. Gralla has said, that survival really is not important.

DR. FIELDS: We looked at patients who went on to receive third-line therapy, both chemotherapy and radiation therapy, and perhaps due to the nature of the disease there are not that many patients that did go on to receive chemotherapy, approximately 30% in each arm, which I think we could probably show you. If we then looked at survival in the people who went on --

DR. KROOK: It was even worse than this, I am sure.

[Slide]

DR. FIELDS: If you looked at the survival of the people who were censored because of third-line therapy, the median survivals I don't think actually changed by a week. So, we don't think that the third-line treatment really played a role, whether it was radiation or chemotherapy. It just didn't change the survival at all. I don't know if that helps.

DR. SIMON: Did you do an analysis of time to either progression of tumor or progression of symptoms, any of the symptoms? Dr. Gralla, I think, mentioned that these

patients typically have three symptoms. So, did you to an analysis, a Kaplan-Meier curve of time to event where the event is either progression of tumor as conventionally defined, or worsening of any of the symptom scores?

DR. FIELDS: Yes, we did do the time to worsening of the symptoms.

DR. SIMON: Where you don't censor out people who progress and go off study, which I suspect is what you did.

DR. FIELDS: Dave, could I ask you if you could help out? Did you censor the people on that Kaplan-Meier curve for time to worsening? I think that was the question.

DR. DUTCHER: Could you identify yourself, please?

DR. FITZ: Yes, I am David Fitz. I am a statistician at SmithKline Beecham. Yes, we did censor the patients.

DR. SIMON: My question then is do you have a Kaplan-Meier curve of time to event where event is either defined, one, as progression of disease or, two, worsening of any symptom score?

DR. FITZ: We have time to progression, time to progressive disease.

DR. SIMON: Event would be defined either as progression of disease or event would include worsening of any of the nine symptom scores?

DR. FITZ: We do not have the composite of that,

no.

DR. SIMON: Because when you do it the other way, you are always sort of selecting this one or that one. You have nine symptoms and there is a multiple comparison problem. I think the clearest analysis, if you want to claim symptomatic benefit is to do time to event where event is either progression of disease or worsening of any of the symptoms.

DR. FITZ: You are referring to a composite of nine symptoms --

DR. SIMON: Yes.

DR. FITZ: -- as well as progressive disease.

DR. SIMON: Right.

DR. FITZ: All of our symptoms are dealt with independently.

DR. DUTCHER: Thank you. Do you want to take a five-minute break? A five-minute break and then we will come back for FDA.

[Brief recess]

DR. DUTCHER: We will have the FDA analysis now.

FDA Review

DR. HIRSCHFELD: Good afternoon, Dr. Dutcher, members of the Committee, colleagues and members of the public.

[Slide]

I wanted to first acknowledge that what we do at the FDA is a team effort, and I wanted to note that the members of the team, most of whom are here in this room, consisted of, starting from the top, the three Robert's. Dr. DeLap has moved on. he is no longer a division director. Dr. Justice is the Acting Division Director. But Dr. DeLap has been very involved with topotecan from when it first came to the FDA, and was involved in the review of this particular application. Grant Williams is the team leader, and then Dr. Chen is the biometrics team leader. Dr. Smith did the statistical analysis for this particular supplement. Dr. Rahman and Dr. Keiffer did the analysis for the biopharmaceutics, and we always need someone who has to tie everything together and keep everyone on schedule, and that is Debbie Catterson.

[Slide]

The application that was submitted to us consisted of a Phase III randomized comparative study which you have heard about in some detail in the prior discussion, which consisted of 211 patients with a definition of sensitive, which I will touch on in a moment, of small cell lung cancer, and 3 Phase II studies of 319 patients with sensitive or refractory SCLS.

[Slide]

At the risk of repeating much of what was said

before but trying to emphasize a few different point than in Dr. Gralla's presentation, I wanted to begin the discussion of small cell lung cancer by stating that certainly I have hope, and the hope is that -- there are several aspects to it -- one is that something can be done about cancer in general and small cell lung cancer in particular and lung cancers and, secondly, the hope that the mechanism to be able to bring laboratory discoveries to patient care through the free enterprise system.

Rather than viewing the FDA as a bump in the road, as we have been characterized before, I would like to view our role as partners and that we are able to interact in meaningful ways with the research community and with the pharmaceutical industry. I particularly want to acknowledge the excellent relationships and collegiate interactions that we have had with SmithKline Beecham in analyzing this particular supplement as well as the whole topotecan program in general.

There are more than 40,000 patients in North America who are diagnosed with small cell lung cancer, and in this number is another hidden statistic, and that is that there is almost an epidemic of women who are contracting lung cancer in general and small cell lung cancer in particular. In fact, there are more women every year who get and die of lung cancer of all types than breast cancer,

about 50% more women, and the number of women who die from small cell lung cancer is approaching the number of women who die every year with breast cancer. This is an important epidemiologic fact and any therapy which is directed lung cancer in general and small cell lung cancer lung cancer in particular should be viewed with the same alarm and the same degree of enthusiasm and support as therapies directed towards breast cancer.

It is categorized at the present into limited and extensive, and I just want to touch on the fact that limited is an operationally defined term and that there is no universal definition for it. So, it tends to vary from protocol to protocol, study to study, continent to continent.

[Slide]

Through reviewing much of the same literature as Dr. Gralla reviewed, I found that untreated there is a median survival of about 2-4 months, depending on the series, and there has been an impact of chemotherapy on this disease. Unfortunately, it has not been curative but those of us in oncology really realize that it is very difficult to cure and we accept progress in any disease as a sign of hope and an indication to continue on.

For limited and extensive disease, as indicated earlier, the range for median survival is in the 10-14-month

range, and 5-year survival for limited disease can be as high as 8% depending, again, on the series. For extensive disease it is just anecdotal reports.

[Slide]

There are a number of agents which are in current use. As was pointed out, none of these is approved for second-line treatment but we all know that most agents in oncology are used off-label, and these have a variety of modes of action but you notice that although they all have different modes of actions, none of them are a topo-1 inhibitor. But what is interesting about this disease is that all these agents with different modes of action are able to achieve some level of response in patients. So, the small cell, the oat cell so to speak, biologically is quite interesting. It is sensitive to radiation; sensitive to chemotherapy, but is able to escape whatever modalities are administered to it.

So, combination chemotherapy has had the most effect and, as discussed earlier, both combination of cisplatin with etoposide or cyclophosphamide, doxorubicin and vincristine, which in the adult literature is called CAV and in the pediatric literature we usually call it a form of VAC, is what is the standard method of therapy.

[Slide]

As has been discussed earlier, there is a fairly

high relapse rate. So, that brings us then into the definitions which we will use for the rest of what I hope to be rather brief discussion on my part, and that is that patients that never respond to chemotherapy or relapse within 90 days of the last dose have disease that is termed refractory or resistant, and those that relapse greater than 90 days have disease that is termed sensitive.

[Slide]

Second-line therapy currently consists of combination with either the original regimen if the patient is considered sensitive, or another regimen if the patient is considered refractory or resistant. The therapy goal is usually palliation and improved quality of life.

[Slide]

The randomized study that was submitted with this application is trial 090, and it was an open, multicenter, comparative study which was designed to evaluate the efficacy and toxicity of topotecan for the treatment of patients with sensitive small cell lung cancer who have relapsed at lest 60 days, and this is the difference between this particular trial and looking at the more general definition of sensitive, which is 90 days. The reason for the change in definition was in order to increase the accrual rate so that more patients would meet the eligibility criteria in a given time frame.

[Slide]

The primary objectives were response rate and response duration.

[Slide]

The secondary objectives were time to response, time to progression, survival, symptoms of disease and toxicity.

[Slide]

The treatment regimens, as discussed earlier, was the regimen which historically was considered the Phase II dose at the time of the writing of this protocol, which is 1.5 mg/m^2/day for 5 consecutive days on a 21-day cycle, and that was compared to a fairly standard regimen of cyclophosphamide at 1 g/m^2, doxorubicin at 45 mg/m^2 and vincristine 2 malignant, which is administered on day 1 of a 21-day cycle.

[Slide]

Dose modifications were for the following criteria: grade 3-4 neutropenia; grade 4 thrombocytopenia; any clinically significant non-hematologic toxicity, with the exclusion of nausea; or total lifetime cumulative dose of doxorubicin or comparable dose of epirubicin.

[Slide]

Tumor measurements were done by noting malignant lesions which were measurable in 2 dimensions, with clearly

defined margins by diagnostic studies of greater than or equal to 2 cm, or a palpable lymph node lesion with at least 1 diameter greater than or equal to 2 cm and this had to be confirmed by a second physician, or a skin lesion with a diameter of at least 1 cm and this had to be confirmed by photograph.

[Slide]

The response criteria were the standard response criteria that are used in measuring solid tumors. Complete response had to have complete disappearance of all known measurable and evaluable disease determined by 2 measurements not less than 4 weeks apart and, of course, no new disease.

Partial response was a greater than 50% decrease in the sum of the products of the greatest length and perpendicular width for, again, the same time period of greater than 4 weeks, with no simultaneous increase in the known lesion or the appearance of any new lesions,

The response rate in this case was defined as percentage of the total of evaluable patients which have a complete or partial response, where evaluable is defined as a patient who received therapy, although we will look at the data from intent-to-treat and from using this definition in the protocol.

[Slide]

Time to event was defined as time to response, which was the time from the first infusion and not from the time of randomization, just to be consistent in understanding the terms here, to the time of the initial documented response. The time of progression was from the first infusion to the time of the first documented progression. The duration was the difference from the initial documented response to the first sign of the progression.

[Slide]

There was a symptom response scale that was used, which was a 4-point ordinal scale. To be scored on the scale, a patient had to have a decrease of at least 1 category for 2 consecutive visits, and this was considered a positive response. There were questions which were for each of these 9 symptoms: Did you have the following symptom during the past 3 weeks, meaning since the last cycle, and they were "not at all," "quite a bit," "very much." This questionnaire was carried out on all the continents in all the sites, and while I was reading the protocol I had an impression of people yelling in all these different languages, "more," "less,"

[Slide]

That, of course, brought up one of the difficulties in the person who administered these questions

and the exact timing, and the phrasing, and how they were translated into all the different languages, which could introduce some ambiguities into understanding it, and we will discuss that a little further when we present the data.

[Slide]

The sample size calculation was predicated on a power to show non-inferiority of topotecan, or the response rate of CAV minus Hycamtin response rate would exclude a 14% difference in favor of CAV for a 2-sided alpha of 0.05, 90% power.

The assumptions were based on the global experience with topotecan and the highest reported response rates for CAV in the published literature as second-line treatment.

[Slide]

The demographics of the patients in this randomized study were fairly balanced. There were 107 patients who received topotecan and 104 who received CAV. There were more females in the topotecan arm than in the CAV arm. Otherwise, for age, race and body size they were approximately balanced.

[Slide]

These numbers are discussed in the subsequent discussion but I will just repeat them, the patients who had limited disease at the entry were balanced, about 17% and

15% for topotecan versus CAV. Prior radiation was 65% versus 56%. There were more patients in the CAV arm who had some prior surgery. Cranial irradiation was balanced, performance status and metastases. As the first regimen 77% and 79% had a platinum-containing regiment with etoposide. First-line response as a CR was balanced, about 40%, and the median time to progression was also balanced as the maximum lesion diameter.

[Slide]

In the last demographics slide comparing the 2 arms, there was a balance between those who had prior CAV, 35% versus 31%, and the response was about the same in these 2 arms. That is, having prior CAV didn't initiate a bias against responding to CAV a second time. That is jumping ahead but I wanted to make the point now.

Those who relapsed less than 90 days, that is, who were fit into this special definition of sensitive in order to increase accrual, were balanced between the 2 arms, 27% versus 24%. So, about a quarter of the patients were in this foreshortened category and the response rate, as indicated in the prior discussion, was lower for these patients.

For those who had prior CAV and relapsed less than 90 days, again, there was a balance between these 2 arms and none of these patients had a response.

[Slide]

In terms of exposure to intended dose, there were more courses of topotecan administered than CAV, and 75% of the courses had the intended dose for topotecan versus 78% for CAV. The courses that were delayed beyond 25 days was 27% versus 16%. For the reduced dose, it was 38% versus 29%. And, those patients that were considered non-evaluable was 15% versus 19%.

[Slide]

Now we come to the results. Based on the intent-to-treat, that is those patients who were enrolled and randomized, there was a response rate of 23.2% versus 17.1%, and the difference between these was 6%, which was no difference.

In the treated patients the response rate was, as discussed earlier, 24.3% versus 18.3%. Again, the difference is 6% and there was no difference between these.

The median duration of the response was 14.1 versus 15.3 weeks, and these are the 95% confidence intervals, again no difference.

[Slide]

The secondary endpoints were the time to event and the median survival. They were essentially equivalent in the two arms.

[Slide]

The symptom response scale -- and what I will point out here is how many of the patients reported those symptoms to be being with. So, we had 107 and 104, to refresh your memory. Of those patients who had symptoms recorded at baseline, there were 77 who reported the symptoms with topotecan and 76 on CAV. So, they were approximately balanced. Of those 77, and the arithmetic can be worked out readily, most of the patients reported shortness of breath and cough and anorexia and fatigue. There was a new category which was not in the previous studies, which was interference with daily activity. Of those patients who had this symptom and who indicated improvement, most of the categories did show a bias toward improvement for those who received topotecan, with the difference of hemoptysis where there was a bias in favor of CAV.

[Slide]

There adverse event some difficulties in looking at the symptom data, much of which was touched on in the earlier discussion but just for completeness I will touch on our perspective, and that is that the study was, of course, unblinded. It was clear when someone was coming in 5 days in a row versus 1 day. One category change was sufficient to indicate a response and, again, not being sure how a person feels from one week to the next or how the words were

translated into all the various languages and if "a little bit" and "somewhat" always means the same thing, especially when you are looking at 9 different symptoms and you are trying to remember back 3 weeks. And, the regimens had different exposure times to the ancillary medications and the care providers.

So, while it wasn't possible to distinguish or extract a difference in exposure to ancillary medications and relate that directly to the symptom improvement, just being in the clinic could have both a positive and a negative effect on the patient, and that probably varies from patient to patient and from the relationship of the care giver to the patient, and whether they are seeing the same care giver from time to time again. So, I just point these out, that these factors decrease the reliability but I think the trend can still be described.

[Slide]

Hematologic toxicity was prevalent on both arms to about an equal degree. There was more thrombocytopenia on the topotecan arm than on the CAV arm, and there were more patients with grade 3 or 4 anemia on the topotecan arm thana the CAV arm.

[Slide].

The infectious complications were about balanced, as described earlier, except t here were a few more

patients, literally a couple, who seemed to die from sepsis on the topotecan arm.

[Slide]

What this translated into clinically was that the patients on the topotecan arm got significantly more platelet transfusions and red cell transfusions than on the CAV arm, and it is not clear whether this is protocol driven or clinically driven, but this is clearly a trend that bears watching.

[Slide]

In terms of the non-hematologic toxicity, all grades and whatever source, almost every patient had the opportunity to experience these toxicities and they were prevalent in most courses. Those that were considered therapy-related were approximately balanced, 80% to 85%, and those courses that were therapy-related were exactly balanced.

[Slide]

Those adverse events in 10% of courses from all causes are displayed on this slide in decreasing order of frequency. You can see that the grade 3-4 toxicities were in a relative minority of all the patients. So, overall both these regimens were fairly well tolerated when it comes to the non-hematologic toxicities.

[Slide]

Of those courses with therapy related, where it was probably or definitely related, these were the major toxicities in terms of frequency. I didn't include in this slide the neurotoxicity because that was described earlier, associated with the CAV, probably the V in the CAV. But, again, only a relative minority of the patients had serious non-hematologic toxicities that could be considered related to the therapy.

[Slide]

Patients who withdrew as a result of an adverse event were 9.3% on topotecan and 12.5 on CAV. Those who withdrew subsequent to what was termed therapy-related adverse event were balanced between the arms and it was a little less than 10% of all patients.

[Slide]

The deaths on study within 30 days of therapy, regardless of cause, was 13% for topotecan and 7.7% for CAV. Due to hematologic toxicity, it was 3.6% versus 1.8%, and therapy-related was 4.8% versus 3.8%, which is in line with other studies for small cell lung cancer, although no other study had these precise eligibility criteria.

[Slide]

So, to summarize the efficacy endpoints, the response rate was 23.2% versus 17% on the intent-to-treat. The difference is 6% which is the same number statistically.

The duration of the response was 14 versus 15 weeks. The time to progression was 13 versus 12 weeks. The time to response, as I pointed out earlier, was 6 weeks, and the median survival was 25 versus 24 weeks.

[Slide]

So, to summarize this randomized study, topotecan demonstrated activity that was similar to CAV in sensitive patients with small cell lung cancer. There was a trend to improvement on a symptom scale on the topotecan arm but this is very difficult to interpret and would have to be replicated. And, there were more transfusions on the topotecan arm, both platelet and packed red cells, and there were more deaths that were associated with the hematologic toxicity.

[Slide]

I will summarize the Phase II studies on this one slide by just stating that they were done. They were done rather well. They used the same regimen. They were completed in different geographic locations. They admitted both sensitive and refractory patients, and the sensitive patient definition was that which was used in the rest of the literature, which is patients who relapse greater than 90 days following their last infusion.

[Slide]

So, to integrate the response data on all the

studies, both the randomized and the 3 Phase II studies, in a population of 426 patients there was an overall response rate of 14%. In the sensitive patients it was 20% and in the refractory patients, using the standard definitions, it was 4%.

[Slide]

The time to event endpoints in weeks, overall the time to response was 6 weeks and there is really no difference between refractory and sensitive. The duration of response was 18 weeks total, but it was 25 weeks overall, which replicates the findings in the randomized study. The time to progression was 11 weeks overall, and the survival was 21 weeks overall, and it was more favorable in the patients who were sensitive.

[Slide]

Hematologic toxicity was found, in terms of grade 4 hematologic toxicity, in 31% of the patients or 12% of the courses. Neutropenia, which is the most significant, was found in 74% of the patients or essentially 40% of the courses. Thrombocytopenia, and this is again grade 4 thrombocytopenia, was found in 28% of the patients or a little over 10% of the courses. Grade 4 anemia was in 3% of the patients, but if we add grade 3 and 4 together the number becomes significantly higher, more on the order of 40%, I believe.

[Slide]

Febrile neutropenia, using the definition of fever greater than grade 2 or any grade febrile neutropenia, appeared in 8% of patients. If we look at fever greater than grade 2 with grade 4 neutropenia, it appeared in 4% of patients. If we look at infection, it appeared in 13% of the patients and sepsis in 4% of the patients.

[Slide]

The non-hematologic toxicities grade 3 or 4, regardless of scores, were in a relative minority of patients, the most frequent being dyspnea and pneumonia, asthenia, convulsions and abdominal pain.

[Slide]

And those adverse events which were leading to withdrawal of any source were sepsis, 2%; thrombocytopenia, about 1.5%; asthenia and neutropenia, about 1.5%.

[Slide]

Of the patients who received topotecan who died within 30 days, the death rate was 16.4%. Most of these were due to progression of disease. Treatment related is a little over 5%, and those related to hematologic toxicity, which is a subset of this number, here, was 3%.

[Slide]

So, the strengths and weaknesses of the application from my point of view are that the patient

population size was sufficient for statistical analysis. It was appropriately powered. There were well designed and executed studies, with a replication of the positive results. There were prospectively defined endpoints and analyses, and there were disease-related symptoms that were examined in at least two of the studies.

The weaknesses were the hematologic toxicity which was present. There was an unfavorable risk/benefit ratio for refractory patients. The regimen required 5 visits for every 21-day cycle.

[Slide]

In conclusion then, topotecan does have clinical activity in sensitive small cell lung cancer patients with a response rate of 20%, and in this case I would categorize that sensitive is those patients who are greater than 90 days since the last infusion of chemotherapy. In the comparative study topotecan showed a trend toward improvement on a disease-related symptom scale which we can presume and attempt to extrapolate or infer resulted in some patient benefit other than the response. The most frequent complications were hematologic, and the treatment-related death rate was about 5%. That is it.

Questions from the Committee

DR. DUTCHER: Thank you. Questions for Dr. Hirschfeld from the Committee?

DR. SWAIN: You said that there were 33% of patients that had dose reductions, and in the sponsor's presentation they said most of those were for hematologic reasons. What were the specific hematologic reasons for all those dose reductions and to what level were they reduced?

DR. HIRSCHFELD: Specific hematologic reasons were thrombocytopenia and neutropenia, and the levels were actually prescribed in the protocol and there were no violations that we could find in terms of the dose level reductions on the protocol schedules.

DR. SWAIN: And, did most of the patients just require one dose reduction?

DR. HIRSCHFELD: Most of the patients required one dose reduction and, as we found in the ovarian application, there was not any evidence for cumulative toxicity, and most of the dose reductions that occurred, occurred in the first cycle.

DR. KROOK: Steve, how many people would have been eliminated between the 60 and 90 days on 090? You have obviously presented some statistics which suggest that in that group if you lower the number of days they have increased their accrual but, obviously, these are the people who haven't done well. So, what percentage of the entries, do you know, was between 60 and 90? Would that change the power of the study?

DR. HIRSCHFELD: About a quarter of the patients were in the 60-90-day window there, and it would change the power of the study but I don't think it changed the conclusions.

DR. WILLIAMS: Steve, do you or the company have the results in those patients? Because you are proposing that we change it to 90 rather than 60 as in the pivotal study? What was the response rate in the group of patients that was between 60 and 90?

DR. HIRSCHFELD: I think Dr. Beckman has those results on a slide, but we look at those results and it was less than the overall response rate.

DR. WILLIAMS: So, we would have to decide whether we thought an overall 14% response rate was worth it or not.

DR. HIRSCHFELD: In a small number of patients.

DR. WILLIAMS: Right, but our usual role is not to make a conclusion on a subset, unless there is convincing evidence that a subset is different.

DR. DUTCHER: Other questions? Dr. Krook?

DR. KROOK: I just have a comment. As I read Steve's preparation here, there was a comment that I circled and he writes: Overall, the probability of having a drug-related death is about the same as having a response for a patient with refractory disease. That hit me, as I sit with a patient with refractory disease, when they become equal

you tend to shy away. And, I think the data supports that.

DR. HIRSCHFELD: That is the statistical basis for our recommendation for sensitive, to do that. I would also point out that this is a single agent and it is offering a new mechanism of action in terms of small cell lung disease, and we all know a secret, that most people tend not to treatment with single agents and, if there were approval of topotecan for this indication, people would begin to look at combinations, perhaps at different doses than the single-agent dose.

DR. HIRSCHFELD: Cooperative groups already are. The other comment is that as one finishes chemotherapy, with all the problems of 6 cycles or whatever you want, that is, once every month or one day a month, and if this is the dose recommendation, at least where I practice, it becomes a real stumbling block for people to come 5 days. It really directs their life. That is a comment, nothing else.

DR. OZOLS: I guess you don't have the data, but the percent of those 30-odd percent patients who had dose reductions, the response rate in that group of patients, is it any different?

DR. HIRSCHFELD: No, it is not different.

DR. OZOLS: It is not different or you don't have the data?

DR. HIRSCHFELD: Looking at those who were dose

reduced, we didn't find a statistical difference. Again, most of the reductions are in the first cycle and most of the responses only occur at 6 weeks.

DR. SCHILSKY: I have a sense that what we are going to come down to is some sort of discussion about risk/benefit ratio in patients with sensitive disease, and so it again comes down to what is the definition of sensitive disease. So, in your assessment, since you have looked at all the infection, would you consider the definition of sensitive disease to be patients who relapse greater than 60 days or patients who relapse greater than 90 days, keeping in context the toxicities of the treatment?

DR. HIRSCHFELD: I am glad you asked that. It my opinion, because that is all I can give you, we don't have enough data on the 60-day time window. We only have one study. We only have 22 patients. And, while there is a response rate in those patients and we can say there is activity, it hasn't been replicated. We have far more data on the patients with the 90 days and, certainly, I would feel very comfortable with a definition of sensitive of 90 days. If we can go down to 60 days, that would just be an opinion and I couldn't state anything further.

DR. WILLIAMS: I think part of that depends on whether you would emphasize more the data from the controlled trial versus the increasing mass of data from all

the trials together. We have one controlled trial and we have other Phase II trials. So.

DR. SCHILSKY: But just to be sure that I am clear, in the controlled trial abut two-thirds or so, or three-quarters of the patients were enrolled with the greater than 90-day requirement where the protocol was amended, and in all the Phase II trials, all of those patients were greater than 90 days.

DR. HIRSCHFELD: That is correct.

DR. SCHILSKY: So, the great majority of the data is for that group of patients, and the data on the controlled trial, which is in a sense supported by the Phase II studies, is for that group of patients.

DR. HIRSCHFELD: Correct.

Committee Discussion and Vote

DR. DUTCHER: Thank you. Any other points for discussion before we address the questions?

[No response]

We will take a look at the questions then. I think we want to thank Dr. Hirschfeld for a very concise presentation, keeping us ahead of schedule.

The first question, study 090 does not provide evidence of a survival of time to progression benefit of topotecan versus CAV, and it would be hard to document a clear survival effect of CAV in this setting. The evidence

for benefit thus consists of a response rate and response duration. Does the response rate of 24% in this setting, with a duration of response of 14 weeks, as presented for trial 090, provide substantial evidence of efficacy in the second-line treatment of patients with sensitive small cell? Dr. Ozols?

DR. OZOLS: Yes.

DR. DUTCHER: Dr. Krook?

DR. KROOK: I would answer yes also.

DR. DUTCHER: Any comments? Dr. Simon?

DR. SIMON: Unless it is supported by symptomatic evidence of benefit or quality of life or delaying time to progression of symptoms, I don't see why response rate in itself would be evidence of clinical benefit.

DR. WILLIAMS: I want to clarify. I think this question is intended to get just to that point, is small cell lung cancer a somewhat different disease than, say, non-small cell in terms of whether a response is of obvious clinical benefit to you? Do you think it is self-evident that advanced small cell patients who get a PR of this duration is really clear evidence of patient benefit in those cases? That is really the question.

DR. DUTCHER: In view of the rapid demise without treatment demonstrated on many of the studies, as opposed to maintaining some kind of functional plateau, whether it is

improvement or not, I think the answer is that it is different, in my opinion.

DR. SIMON: I don't think we really have a comparative group to know what the demise is for patients who were sensitive in the way it is defined in this setting that would be eligible for this study. I don't think we really have had any data presented that was satisfactorily convincing to me that those patients would have a demise any more rapidly than the patients on the study would.

DR. KROOK: Perhaps Dr. Gralla, who reviewed this literature more recently than most of us -- there were a couple of best supportive studies which were done, and I don't know how long the interval between last treatment and time started ticking between the relapse. I don't know that but it is probably known somewhere. I mean, I think that is the question. If you have in best supportive care an interval of 3 months or 4 months and we have arms that are best supportive care from the Italian study -- maybe it is there; I don't know.

DR. GRALLA: Really, Jim, the best supportive care studies were done in the non-small cell, not the small cell, unfortunately, and of course the survival is very brief in those patients. In the Italian study, basically they do not give you that information that you and I would both like to see. Again, the demise for the patients who receive just

supportive care in the Italian study and for those who received an ineffective regimen in the SWOG study was very brief. That is really all you can say.

DR. OZOLS: And I think you do have to make some inferences from the natural history of the disease, how lethal it is and the time to survival, and so forth. But I don't think you could ever do a study where you could address that question. I think either patients have had a good response initially, or they have recurrent disease. The group I would have a hard time even doing that is a non-treatment arm.

DR. WILLIAMS: I would encourage you to, you know, use your judgment and experience also about this. Is it obvious that responders get benefit or not in terms of they are symptomatic and they become asymptomatic, in your experience. I think that is legitimate, to call upon that.

DR. OZOLS: Lung cancer, for sure, is a very symptomatic disease, and patients do benefit even without getting an objective response, which is just an arbitrary measurement, but patients do benefit from chemotherapy and their symptoms do benefit and I am sure there is symptom improvement.

DR. SIMON: To me, there are two ways you could approach a new drug for second-line treatment. One would be showing some kind of an equivalence to what everyone would

admit is inadequate therapy. If we talk about, well, is the response the same as it is for CAV, that is the route there. I personally don't see how you can satisfactorily demonstrate benefit via that route, given that there is really no very strong data that CAV is of benefit.

The other route is to show that you have a drug or regimen that moves the field forward and provides additional benefit to what is ineffective -- inadequately effective therapy. That is the route, I think. That is why I was looking at the symptomatic data to see whether we had evidence of superiority to CAV.

So, to me, it very much depends upon the credibility of the symptomatic data to show that this drug provides something more than a very ineffective therapy. And, I think there are questions about the symptom improvement. I personally don't think that the response rate, brief as it is, really is evidence of clinical benefit.

MS. BEAMAN: I agree with Dr. Simon, and I am sure that we have a clear case here of an additional alternative or another option. It is not better. In most cases it is worse. If we are talking about an additional few weeks with the list of toxicity symptoms here, quality of life is totally being disregarded. There is nothing to show that it is even comparable to what is already there. It is another

option.

DR. SWAIN: It is really a difficult problem because, as has already been said, you are not going to compare this group to no treatment. I mean, these patients really historically, though we can't get a grasp on exactly the group, do not do well. I mean, they die rapidly. So, I have a real problem with what Rich said, that the CAV is really ineffective treatment. I think it is marginally efficacy and provides some benefit to patients. So, it is the best we can do and the best comparator that we have. So, for me, I am more convinced or more accepting of the response rate in time to progression.

DR. SIMON: I wasn't arguing for a placebo; I was arguing for demonstrating that this drug is in some way better than CAV, and I don't see that.

DR. SWAIN: It doesn't have to be better.

DR. SIMON: But we don't really have any evidence of benefit of CAV.

DR. WILLIAMS: Well, we are not requiring that you find it better than CAV, but that you find that it and CAV do demonstrate clinical benefit in whatever way you think is the most appropriate to do that in this disease.

DR. OZOLS: I think for lung cancer patients this type of response rate and improvement in survival, both of these regimens do provide benefit.

DR. JUSTICE: I would just like to clarify. I think the intent of this question isn't the approval question, it is basically do you think response and response duration is in, and of itself, sufficient? It doesn't' ask the question whether symptomatic improvement would be enough to support approval in addition to this. So.

DR. DUTCHER: Historically the small cell -- I mean, if the workup takes 4 weeks, then you have hit the half-life of the person's expected survival without treatment. So, any treatment second line that can prolong their survival -- we are talking about 6 months -- is perhaps not satisfying to those of us who would like to treatment this disease, but it is probably what you would expect to see in this disease with treatment. That is what we have seen with CAV historically. So, I think I would accept CAV as the historical or as the concurrent control of what is done right now, what we know.

So, the question they are asking is, is response sufficient? Is the response that is similar to CAV sufficient to suggest efficacy? Shall we vote?

DR. OZOLS: I have one more comment. I think if we didn't have any treatment effect, I don't think we would see any patients alive here at one year, and there is, you know, a substantial -- I can't remember whether it was 10% or 15%, but there are some patients who have relapsed after

their first treatment who were still alive, and to negate a benefit in that I think is not correct.

DR. SIMON: I think when you have a 20% response rate of a median duration of 14 weeks, and you start giving benefit to that drug for what one-year survival is, I think that is unrealistic. I think if we have patients alive here at one year, it is because of the patient selection, not because of the 20% or so response rate with a 14-week duration.

DR. TEMPLE: Either before or after you vote, just be very explicit in telling us, if you do think it is a benefit, why and what the basis of it is. You are bounding around that. I mean, there is an impression that survival of this kind just wouldn't be seen untreated, but be very explicit about that as you go.

DR. DUTCHER: Okay. Does the response rate of 20% in this setting, with duration of response of 14 weeks, as presented in the trial, provide substantial evidence for efficacy in the second-line treatment of patients with sensitive small cell lung cancer?

Those who vote yes?

[Show of hands]

Eight "yes." One from Dr. Margolin. Nine "yes." No?

DR. SIMON: No.

DR. DUTCHER: So nine "yes" and one "no."

DR. TEMPLE: Let me say what I think we will understand, that the Committee thinks that the survival, small as it is, is greater than would have been seen in an untreated population, reservations about exactly who is in the trial notwithstanding. That is what your belief is. Is that right?

MR. GIDDES: It gives hope.

DR. TEMPLE: No, giving hope -- that is interesting but you are telling us that it is clinical benefit and, therefore, you must have some reason for thinking that.

DR. OZOLS: If you look at the sum total of lung cancer data that has been generated over the last few years with these agents, there isn't a direct correlation between response and the number of patients alive at one year. We are sort of building up on that with the one-year survival. Now, is it completely established that that is due to drug effect? I think that is the case to some degree. I mean, it is to the point where we are not willing to have a no-treatment arm anymore. With some of the drugs that have response of 20% or 40%, the percent of patients that are alive at one year has been increasing, and I think it is due to drug effect. Maybe our objective response criteria are just not the end result to correlate with survival.

DR. TEMPLE: Okay, but the conclusion then is that in both groups the survival, whatever it was, is greater than would have been expected in an untreated population and, therefore --

DR. OZOLS: I think that is right.

DR. DUTCHER: Yes.

DR. TEMPLE: Okay.

DR. DUTCHER: Question number two, do the data on improvement in the disease-related symptom scale provide supportive evidence for the efficacy of topotecan in the second-line treatment of patients with sensitive small cell?

DR. OZOLS: Yes again.

DR. KROOK: I would say yes, but I think it also shows evidence of improvement with CAV also. I mean, on either arm it shows it. You may say, gee, one is higher than the other, but when you look at it all it is an overall improvement in both arms. It is not just the topotecan arm.

DR. SIMON: I would agree that provide supportive evidence. I think though there is an issue of IND bias. A third of these patients had CAV before and that sort of suggests that you could have a greater problem of IND bias. The fact that this was conducted in such a multinational study, that you had one group in the clinic more than the others -- so, I wish that it had been done in a more controlled manner because I think the symptomatic data is of

questionable reliability, and I think it could have been done differently. I would say that given that that is what we have, it does provide some supportive evidence.

DR. KROOK: But certainly it doesn't look worse. The symptoms don't look worse.

DR. SWAIN: Also, I think Dr. Gralla told us that in the responders -- I can't remember what he said exactly, but 2 of the symptoms were better in 7/9 of the patients who had symptoms. I think it was dyspnea and hemoptysis.

DR. DUTCHER: Okay. All those who think that the data on disease-related symptom scale provide supportive evidence for the efficacy of topotecan in second-line treatment of patients with sensitive small cell -- all those who would vote yes?

[Show of hands]

Eight "yes." Dr. Margolin votes "no" and I am going to abstain because I can't interpret the data very easily.

Toxicity data from trial 090 are outlined in the following tables. Given the incidence and severity of hematologic toxicity outlined above, and considering the efficacy data outlined in the first two questions, is this trial a well-controlled trial demonstrating the safety and efficacy of topotecan in the second-line treatment of sensitive small cell?

DR. KROOK: I would answer that question yes. Most of would discuss the treatment-related safety and efficacy as well as the benefits, and then it comes down to a decision between patient and physician.

DR. SWAIN: I guess I would be concerned since 33% of the patients did require dose reduction with the starting dose in this pretreated group of patients with all the platelet and red cell transfusions. So, I would certainly say that that has to be really emphasized.

DR. SCHILSKY: I mean, I guess this is where the risk/benefit issue comes in. So, I am curious to know how we are defining the word sensitive in this question, because I think I would feel more comfortable voting yes if we divided sensitive as relapse greater than 90 days and relapse greater than 60 days.

DR. WILLIAMS: Define it the way you want to vote.

DR. DUTCHER: Well, I think the data support the 90 days. I mean, the bulk of the data is with 90 days.

DR. SWAIN: But the trial was designed for 60 days and you still had, I guess, 20 patients on each arm that were in the 60-90 window.

DR. KROOK: But, you know, the issue then would be do you change the toxicity between the 60 and 90 in the others, and I don't know that we saw that. I mean, we talked about response rates being less in that group but I

guess you could say maybe toxicity is less in that group too, if this is a toxicity question.

DR. SCHILSKY: I think in my mind it becomes an issue of, you know, the more stringent you make the criteria, in a sense, the larger number of patients you are exposing to the toxicity, which is substantial, without likelihood of benefit. You know, I guess we all have to settle in our own minds where we think we sort of cross the risk/benefit line. But the response rate was -- I forget exactly what it was, 17% --

DR. DUTCHER: Thirteen.

DR. SCHILSKY: Thirteen percent in that group of patients who were in the 60-90-day window, and that starts, in my mind, to be a pretty trivial response rate for this level of toxicity. So, I am a little uncomfortable with allowing that group of patients in.

DR. OZOLS: Well, I would just like to have that option and not, you know, make it so strict to be 90 days. I think in reality we are really drawing some fine lines here between 60 and 90, and I think physicians are going to look at patients who have response to initial therapy and see how long it lasted. I mean, just to tell somebody they can't get it because, you know, it was 75 --

DR. KROOK: Or 59.

DR. OZOLS: Or 59.

DR. DUTCHER: The other thing, I am still concerned that there is room for dose reduction --

DR. OZOLS: Yes, I agree.

DR. DUTCHER: -- and it is still therapeutic. I would like to see some of that data spelled out in the package insert or in some kind of place where people could look at it, because I think it goes back to Miss Beaman's point that here you have five days of treatment, and next week you are getting platelets, and next week you are getting red cells, and then it is time for treatment again. So, the six months of response are going to be spent in the clinic.

DR. WILLIAMS: I am not sure that data is really valid to evaluate because you have people that are being reduced because they are sensitive to it. It might mean that they have a higher AUC. So, you don't really know that that applies to giving a lower dose up front.

DR. DUTCHER: I agree with you, but I would like to get at that data somehow because I think it is an issue, especially in heavily previously treated patients.

DR. OZOLS: I suppose you could maybe look at that as predictors of who is going to get a toxicity. Those patients who had severe hematologic toxicity with their first chemotherapy, are they the ones that are likely to have severe hematologic toxicity with topotecan, and should

you automatically reduce dose? If the patients initially had EP and had dose reductions on EP, should they not start topotecan at 1.5? Should they automatically start lower? I think that is what many times people are doing. If you had severe hematologic toxicity from your previous regimen, I think it certainly wouldn't be inappropriate to consider dropping the dose topotecan when you start.

DR. DUTCHER: But then, of course, do you hit the efficacy?

DR. OZOLS: You could escalate back the second dose.

DR. DUTCHER: Any other comments on this question? Is trial 090 a well-controlled trial demonstrating the safety and efficacy of topotecan in the second-line treatment to the doctors discretion -- sensitive small cell lung cancer?

DR. KROOK: Yes.

DR. DUTCHER: All those who vote "yes?"

[Show of hands]

Seven "yes." All those that would vote 'no?"

Three "no." For the record, both patient representatives are voting "no" which I think is interesting.

Data on safety and efficacy were descried in an additional 168 patients with sensitive small cell lung

cancer in Phase II trials submitted to the NDA. As described in the medical officer review, results were similar to those found in trial 090. Should topotecan be approved for second-line treatment of sensitive small cell lung cancer? Discussion?

DR. KROOK: I believe it should be approved, but I think we go back to my colleague off to the right for the definition of sensitive, but I also realize that what is put in the book, or otherwise, if it is approved, I am not sure that you are going to have somebody around trying to count the days. So, that is the one issue I have. I think that people who will be treated with this -- I am not sure the definition we set as sensitive will be followed. But I think we see an effect. I think we will see people who -- you have to define how they feel better, and I think it can be done in a variety of ways, whether it is done with dose response or otherwise, I think we have seen effectiveness and I think survival will increase some, a bit.

DR. OZOLS: I basically agree with Jim. I think that it should be approved, and I think that it is certainly fair to put in the insert what people have traditionally used, 90 days, but in this particular trial it was 60 days, and leave it at that and let the physician decide.

DR. KROOK: I also think that as a practicing physician I would probably choose CAV first. Now, the

company is behind me --

[Laughter]

-- I am saying that the five-day topotecan is a difficult thing for most people, particularly when you have patients who live a long way away. It makes it impractical, particularly if we are seeing equal efficiency.

DR. DUTCHER: All those who would vote "yes" for approval?

[Show of hands]

Nine. Nine "yes." No? Dr. Simon and Dr. Margolin. I count two "no." It doesn't add up. Eight "yes." So, the vote is eight "yes" and two "no." And, with data presented about what is considered sensitive response rates perhaps made available.

Any other issues? No? Very concise. Thank you all for getting us through this.

[Whereupon, at 4:15 p.m., the proceedings were adjourned.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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