FIFTY-THIRD MEETING

OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE

CENTER FOR DRUG EVALUATION AND RESEARCH

FOOD AND DRUG ADMINISTRATION

8:33 a.m.

Monday, June 23, 1997

Versailles I and II
Holiday Inn Hotel - Bethesda
8120 Wisconsin Avenue

Bethesda, Maryland

APPEARANCES

COMMITTEE MEMBERS:

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APPEARANCES (Continued)

COMMITTEE MEMBERS PRESENT: (Continued)

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APPEARANCES (Continued)

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Director, AIDS Activities Division
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San Francisco, California

PATIENT REPRESENTATIVES:

MICHAEL MARCO, B.A. (Taxol)
AIDS Advocate
Treatment Action Group: Opportunistic Diseases
New York, New York

L. JOEL MARTINEZ, J.D. (Zyrkamine)
AIDS Advocate
The Center for AIDS: Hope and Remembrance Project
Houston, Texas

FDA STAFF MEMBERS:

ISAGANI CHICO, M.D. (P.M. Session)
ROBERT DeLAP, M.D.
JOHN JOHNSON, M.D. (A.M. Session)
ROBERT JUSTICE, M.D.
ALBERT LIN, M.D. (A.M. Session)
GRANT WILLIAMS, M.D. (P.M. Session)

ON BEHALF OF ILEX ONCOLOGY, INC.:

LARWENCE KAPLAN, M.D.
Associate Professor of Clinical Medicine
University of California at San Francisco

ALEXANDRA LEVINE, M.D.
Division of Hematology
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APPEARANCES (Continued)

ON BEHALF OF ILEX ONCOLOGY, INC.: (Continued)

PEDRO SANTABARBARA, M.D.
Vice President, Medical Affairs

DANIEL VON HOFF, M.D.
The University of Texas
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ON BEHALF OF BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE:

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Vice President
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PARKASH S. GILL, M.D.
University of Southern California
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SUSAN E. KROWN, M.D.
Clinical Immunology

BENJAMIN WINOGRAD, M.D.
Director, Oncology Clinical Research

ROBERT YARCHOAN, M.D.
National Institutes of Health

ALSO PRESENT:

PATTY DELANEY
PETER DOHERTY
MIKI ILAW
ROBERT JORDAN
RICHARD KLEIN
JEFFREY MARTINEZ
MATT MINGOIA
JOANN MINOR

BROOKE MORAN
TIMOTHY TRUEMAN
CEASARO SALAZAR

C O N T E N T S

- - -

NDA 20-709 ZYRKAMINE (mitoguazone dihydrochloride) indicated for treatment of AIDS-related non-Hodgkin's lymphoma in patients previously treated with at least one potentially curative regimen

C O N T E N T S (Continued)

P R O C E E D I N G S

(8:33 a.m.)

DR. DUTCHER: Good morning. If people could please take their seats, we are going to begin because we have a very full day. Thank you very much.

This is the Oncology Drugs Advisory Committee meeting, and I would like to introduce Lieutenant Jannette O'Neill-Gonzalez who will read the introductory remarks, conflict of interest.

MS. O'NEILL-GONZALEZ: Good morning, everyone.

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

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

In accordance with 18 U.S.C. 208(b)(3), full waivers have been granted to Dr. Janice Dutcher, Dr. Robert Ozols, and Dr. Kim Margolin.

A copy of these waiver statements may be

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

We would also like to note for the record that Dr. Robert Ozols and his employer, the Fox Chase Cancer Center, and Dr. Richard Schilsky's employer, the University of Chicago, have interests in Bristol-Myers Squibb, the manufacturer of Taxol, which do not constitute financial interests in the particular matter within the meaning of 18 U.S.C. 208. Notwithstanding these interests, it has been determined that it is in the agency's best interest to have Dr. Ozols and Dr. Schilsky participate fully in all matters concerning Bristol-Myers Squibb's Taxol.

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

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

Thank you very much.

DR. DUTCHER: I think we haven't had a meeting for a little while, so I think we should go around the table and introduce the participants for this committee meeting. We will start with Dr. DeLap.

DR. DeLAP: Dr. Bob DeLap, Division Director, Division of Oncology Drug Products.

DR. FORASTIERE: Arlene Forastiere, Johns Hopkins, Baltimore.

DR. GELBER: Richard Gelber, Biostastician, Dana-Farber Cancer Institute.

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

DR. MARGOLIN: Kim Margolin, oncologist, City of Hope, Los Angeles, California.

DR. ABRAMS: Donald Abrams, AIDS Oncology, San Francisco General Hospital, UCSF.

DR. DUTCHER: Janice Dutcher, medical oncology, Albert Einstein Cancer Center, New York.

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

MS. BEAMAN: Carolyn Beaman, Sisters Breast Cancer Network, consumer advocate to this committee.

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

DR. SWAIN: Sandra Swain, medical oncologist, Bethesda, Maryland.

MR. JOEL MARTINEZ: Joel Martinez, the Center for AIDS, Houston, patient advocate.

DR. LIN: Albert Lin, medical officer, FDA.

DR. JOHN JOHNSON: John Johnson, clinical team leader, Oncology, FDA.

DR. DUTCHER: Thank you.

Before we begin the open public hearing, Dr. DeLap has a few words to say and some special recognition.

DR. DeLAP: Well, today marks the occasion of the last meeting as regular committee members for two of our current members, Dr. Forastiere and Dr. Gelber. I would like to express the deep appreciation of the agency, certainly on my part, but also on the part of Dr. Woodcock, our Center Director, and Dr. Friedman, our acting Commissioner.

This is a very difficult task that people undertake for us when they become members of this committee. There is a lot of review work that is performed, a fair amount of controversy sometimes, and some difficult decisions that have to be made. But it adds, I believe, immeasurably to the quality of our work to have the benefit of the advice that we obtain from this

committee.

I have certificates here. I think this is getting more elaborate as time goes on, but we have got certificates here that are signed by Dr. Friedman and by Dr. Woodcock and a nice plaque now that we have that goes on the wall. So, I have one of these for Dr. Forastiere. Thank you very much.

(Applause.)

DR. DeLAP: Dr. Gelber.

(Applause.)

DR. DeLAP: Thank you.

DR. DUTCHER: Thank you very much and Thank you to Dr. Forastiere and Dr. Gelber.

All right. We have a full hour of open public hearing, statements from patients, patient advocate groups, and we welcome all of these comments. This will pertain to both today's meeting and tomorrow's meeting because we did have so many requests for contributions.

So, with that, I am going to turn to the portion of the agenda that lists this, and Richard Klein from the Office of Special Health Issues actually is reading a prepared statement on behalf of the AIDS Action Baltimore, AIDS Project LA, AIDS Treatment Data Network, Gay Men's Health Crisis, National Minority AIDS Council,

Project Inform, and Treatment Action Group.

MR. KLEIN: Thank you. I've been asked to read the consensus statements, and I was going to read both of them together. One is for Zyrkamine, one for Taxol. They are both very long and detailed, and the complete testimony has been distributed to members of the committee. They are available for people to look at and will be entered into the transcript.

So, I thought what I would read is simply the community consensus position which simply states we, AIDS Action Baltimore, AIDS Project Los Angeles, AIDS Treatment Data Network, GMHC, National Minority AIDS Council, Project Inform, and Treatment Action Group, support accelerated approval of ILEX Oncology, Incorporated's Zyrkamine for treatment of AIDS-related non-Hodgkin's lymphoma in patients who have previously been treated with at least one potentially curative regimen.

We urge the sponsor and the FDA to proceed rapidly with its plans for conducting the proposed post-marketing study.

For Taxol, the statement reads, we, AIDS Action Baltimore, AIDS Project Los Angeles, AIDS Treatment Data Network, GMHC, National Minority AIDS Council, Project Inform, and Treatment Action Group, support approval of

Taxol as second-line therapy for Kaposi's sarcoma, conditioned on the labeling requirement of Taxol's usage only with G-CSF to ensure safety in the patient population.

We urge the sponsor to proceed with its ECOG trial, E1D-95, a pharmacokinetic study looking at the interaction between Taxol and HIV protease inhibitors and subsequently make the data widely available to clinicians, primary care physicians, and patients.

New treatment strategies for KS are desperately needed. The currently available and approved treatments for Kaposi's sarcoma in patients with AIDS are clearly inadequate. While palliative care is, of course, needed for those with progressive KS, industry must be willing to develop and test pathogenesis based therapeutics in patients with mild to moderate KS.

Infectious disease doctors, primary care physicians, and dermatologists should refer all KS patients to knowledgeable AIDS oncologists so that they may access all currently approved treatments, as well as relevant clinical trials.

Thank you.

DR. DUTCHER: Thank you very much.

We are going to now hear from a group of speakers with respect to the drug that is going to be

reviewed tomorrow. We will ask each of them to limit their statements to 5 minutes. The first speaker is Brooke Moran. Please state your sponsorship and whether you have any financial remuneration from the sponsors.

MS. MORAN: My name is Brooke Moran. I'm with the American Foundation of Urologic Disease, a 501(c)(3) located in Baltimore, Maryland, dedicated to the expansion of urologic research, education, and public awareness.

I think that Janssen sponsored an educational program for the Prostate Health Council, an educational council of the Foundation, in 1996.

In his book, The Prostate: A Guide for Men and the Women Who Love Them, Dr. Patrick Walsh begins the chapter on treating advanced prostate cancer with the statement -- and I quote. "One day, as new and better drug therapies and combinations are developed, it may be possible to cure prostate cancer at any stage, or at least to restrain it, but that day is not yet here."

He goes on to state that "when prostate cancer is advanced and when it has swept through the prostate to the lymph nodes or bone, the options for treating are limited. Cure is no longer possible. Instead, your doctor's goal is to stave off the cancer, to buy more time, to alleviate symptoms, and finally to ease debilitating

pain." End of quote.

Advanced prostate cancer is like a deadly game of leapfrog for these patients. It is coupled with the underlying fear that once hormonal therapy fails, there are limited options. In the game of advanced prostate cancer leapfrog, one therapy will be effective for a period of time, symptoms will decrease, and hope will be restored. Each day becomes a miracle. Then symptoms re-occur and fear replaces hope.

Now the physician must find a new therapy for his patient that will supersede the previous in its effect and its approach. Innovative, effective, nontoxic therapies for advanced stage prostate cancer that alleviate symptoms, ease pain, and extend life for any number of months are the instruments of hope for these patients and their families.

The Foundation also applauds President Clinton in his March 1996 statements announcing the Food and Drug Administration's accelerated approval and expanded access to new cancer therapies. The FDA is to be commended on instituting these recommendations.

In the past year, new therapies and imaging agents for the treatment and diagnosis of prostate cancer in its various stages have received expedient approval by

the FDA. The AFUD encourages the ODAC committee and the FDA to continue processing and approving safe, effective therapies as expediently as possible.

The inclusion of a patient representative as a voting member of this committee is an outstanding example of the responsiveness of the FDA to the President's statement and the patients' needs. The FDA welcomes the participation of Mr. James Anderson, a prostate cancer survivor, who will sit on this committee tomorrow. It is good to know that the patient's perspective is now an integral part of the committee's deliberations.

As I said, the AFUD is a charitable foundation. Our mission is the expansion of urologic research, education, and public awareness.

Thank you.

DR. DUTCHER: Thank you very much.

Our next speaker will be Mr. Matt Mingoia.

MR. MINGOIA: Good morning to all. Members of the Oncologic Drugs Advisory Committee, my name is Matt Mingoia. I'm not a medical professional and I am not affiliated with or receiving financial support from the Janssen Research Foundation.

I'm the co-Chairman of the US TOO Man to Man Prostate Cancer Survivor Support Group at the INOVA Fairfax

Hospital. The group was formed in October 1992. We now have over 300 survivors in our group whose mission is to provide information, education, and support to the newly diagnosed, survivors, and their families.

My prostate cancer was diagnosed in December 1994. I underwent 39 external beam radiation treatments early in 1995. The PSA did go down from 18.0 to 9.9. The PSA number did rise in 1996, and in March 1996 combined hormonal therapy was started, Zoladex analog and Casodex antiandrogen. A PSA test in late June 1996 indicated a PSA of 0.2, and in December 1996, a PSA of less than 0.1. On June 9th of this year, the PSA rose, still within the normal range, but it did rise.

More medications other than chemotherapy are needed for those of us who may become hormone refractory. The addition of Liazal to our meager arsenal in the fight against prostate and other cancers is absolutely needed for the extension of precious life.

To quote a 1995 article, chemotherapy has not proven particularly effective in the majority of patients with prostate cancer. It is hoped that in the near future more effective chemotherapeutic agents will be developed to treat patients who no longer respond to hormonal therapy.

We would like and need other weapons before

administering chemotherapy. Perhaps the statement "in the future" is now with the introduction of Liazal by Janssen and approval by the FDA. We strongly urge that the drug Liazal be approved by the FDA as a viable addition to the drug arsenal to fight this terrifying disease, prostate cancer.

All prostate cancer survivors thank you for your consideration and approval of Liazal. Also, thank you for past FDA approvals that have suppressed or arrested other dreaded diseases.

Thank you for your time.

DR. DUTCHER: Thank you very much.

Our next speaker is Mr. Robert Jordan.

MR. JORDAN: My name is Robert Jordan. I live in Alexandria. I was diagnosed with metastatic prostate cancer exactly six years ago, stage D1. Statistically I am in a group of less than 10 percent still alive after such a diagnosis, thanks to both radiation and combined hormone therapy. There is increasing research that indicates that two major modalities are better than one. Two is better than one.

I am here primarily to represent all prostate cancer survivors. I was not sent by any group but I have attended meetings of the prostate cancer support group at

GW University Medical Center since its inception in August 1991.

I have no association with Janssen nor have they paid me in any way. In fact, I did not know of their existence until learning about these hearings.

I am 74 years of age, a retired academic library administrator and professor, which partially explains my interest in keeping well informed about prostate cancer. One of the skills I learned as librarian was critical review and evaluation. My urologist, Dr. Michael Manyak, jokingly refers to me as Dr. Jordan.

Since learning about the hearing, I was told that Dr. Manyak is holding a clinical trial on Liazal, but I have not talked to him about this. I did talk to his secretary and Liazal was talked about at my support group. It sounds quite promising.

I am only too well aware that heretofore all the chemotherapies used for refractory prostate cancer are, with rare exceptions, only palliative. By rare exceptions, I mean there are a few individuals that it does help but the percentage is discouragingly low.

Obviously this unfortunate prospect is of keen interest to me as I find out every three months whether or not my PSA has started to rise. I will have my PSA tested

this week. I will find out what my prospects are for living for another few years. A sign that I will then likely have only one or two more years to live if it does start to rise. PSA is a remarkably accurate marker. Only rarely does a rising PSA for those under combined hormone therapy not indicate the onset of refractory cancer.

Knowing something about the severe adverse effects of all chemotherapy, essentially poisons, I was startled and pleased to learn that Liazal is not a chemotherapy and has comparatively mild adverse effects.

Obviously when I learned that for the first time there might be a treatment which could actually extend life several months or more, I became quite personally hopeful that Liazal would be available to me and to others. For someone in my situation, just a few more months to live would be extremely important.

I can see no conceivable reason why FDA should not expedite approval of Liazal.

A final word as to why I am here. Any promising new therapy is of great importance to me as the existing chemotherapies are hopeless. I need a new avenue of hope among options that essentially do not exist. My wife has recently been diagnosed with cancer. I would like to survive her to take care of her if that script is in

store for us.

Thank you.

DR. DUTCHER: Thank you very much.

The next speaker is Mr. Peter Doherty. Is Mr. Doherty here?

(No response.)

DR. DUTCHER: No? Okay, JoAnn Minor is going to be reading statements from Sharon Saquella, a nurse from Anne Arundel Medical Center, and from Saul Serota, a prostate cancer survivor.

MS. MINOR: Good morning. I'm JoAnn Minor with the Cancer Liaison Program within the Office of Special Health Issues at the Food and Drug Administration.

The first letter I'd like to read is from Sharon K. Saquella. She's a nurse at the Anne Arundel Medical Center.

Dear Distinguished Members of the ODAC, I am a registered nurse practicing at Anne Arundel Medical Center in Annapolis, Maryland. As clinical pathway case manager for patients at my hospital who have prostate cancer surgery, I work hard to provide each patient with the education and emotional support he needs to handle his disease. Since 1994, approximately 200 men have had surgery at Anne Arundel Medical Center for prostate cancer.

In an effort to help patients deal with their cancer, I started a prostate cancer support group in January 1994. The group consists of men in all stages of prostate cancer, post surgery, post radiation, on hormones, hormone refractory. If there is any drug that can help these men by prolonging their lives and giving them a better quality of life by easing their pain, I firmly support its use.

I have read literature on the new Janssen drug Liazal and am excited by the possibility of a new drug for the treatment of prostate cancer. To have a non-hormonal, non-cytotoxic drug that shows promise of extending the life of these patients with minimal side effects is encouraging.

I urge the Oncologic Drugs Advisory Committee to recommend Liazal to the Food and Drug Administration for use in the United States.

Thank you for giving me this opportunity to express my views.

Sharon K. Saquella, R.N.

And the second letter is from Saul I. Serota. He is from Marshall, Virginia.

Dear Committee Members, I am a prostate cancer survivor who has been on hormonal treatment for the disease since March of 1994. Recently my PSA has been doubling on

a monthly basis. In view of this, presumably the hormonal treatment has lost its effectiveness.

Liazal appears to offer hope to prostate cancer patients who, like myself, no longer are being effectively treated by hormonal therapy. Patients in my category require a drug such as Liazal for improved quality of life while the scientists seek a cure for this dreadful disease.

I urge approval of this drug.

Yours truly, Saul I. Serota.

Thank you.

DR. DUTCHER: Thank you very much.

Next Patty Delaney will read statements from Robert Frase and Terry Roe.

MS. DELANEY: Good morning. My name is Patty Delaney and I'm with FDA's Cancer Liaison Program in the Office of Special Health Issues.

The first statement will be from Robert W. Frase from Falls Church, Virginia.

I write as an 85-year-old informed patient with prostate cancer which was in remission until about a year ago, but now for the past year has gradually increased to a reading of .97.

My cancer was discovered as a result of a TURP. Tests, not including the then little-known PSA, indicated

no spread beyond the prostate. Radiation was recommended both by my urologist and a second-opinion urologist.

Three months, after five weeks of external radiation at George Washington Hospital, bone pain developed. The score on a PSA test recommended by an oncologist was 120. Choosing between medical and surgical castration, I chose surgical in July 1988. There followed almost eight years of vigorous good health and PSA readings of less than .1. My oncologist now has me on a schedule of PSA and other blood tests every two months.

At this stage we do not know whether the cancer is still androgen dependent, suggesting a trial of flutamide or Casodex, or whether it has become hormone refractory. If the indication is that the cancer is hormone refractory, my extensive reading and listening to lectures by the leading prostate cancer researchers in this metropolitan area suggests to me that the available drugs other than Liazal will produce only short-term results and the likelihood of adverse reactions.

This leads me to urge that if the statistical and clinical results claimed for Liazal by Janssen hold up under careful scrutiny, FDA approval should be expedited. Liazal seems to hold out promise of a longer and better quality of life for hormone-refractory, late stage prostate

cancer than any other treatments now available.

Robert W. Frase.

My second statement I'm reading on behalf of Terry Roe, who is the Regional Director of the US TOO International in Martinsville, New Jersey.

I am a six-year prostate cancer survivor. I also serve as Regional Director of US TOO prostate cancer support groups. I have been a volunteer for them for five years.

During that time I have met many prostate cancer survivors and spoken with hundreds on the telephone. Many are concerned as their hormonal therapy becomes refractory. I am on a regimen of Lupron and that thought continually bears on my mind.

Liazal appears to give hope to those patients who may run out of hope. I strongly urge the approval of the drug by the advisory committee of the Food and Drug Administration. It is an option that is sorely needed.

Thank you. Terry Roe.

Thank you.

DR. DUTCHER: Thank you very much.

Did Mr. Doherty, by any chance, arrive?

(No response.)

DR. DUTCHER: Is there anyone else in the

audience who wishes to make a statement?

(No response.)

DR. DUTCHER: All right. Is there someone?

MS. ILAW: On Taxol?

DR. DUTCHER: Yes, you may. We are going to be discussing that this afternoon, so if you would like to make a statement. If you have a written copy, can you also submit it to us afterwards? Please identify yourself and your affiliation.

MR. TRUEMAN: Good morning, ladies and gentlemen. My name is Timothy Trueman.

I have received no financial remuneration from anybody to be here today. I'm here on my own accord.

I'm a 30-year-old senior undergraduate at the University of California, Santa Cruz, as well as a flight attendant for Continental Airlines and a union representative of the flight attendants there.

Just this past week I returned to my job as a flight attendant after a one year and eight month absence from work. This was made possible by a little known chemotherapeutic called Taxol.

In June of 1994 I was diagnosed with AIDS-related cutaneous Kaposi's sarcoma, KS. At that time I only had one lesion on my leg, but by June of 1995, after

being hospitalized for other HIV-related infections, the KS was quite rampant throughout my entire body. Most of the KS was prevalent on my face and head, and I was experiencing edema associated with the KS. My face looked like -- one of my friends called it a watermelon.

A month prior to that June, I had begun wearing makeup on my face in order to prevent the usual stares and glances that I received from people from having KS so prevalent and highly visible upon my face. So, I had over 20 lesions on my head and face, all of which, like I said, were highly visible. Since I wanted some semblance of normalcy, hence I wore the makeup.

In July of 1995, I began a chemotherapy regimen for treating the KS. It was vincristine and vinblastine in combination, alternating each drug once weekly. This regimen did nothing to stem the growth of existing lesions, nor did it stem the growth of new lesions.

Ever since I was diagnosed with HIV and later KS, I prided myself on becoming knowledgeable with the disease and actively sought out new and promising drugs and therapies. Ignorance about the disease is terrible. I refuse to be one of those who closes his eyes and ears and mouth to this foreign invader that has ravaged my body.

With that, I had read that Dr. Parkash Gill at

the University of Southern California was experimenting with possible various treatments for KS. So, I made an appointment and we concluded that an upcoming trial, a separate trial, for cutaneous KS would be worth trying. By September of 1995, I began this new protocol for cutaneous KS.

Everything was going well for this treatment, but in October of 1995, I was working a trip from New York to Los Angeles and I had noticed that I was a little out of breath. It seemed strange at the time that I had not been physically exerting myself to any great degree. By the next week, it was clearly evident that I was becoming short of breath upon normal physical exertion. Something was definitely wrong.

A few days later I had a chest x-ray and it indicated that there was something there in the lungs, but a definitive diagnosis could not be made.

A day or two after that, I woke up in the middle of the night in a panic attack because I was unable to breathe. The only way I could breathe was when I sat upright. From then on I began to sleep in an upright position on the couch in the living room.

A couple of days later, I saw a pulmonary specialist, and a couple days after that, we conducted a

bronchoscopy. Upon completion of the bronchoscopy and the subsequent biopsy, I was diagnosed with pulmonary Kaposi's sarcoma.

By this point I was unable to walk 20 feet to the bathroom without almost passing out. I could not have normal conversations on the telephone without getting dizzy, and I was unable to stand up in the shower. It was completely impossible. I had to resort to taking baths. At the same time, I was coughing up some horrendous orange-colored sputum, and also I was placed on supplemental oxygen. In the meantime, I had stopped working and stopped going to school.

At that time, the pulmonary specialist told me to speak to my primary care physician about my options pertaining to pulmonary KS, and at that time there were very few. I realized anybody who was diagnosed with pulmonary KS, upon my research, basically had very little time to live and they just try to make you as comfortable as possible for that remaining time. Nonetheless, I began to get my "affairs" in order.

Meanwhile, I returned to Dr. Gill's office and relayed the news. He was extremely concerned about that diagnosis, and then we stopped the trial for cutaneous KS that I was on and he referred me to another clinical trial

which was the Taxol chemotherapy. I agreed instantly. Hell, I had nothing else to lose at this point.

During the very same day, I completed all the necessary paperwork and blood work to begin the protocol, and five days later I received my first Taxol treatment. This was in the first week of November of 1995. I was hopeful. The research nurses, Miki Ilaw and Sue Cabriales, had said that other patients were on this trial and were responding well thus far to the treatments.

After one week, I noticed a lessening of my pulmonary symptoms. I actually was able to walk around the block. The week before I would have passed out if I tried walking around the block.

Treatments were every two weeks and after the second treatment, I was able to travel to St. Louis to be with my family for Thanksgiving. At that time I had much to be thankful for.

By Christmas my lungs had made noticeable improvement and my cutaneous lesions had shrunk in size and had lightened in color. The Taxol thus far was working.

In early January of 1996, Dr. Gill had told me that, though I was in no shape to go back to work, he suggested that I return to school and so I did. After all, I could now walk from my car to the classrooms. School

helped me to occupy my mind while I continued treatment.

After each treatment, there would be continual improvement of my pulmonary and cutaneous symptoms.

In May of 1996, I had another bronchoscopy and the results showed no evidence of pulmonary KS. My pulmonary symptoms were in complete remission.

Hearing this news was one of the best days of my life. I was so happy. Added to the happiness, I was accepted to the University of California for the fall of 1996, though my happiness was tempered by the fact that that I still have HIV and that anything is possible with this disease, but the news was still great. When one becomes ill due to AIDS, one learns to take each day at a time.

Though the pulmonary disease was in remission, I decided to continue the Taxol to help clear up the cutaneous lesions. I began to stretch the treatments to every three weeks, then every four weeks, and finally every six weeks. Then in March of this year, I finally stopped the treatment.

In September of 1996, I began the fall term at the University of California as a junior film student, and in December of 1996, my cutaneous lesions had cleared to the point at which makeup was no longer necessary and to

this day I don't wear makeup. There is virtually no evidence that KS ever existed on my face now.

On June 14th of this year, I returned to my job as a flight attendant and I flew to New York for a very enjoyable layover.

Today, with the exception of a few tatoos left by the KS, it all seems like a bad dream. I realize that I am not cured of HIV and AIDS by any means, but with Taxol and a few other anti-HIV drugs, I have a life again and my life is very normal and that I am very thankful for.

I will forever owe a debt of gratitude to Dr. Gill, Miki, Sue, Byron, and especially the makers of Taxol, Bristol-Myers. Without all of them, I would not be here before you today. I'm an extremely lucky man.

Do you know what it is like to be brought to the edge of death and then be brought back again? Do any of you know? People write about how near-death experiences are life-transforming, and I'm here to tell you that they are. I have been given a second chance at life and a life that is ever so precious and fragile, a life that will never be taken for granted again. I've been given the ability to live and love as never before and I'm doing just that. I have found more meaning in life in the past 20 months than most people do in a lifetime and all this from

a few people and a drug that is derived from the bark of the Pacific yew tree.

I realize the battle against AIDS is not over and people are still dying. With the weapons like Taxol to combat KS, we are one step closer to making HIV/AIDS manageable. Taxol will help people to live and I am living proof.

I highly urge your approval of Taxol to be used for a treatment against Kaposi's sarcoma.

Thank you.

DR. DUTCHER: Thank you very much.

Is there anyone else here who wishes to speak on behalf of Taxol? Yes.

MS. ILAW: Good morning. My name is Miki Ilaw, a research nurse at the University of Southern California, Los Angeles.

I do have to say that Bristol-Myers did pay for my way to be here today, but even if they didn't, I still would have come here on my own because I've been giving this drug for more than two years and I think that this is probably the best chemotherapy I've ever given for Kaposi's sarcoma.

I used to work as a nurse in the AIDS ward in Los Angeles County Hospital until four years ago when I

went into AIDS research specializing in KS, which I've found a very difficult disease to learn and to follow, probably the most challenging job I've ever had. Most of my patients were young, good looking, creative, intelligent, dynamic professionals who seemed to have so much going for them. They had the world at their feet until the first KS lesion appeared.

I had great empathy for this but I did not truly appreciate the feeling of absolute devastation until a couple of months ago when I fell while walking my dogs and my face hit the cement. I felt like everywhere I went, people stared at me, even after the wounds healed.

One single KS lesion on the body, especially on the face or anywhere that can be seen right away, can be truly devastating. Having multiple KS lesions drove a lot of patients into acute depression and suicidal thoughts. The swelling of these lesions on the face and on extremities caused a great deal of pain and shame or fear of being seen. KS completely changed people's lives.

I screened and treated so many wonderful patients. I saw them come and go. They were some of the nicest people I ever met, and it was hard not to get attached. I stayed for a year and I decided to leave because it took a toll on me. I cried every day at work

and even when I got home. They all touched my life and my heart. I saw too much pain and suffering and death, so I decided to leave and work somewhere else researching immune modulators and protease inhibitors. All my patients were healthy. They didn't need me, so I got bored, and needless to say, I went back to my old job in spite of the rough road ahead.

The population did not change. Once again I saw so many young, dynamic patients with advanced KS. Each time I walked down the hallway to the KS clinic, sometimes I couldn't bear to look at these sadly disfigured faces. There was just too much physical and emotional pain, some in wheelchairs, some in oxygen tanks, sometimes you could feel the anger in their eyes. Why did it have to happen to me?

And then there was Taxol. The last two years of my research work in KS have been the most rewarding time of my life. The dramatic responses that I saw and still continue to see continue to amaze me to this time. I saw a lot of my patients come and go, not to die but to go on to a new life.

Four years ago, patients were reluctant to get chemo. Most dreaded their KS clinic appointments. Some would even skip it. They were happy to see me, but they

hated the thought of getting chemo afterwards. The infusion room would always be quiet and grave. Patients would always complain of nasty side effects, chills and fever, nausea, vomiting, severe fatigue and so on and so on. It was easy to see someone on adriamycin, bleomycin, and vincristine. They always appeared sick, cachectic, pasty looking. Some even told me I would rather die than get chemo.

All this changed, thanks to Taxol. Since we started this protocol, I still have many patients who are alive and well and leading very productive lives. Some went back to school or to work or both. I have never seen the dying come to life so many times. I have never cried and loved so much and actually have fun giving Taxol. I have never thanked God so much for giving these beautiful human beings a second chance at life. I've had some complete turnarounds that still amaze me to this day.

I can go on and on about how great this drug is, but briefly Taxol is an excellent chemo for advanced symptomatic KS, usually very well tolerated. Some patients actually look forward to getting this drug, and most of all it has improved one's quality of life immensely.

Lastly, the atmosphere in our infusion room has changed from grave and scary to a happy ambience where my

patients actually warmly talk to each other and gladly share their painful experiences with their illness and their road to wellness. They help one another. Some become friends. Some give back to their community by doing volunteer work for other AIDS patients.

As a research nurse, I feel very fortunate and truly grateful for being given the opportunity to see the wonders of Taxol on this horrible disease. For what it has done and still does for so many patients, Taxol would truly be a great addition to the current KS treatments that we already have.

Thank you.

DR. DUTCHER: Thank you very much. Can you please make sure we have a copy of your statement?

Is there anyone else in the audience who wishes to make a statement? Yes.

Just a reminder that this is the only time of open public hearing today, so please, any who wish to speak should speak.

MR. SALAZAR: I want you to know I'm not being paid to be here. Bristol-Myers paid for my airline ticket here and that's it. And if they wouldn't, I'd pay my own way to be here.

Hi. My name is Ceasaro Salazar.

About two years ago, I was told I had AIDS and Kaposi's sarcoma. When I went to the hospital, my face was swollen and disfigured. My eyes were swollen shut. I had over 200 lesions over my body. I had a large KS lesion on the tip of my nose.

Do you know what it is like to be young and to loose your looks suddenly, or at any age?

I would lock myself up in the house. I wouldn't even open up my front door. I was embarrassed and ashamed of myself and the way I looked.

Then I was told about a treatment called Taxol. It was truly the best thing that could have ever happened to me.

The next day, three-fourths of the swelling on my face had gone down. The KS on the tip of my nose was much lighter. It was no longer purple. It was a nice pink to a red. I was so happy for the first time in a very long time. I was able to look in a mirror and smile.

I had no side effects from Taxol, no nausea, no hair loss. I want you to know I am bald by choice. Call it a fashion statement if you'd like.

But before Taxol I didn't want to live. I wasn't even living. I was just existing, and what is existing without living? Nothing.

And now, because of Taxol, I am indeed a new person, alive to see a better day. My quality of life has improved dramatically.

Before Taxol, I didn't want to live. I didn't want to do anything. I didn't care what I was doing, and now I have a reason to live. I have a reason to look forward.

I take care of a lot of animals. I have a garden. I do a lot of stuff now. I'm able to go outside. It has really changed me. It really has.

So, I must state at this time that Taxol is a highly effective way to treat Kaposi's sarcoma. My body is living testament to this fact that Taxol indeed does work.

So, it is with a heavy heart I ask all of you, please, approve Taxol for use as treatment for Kaposi's sarcoma so perhaps others like myself can benefit from Taxol. May we all live a better life today, tomorrow, and years to come.

Thank you.

DR. DUTCHER: Thank you very much.

Is there anyone else? Yes.

MR. JEFFREY MARTINEZ: First of all, I'd like to say that I'm here at the invitation of Bristol-Myers Squibb and that they graciously compensated for all my

expenses while here.

Ladies and gentlemen, hello. My name is Jeffrey Martinez. I'm a patient of Miki Ilaw Jacobson, who spoke just prior, and Dr. Gill of USC.

I'm here to tell you how Taxol changed my life. That is really putting it mildly. Saved my life, that's more like it. For I firmly believe that if it wasn't for Taxol, I would not be here today.

To look at me now, no one would ever suspect the really hell that I was going through two years ago, prior to the Taxol study. To give you an idea of how Taxol changed me, let me tell you what I was like prior to the Taxol.

Early in 1995, due to fast-spreading, very fast-spreading, KS tumors, I had to start a three-drug chemotherapy combination. That was adriamycin, bleomycin, and vincristine, ABV for short. At that time it was just about the only effective treatment for KS that was available. It seemed to keep the lesions under control for the most part. However, it never really made them go away completely. What did go away was my health, my energy level, my appetite, my weight, my outlook on life, most importantly my hair -- not really. I was used to short hair, bad hair days anyway.

(Laughter.)

MR. JEFFREY MARTINEZ: I was getting the chemo infusions, the ABV, every two weeks to start with. For the first couple of days after the treatment, I'd feel very miserable and pretty much lifeless, and then a week or so later, just when I was starting to feel better, it would be time for another treatment. Up and down. It was like being on a constant, never-ending roller coaster. I really hated having to get the treatments. It created a lot of anxiety.

What else could I do? The KS would eventually destroy me if left untreated. I had to face the fact that I would have to do this for the rest of my life, and at the rate that my health was deteriorating, I was sure that the rest of my life was just around the corner.

In August of 1995, I had what I sort of called a farewell birthday party, a family gathering. I was pretty sick and weak by then, but I was determined to have a celebration. I was sure it would be my last one. I would have bet on that, and obviously two years later I'm still here and I would have lost that bet.

In fact, Janice, if it would be okay, I did bring a picture of me at that point right before I started Taxol. I'd like to pass it around to the panel. They

would get an idea, if that would be all right.

DR. DUTCHER: Yes.

MR. JEFFREY MARTINEZ: This is right before Taxol. That is about two years ago.

By September I had reached my lowest point. I was constantly fatigued and could barely walk. I had fevers, night sweats, coughing, vomiting. With the nausea, I could barely eat a thing. My weight had dropped to an all-time low of 132 pounds. I nearly developed pneumonia, was almost hospitalized. It seemed like the chemo was killing me.

I had to stop the chemo for a while. I just couldn't take it anymore. I was in bed practically the whole month of September. All I could do was think about my own mortality and I'd talk with my partner about dying, my last wishes, his ability to let me go. It seemed that there was not much hope left. All I could do was pray for strength to get through this.

By October the lesions were starting to act up again. I knew that it was time for round two. Then a miracle happened. It came in the form of Taxol, a new drug with little side effects, very promising results.

A new study was underway. I was asked if I would like to participate in the study. They didn't have

to pull my arm on this one. I would rather drink Drano than have to go back to that ABV stuff. It was horrible.

And so we started. We took a few lesion measurements to get a baseline to go from, and over a period of time -- it was a very quick period of time -- I could see how the lesions shrank, faded, and some ultimately disappeared. It was amazing. I hadn't experienced that with the ABV. ABV basically just controlled the lesions from spreading, but it really did little to make them disappear.

I think that a big part of the success of Taxol is that it did not make me sick like the ABV. My health began to improve immediately, thus making the fight against the lesions easier.

I still can't get over the fact that Taxol caused no significant side effects on me, no nausea, no vomiting, no fatigue, no appetite loss, no weight loss, no hair loss for at least six months, and especially no anxiety. I actually looked forward to the treatments. As Miki said, she looked forward to giving the treatments. I looked forward to getting the treatments.

Taxol gave me lots of energy and definitely uplifted my spirits. I was no longer tired, run down, and listless. That sounds sort of like a commercial, but my

friends were amazed at how I had improved. Some had actually commented they would try the new drug just to get the energy it created.

(Laughter.)

MR. JEFFREY MARTINEZ: None of them even had KS.

I did forget to mention one major side effect, though, weight gain. The Taxol must be fattening. I'm up to 182 pounds. That's 50 pounds difference in less than two years. I never thought I would have to diet again, but hello, Jenny Craig.

(Laughter.)

MR. JEFFREY MARTINEZ: There's another benefit of Taxol I think is worth considering, and that is an economic one. When I was on ABV, I was left disabled much of the time. For me that was difficult. I'm self-employed and I do not get any sick pay. With the ABV, I was just out, and with the Taxol, there were no side effects, nothing. I could work all the time. It was wonderful.

It has now been six months since my last Taxol treatment. I check myself every day and the lesions just aren't coming back. My health is better now than it has been in years. I know that Taxol is a major factor in my comeback, and that's not to say that it's the only factor.

I did have the love and support from my partner, family, and friends, expert care from my physicians, Miki and Dr. Gill. With the new treatments using protease inhibitors to further boost our immune systems, who can say for sure how much of a factor Taxol played in my recovery. All I can say for sure is that Taxol was with me on the road to recovery a full nine months prior to the use of protease inhibitors.

Two years ago I thought I had reached that infamous point of no return and I had walked up to that line but never crossed it. Taxol helped pull me back. It's a godsend. I really, really believe that.

Taxol needs to be available to more people. To me there's no doubt about it. It will save lives and lots of lives, I'm certain. Thank you, Bristol-Myers, very much. Thank you for bringing this drug to us.

Thank you very much for taking the time to listen to my testimony of what I experienced. It was important for me to give it. Thank you. It has been a pleasure to be here and I really mean that, "to be here." Thank you.

DR. DUTCHER: Thank you very much.

Are there any other people in the audience who would like to make any comments?

(No response.)

DR. DUTCHER: I think then we'll move on to the rest of the morning's session. We're going to begin with the sponsor's presentation. We're going to begin with the discussion of mitoguazone for AIDS-related lymphoma and we'll begin with Dr. Santabarbara from ILEX Corporation.

DR. SANTABARBARA: Dr. Dutcher, members of the Oncologic Drugs Advisory Committee, Dr. DeLap, members of the Food and Drug Administration, ladies and gentlemen, good morning.

My name is Pedro Santabarbara and on behalf of ILEX Oncology, it is my pleasure to introduce this morning's session on mitoguazone, NDA 20-709, sponsored by ILEX Oncology and co-sponsored by SANOFI Pharmaceuticals.

Accelerated approval is requested for mitoguazone as treatment of AIDS-related non-Hodgkin's lymphoma in patients who have received at least one potentially curative regimen.

The clinical package that will be discussed consists of two multi-center phase II studies in 90 patients with previously treated AIDS-related non-Hodgkin's lymphoma. These are referred to as study 004 with 35 patients and study 007 with 55 patients.

The dose and schedule was common in both

clinical trials. Mitoguazone was administered at 600 milligrams per meter squared over a 1-hour intravenous infusion on days 1, 8, and every 2 weeks thereafter.

The agenda today is listed. The background on mitoguazone will be presented by Dr. Daniel Von Hoff. The background on AIDS-related non-Hodgkin's lymphoma and the results of efficacy and safety of mitoguazone in our pivotal trials will be presented by Dr. Alexandra Levine. Then I'll come back to moderate the question and answer session.

In addition, other experts, Dr. Lawrence Kaplan, Dr. John Kuhn, are here with us this morning and will be happy to answer questions that you may have.

Now it is my pleasure to introduce Dr. Dan Von Hoff. Thank you.

DR. VON HOFF: Thank you, Dr. Santabarbara, and good morning, ladies and gentlemen.

Mitoguazone, also known as MGBG or Zyrkamine, was synthesized in 1898 as part of a program looking for new anthelminthics. It has the structural formula shown here.

The compound has a unique mechanism of action. It's an inhibitor of polyamine biosynthesis through the inhibition of the enzyme S-adenosyl-methionine

decarboxylase, or SAM-DC.

Polyamines are important for stabilization of DNA and are increased in rapidly dividing cells, particularly tumor cells. Polyamine biosynthesis is an interesting target, particularly in patients with lymphoma because polyamines are elevated in the serum and urine of patients with lymphoma.

In work by Russell and colleagues, there was a 4.9 to 5.3-fold increase in urinary spermidine in patients with non-Hodgkin's and Hodgkin's lymphoma compared to urinary spermidine in normal volunteers.

Hospattankar and colleagues showed that the total serum polyamine levels were considerably higher in patients with non-Hodgkin's lymphoma and Hodgkin's disease than in normal volunteers. These findings make inhibition of polyamine biosynthesis an attractive target for patients with lymphoma.

The clinical history of mitoguazone is of note. It was first given to patients at the National Cancer Institute by Drs. Regelson, Holland, Freireich, Frei, and Karon in the early 1960s. Doses ranged from 21 to 286 milligram per meter squared daily for 2 to 208 days. Dose limiting toxicities with a daily administration included severe mucositis, diarrhea, leukopenia, thrombocytopenia,

and hypoglycemia. Activity was noted in patients with leukemia in non-Hodgkin's lymphoma. However, phase II testing was not pursued because of the toxicity profile of the agent.

Interest in mitoguazone was renewed in the 1980s when the first pharmacology done with mitoguazone showed that the terminal half-life was greater than 100 hours. Based on that data, it was determined that to avoid drug accumulation, mitoguazone should be administered at a dose of 600 milligrams per meter squared on a weekly or biweekly schedule rather than the daily schedule used in the 1960s.

Using this less frequent schedule of administration, hundreds of patients with solid tumors were treated without severe toxicity problems in phase II trials. The most impressive activity was noted in patients with refractory lymphoma. At Memorial Sloan Kettering and in the Southwest Oncology Group, there were response rates of 30 to 46 percent for patients with Hodgkin's disease and 24 to 38 percent for patients with non-Hodgkin's lymphoma.

Toxicities noted in these trials were not graded but were said to be mild and included transient facial flushing during infusion in all patients, vomiting, mucositis, muscular weakness, and myalgia, which were

eliminated in patients going on the every other week schedule, and skin rash in 10 percent of patients.

Now, the rationale for conducting a trial of mitoguazone for patients with AIDS-associated non-Hodgkin's lymphoma included the following parameters: the activity of mitoguazone in patients with refractory non-Hodgkin's lymphoma not associated with AIDS, the fact the drug caused minimal myelosuppression and minor other systemic toxicities in prior NCI studies, the high polyamine levels noted in immunocompetent patients with non-Hodgkin's lymphoma, and the evidence for good penetration into brain tumor tissue, 5 to 19-fold higher than plasma, which is a frequent sanctuary for lymphoma in patients with AIDS.

During the clinical trials, which you will hear about shortly, my colleagues, Dr. Kuhn and Rizzo, have performed pharmacokinetic studies with mitoguazone in patients with AIDS-related lymphoma. As noted here, they have confirmed the long terminal half-life of 175 hours in these patients. There was no accumulation of drug on the every other week schedule used in these pivotal trials.

In addition, we have conducted in vitro studies of the effects of mitoguazone on P450 isoenzymes and have found no inhibition of the 6 isoenzymes studied. Based on this finding, metabolism-based drug-drug interactions are

not expected with mitoguazone, which is particularly important for patients included in the indication we will discuss today.

Dr. Alexandra Levine will now present background information on AIDS-associated lymphoma and the results of the pivotal trials of mitoguazone.

Thank you.

DR. LEVINE: Thank you very much, Dr. Von Hoff.

I wanted to start with background related to AIDS lymphoma.

Lymphoma is the cause of death in approximately 12 to 16 percent of patients with AIDS. The incidence of AIDS lymphoma is increasing as people are living longer and longer due to effective antiretroviral intervention. AIDS lymphoma is associated with a median survival of only 7 months from the time of initial diagnosis.

The disease is usually associated with either high or intermediate grade pathologic types and the pathology most frequently seen includes large cell, immunoblastic, or small non-cleaved lymphomas. There is a very high proclivity to widespread extranodal disease and to central nervous system involvement at the time of initial diagnosis. The disease is associated with substantial morbidity and mortality and is also associated

with significant immunocompromise.

Over the years, several factors have shown importance in multivariate analyses related to poorer survival. Those factors which are associated with poorer survival include some factors related to HIV, CD4 cells less than 100, or history of AIDS before the lymphoma diagnosis. Some factors relate to the lymphoma: bone marrow involvement or stage III/IV disease, elevated LDH. And lastly, some factors relate to the host: poor Karnofsky performance status, less than 70 percent, or older age, over 35 or 40, or history of injection drug use, each of these associated with poorer prognosis.

Recently a trial was published in the New England Journal this month. It was ACTG trial 142. This is in patients with newly diagnosed AIDS lymphoma who were randomized to receive either low dose mBACOD or standard dose mBACOD with GM-CSF. In that trial of 192 patients, there were several factors that were found to be independently associated with poor prognosis and decreased survival. They were age greater than 35, history of injection drug use, stage III or IV disease, and CD4 cells less than 100.

Now, if individuals had two of these factors or less, the median survival was 45 weeks and 22 percent are

alive at 3 years. On the other hand, if individuals had three factors or more, the median survival was only 18 weeks and no patient was alive at 3 years.

The patients that we will talk about today have relapsed or failed initial therapy and therefore in trying to look into the literature to see the expected survival of patients in that group, first I will start with the ACTG 142 trial. If one looks at the survival from the time of documented progression on mBACOD, median survival, 58 days or 52 days on the two arms of the study.

There's another study in the literature from Tirelli. This uses VP16, prednimustine, and mitoxantrone in patients who have failed initial therapy for AIDS lymphoma. If one looks at their median survival from the time they began VPM, it was 60 days. So, these are the numbers we have to compare in the literature.

I will now go through data related to two phase II evaluations of mitoguazone, studies 004 and 007, in patients with AIDS-related lymphoma who have received at least one prior potentially curative regimen.

The first study 004 was done in 10 different institutions around the United States. The second study was performed in 18 institutions, including 6 of the initial sites.

The study endpoints are listed here. We looked at response rate, duration of response. We looked at qualitative and quantitative toxicities, and lastly clinical benefit. This was studied retrospectively in 004 and prospectively in study 007.

The response criteria were those published from SWOG. Complete resolution of disease or partial resolution of disease required a duration of at least 4 weeks. Progressive disease, indicated by an increase in 50 percent or 10 square centimeters, whichever is smaller, in the sum of the products. These patients were seen every 4 weeks. They had physical exams and x-rays, and every 8 weeks they underwent scans or invasive procedures as clinically indicated.

The main inclusion criteria are provided in your books. I wanted just to mention a few.

Number one, the patient had to be at least 14 days from the last prior chemotherapy. If the patient was less than 14 days, this was allowable with obvious lymphoma progression.

Use of biologic agents was allowed within 7 days of institution of mitoguazone.

The Karnofsky performance status was required to be 50 percent or more. In study 007, that was amended

to 60 percent or more.

The patient had to have bidimensionally measurable disease.

And patients with leptomeningeal disease could be included but they were required to be treated with intrathecal chemotherapy and radiation to brain as well.

The exclusion criteria are listed. They are standard but I did want to mention that limited Kaposi's sarcoma that did not require treatment was allowable on this trial.

7 of the 90 patients had major eligibility deviations, and I wanted to go through these right now. 4 of these individuals, at the time that was determined after study entry, had no measurable disease. In addition, 2 of these 4 had had mitoguazone as sole prior treatment or radiation as sole prior treatment prior to the mitoguazone. 2 individuals, upon pathologic review, were found not to have AIDS lymphoma. 1 had multiple extramedullary plasmacytoma. 1 had Hodgkin's disease at review. Lastly, 1 patient had primary CNS lymphoma. Despite the fact that these major eligibility deviations were there, all patients are included in the intent-to-treat analyses which will be provided.

The patient characteristics are listed here,

and I'll go to the last column, looking at all 90 patients. The median age was "old," 39 years. 94 percent are male. 69 percent Caucasian; 23 percent Hispanic; 7 percent African American.

In looking at the prior chemotherapy regimens, 67 percent had had one regimen of chemotherapy prior to mitoguazone. The others had had between two and six prior regimens before entering these studies.

It was required that these patients have curative intent chemotherapy as their initial therapy, and these in fact are the regimens that were used. Approximately a third of these patients initially received mBACOD. Another third received either CHOP or CNOP. 12 percent received BACOD, 7 percent VAC, 3 percent MACOP or B/MACOD, 7 percent other intensive regimens. As I already have alluded, 3 individuals had no prior curative therapy, having received either radiation or had primary CNS lymphoma or had the mitoguazone as the first treatment.

Looking at the response to first-line therapy, 28 percent of these had attained complete response with the initial treatment, 27 percent had received partial response after initial treatment, 33 percent had documented progressive disease after their first treatment.

The pathology review is presented here, and I

will get into this a little bit later toward the end. Approximately a third of these patients, 29 percent, had intermediate grade lymphoma. All the rest had high grade lymphomas, and the most common types were immunoblastic B cell or plasmacytoid in 26 percent; small non-cleaved, non-Burkitt in 37 percent. So, again, two-thirds high grade, one-third intermediate grade lymphoma.

The vast majority of these patients, as I would expect in this disease, did have extranodal involvement. 88 percent had disease outside of lymph nodes. The common sites of extranodal involvement included lung, liver, gastrointestinal tract, bone marrow in 18 percent, skin or subcutaneous tissue, central nervous system, and other multiple sites. Although we are looking at lymph node parameters in time on these patients, I think it is important to note that 88 percent had extranodal disease that we were following on this protocol.

I wanted to give some flavor as to who these patients were as far as their prognostic factors, and the next few slides will deal with this. This was a frail group of individuals.

36 percent had had history of AIDS prior to the time of lymphoma. The median CD4 count in this group was 52. Performance status, less than 70 in 37 percent. Age

greater than 35 years in 67 percent. Elevated LDH in 63 percent. Stage IV disease in 74 percent.

Using the prognostic factor model, as in study ACTG 142, we looked at the number of poor prognostic factors in these patients. As you see, 72 percent had three or more poor prognostic factors at the time that they came onto study. They were ill individuals who were frail.

Another indication of this is the concurrent medications that these patients were taking at the time that they started mitoguazone. First of all, as you see in the footnote, only 1 patient was not receiving other concurrent medications. All of the others were on concurrent meds, a median of 7 concurrent medications, up to 14. 84 percent on systemic antibiotics, 57 percent on systemic antifungals, 49 percent on antivirals. In addition, 62 percent of these were on analgesic narcotics at the time that they came onto mitoguazone. They were ill.

Mitoguazone was given at a dose of 600 milligrams per meter squared on day 1, day 8, and then every 2 weeks until 4 cycles or 8 treatments beyond complete remission or disease progression or undue toxicity or refusal of further therapy.

The median number of doses given in each of the

studies was 3, ranging up to 31 doses in study 4 and up to 58 plus doses in study 7, 1 patient still receiving drug. A total of 26 percent of the individuals in study 004 underwent dose reduction in the course of treatment, and this includes 2 people who actually started at a higher level, at 900 milligram per meter squared and then were reduced down to 600 per meter squared. 9 percent of individuals in study 7 eventually underwent dose reduction.

I'm going to talk now about the responses to mitoguazone, but before I do so, I'd like to say that the basis of this response data was not in our own study group but rather an independent panel who were asked to come in and review each of these cases very carefully. The panel spent two entire days together and then for a period of months went back over and over to get every single CT scan, every single pathologic material, and so forth.

The complete remission on mitoguazone, 6.7 percent; partial remission rate, 7.8 percent. So, the total objective response rate, 14.4 percent. 95 percent confidence intervals, 7.2 to 21.7. An additional 14.4 percent sustained stable disease while on study, again lasting 1 month or more. The other individuals had progressive disease.

The duration of response is listed here.

Median duration of complete response, 76 days, going out beyond 675 days. The median duration of partial response, 142 days, going out to 672 days.

Looking at secondary efficacy endpoints, in responders the time to progression was 163 days. The survival from study entry, 269 days, going out to over 1,181 days.

In the 13 patients who attained stable disease parameters, time to tumor progression was 75 days and median survival from entry, 203 days.

Looking at all patients together, the time to progression was 40 days and the median survival from study entry, 84 days.

I wanted to clarify the responders and show you who they were. First of all, there were a total of 6 individuals who had a complete response to the mitoguazone. Of those 6 individuals, 3 had 3 or more poor prognostic factors coming onto study, in other words, would be associated with very short survival.

Looking at the response to first therapy in these individuals, 5 of the 6 had responded with a complete response the first time out and 1 patient who had relapsed, CR in the immediate treatment before mitoguazone. So, most of these patients had had a CR before going on to develop

CR again with mitoguazone.

On the other hand, this patient, which I will talk about again, is an important one. This individual had documented progressive disease with his first-line treatment. He then went on to develop complete response to mitoguazone.

The baseline features in the patients who eventually developed partial response are demonstrated here. There are 7 individuals who had a partial response. 5 out of the 7 had three or more poor prognostic factors. In addition, if we look at their response to first-line therapy, 3 had CR. 1 of those relapsed on multiple occasions, and on the chemotherapy regimen immediately before mitoguazone, had progressive disease, then got mitoguazone and underwent response, had a partial response. 1 individual had a PR with first-line treatment and subsequently a PR with mitoguazone. 3 individuals had progressive disease on their primary therapy and then went on to develop partial response on mitoguazone. We believe that we certainly helped these individuals.

I wanted to go through some of these patients with you. Patient 02 on study 4 is a partial responder. This is a 25-year-old male who was originally diagnosed with lymphoma in February of 1992. The pathology at that

time was said to be diffuse mixed lymphoma. At the time he was treated with CHOP. He had a complete response to CHOP, but 5 months later he relapsed in multiple nodal regions. He had three poor prognostic factors at the time he came on mitoguazone, and he had symptoms, neck pain and all three systemic B symptoms, fever, night sweats, and weight loss.

Now, at the time that this patient came onto study, his biopsy at the time of relapse was originally considered to be a B cell marginal zone lymphoma. This became an issue at the FDA review and I wanted to read to you the formal report by the pathologist, Dr. Peter Banks, a hematopathologist.

"Although the process was a B marginal zone lymphoma, it displayed features more aggressive microscopically than those of low grade B cell lymphoma. Instead, the features are those of intermediate grade lymphoma with the so-called large cell variant, B marginal zone lymphoma featuring large vesicular nuclei and abundant mitotic figures. In short, I believe it would be in error to stratify this patient's lymphoma as low grade."

The patient was originally treated with mitoguazone. He had a very nice response. He felt much better, and at that point he was noncompliant. He left for a period of 2 and a half months. He went to visit his

parents. He began college, was lost to our follow-up. Within about 2 months, the disease had come back again, and at that point he showed up for continued care.

This is the CT scan at the time he came back. The data on this is 3/29/93. Big lymph nodes in the anterior cervical region and the posterior cervical regions as well. This is the CT scan from the moment that he came back after his visit to the parents.

This is the CT scan from 2/21/95, essentially 2 years later. He continues to be in partial response with mitoguazone.

The duration of this patient's response, 672 days, survival 1,045 days. This patient experienced no drug-related grade 3 or 4 adverse events. We believe that he had significant clinical benefit on retrospective review. Number one, decreased pain and improved neck mobility; number two, increased weight. He maintained his performance status. All three systemic B symptoms resolved. He claimed that he had increased appetite and libido and he was able to return to full-time work. I truly believe that we helped this individual for a significant period of time.

The second case is patient number 9 on study 7. This is a 50-year-old male who was originally diagnosed

with lymphoma in January of 1995. He had small non-cleaved lymphoma at that time. He was treated with a continuous infusion of cytoxan, adriamycin, and etoposide, but despite this continuous infusion therapy, he had objective progressive disease on that treatment. His site of involvement when he began mitoguazone was head and neck, bulky disease there, as well as involvement of subcutaneous tissues and lymph nodes. He had four poor prognostic factors. He had significant baseline symptoms, laryngeal edema and tracheal obstruction.

This is the CT scan on this individual on 3/8/96, a large mass here, another mass on the other side of the neck, and you can see the displacement of trachea and so forth.

This is a repeat scan on 4/27/96, about 6 weeks later, marked regression of the adenopathy, returned to normal anatomy and resolution of his symptoms of laryngeal obstruction.

The duration of response in this individual was 142 days, survival 663 plus days. This individual did have one possibly drug-related grade 3 episode of anorexia. It lasted 2 weeks.

The clinical benefit to this patient was prospectively collected. Resolution of the tracheal

obstruction. Despite the 2-week episode of anorexia, he gained a total of 4.7 kilos and he was able to maintain his performance status. Again, I believe we helped this individual significantly.

I also wanted to show you somebody who attained stable disease parameters. This was a 43-year-old male who was originally diagnosed with small non-cleaved lymphoma in October of 1992. He first received local radiation therapy and then at relapse received CHOP. His best response to CHOP was progressive disease, and when he came to us, he had multiple evidence of lymphadenopathy as well as bone marrow involvement. He had five poor prognostic factors, and his baseline symptoms are listed here. He was literally incapacitated by pain. He was on an IV morphine drip. He was hot. He had all three systemic B symptoms, fever, sweats, weight loss. He had nausea and vomiting. He was extremely ill. I wish I had a picture at that moment. He was terribly ill.

This is a smear from the bone marrow showing the malignant cells. The bone marrow was 100 percent cellular, 100 percent replaced by these cells.

This is a bone marrow smear that was taken about 1 month later, return to normal cellularity, no evidence of lymphomatous disease.

This is a photograph of the patient 4 months later. He traveled back to his home in Maine. He told me that I was allowed to use this photograph whenever I wanted to. His pain was completely resolved. He returned to a normal state of well-being. It was an unbelievable case in a clinical sense to me.

To summarize, the duration of his stable disease was 104 days. The problem with the trip to Maine was that he was in Maine as opposed to in Los Angeles getting a repeat CT scan to confirm complete response. Therefore, he is considered stable disease. His survival was 338 days. He had a possibly related episode of adversity, a grade 3 episode of fever, leukopenia, and dehydration. This was at the time of his relapse when he came back from Maine at the end of the mitoguazone study.

The clinical benefit was significant in him. Improved bone pain. He discontinued the morphine and all pain medications. Improved nausea and vomiting, improved appetite. He gained weight. All three of those B symptoms went away, and he obviously had a markedly improved performance status.

Now, that patient certainly had evidence of clinical benefit. What I'd like to do now is go through other evidence of clinical benefit in the individuals who

responded or had stable disease. In other words, did that translate to actual clinical benefit to these patients?

In going through this, on study 007 and 004, we looked at lymphoma-related symptoms and signs. On 007 we had a clinical benefit case report form which included B symptoms and pain. We also used a visual analog pain scale and we had an ongoing analgesic consumption report.

On study 004, this was retrospectively acquired, but we did use a specific form that was used for the extraction of this data and an independent reviewer did extract the data.

In both studies we looked at performance status. In both studies we looked at weight.

Looking at the lymphoma-related symptoms in patients who responded, there were a total of 8 patients who had B symptoms. 5 of those 8, 63 percent, had improvement in B symptoms along with objective response. Of the stable disease patients, 3 of 3 had resolution of B symptoms.

In those patients with pain, 8 patients had pain on study of the responders. 7 of the 8 had improvement in that pain, and those who attained stable disease parameters, 7 of 7 had improvement in pain.

If we look specifically at the visual analog

scale, the pain rating on study 007 where this was done prospectively, in the responders a total of 4 had pain at baseline. 3 of those had objective decrease in pain. 1 of them had insufficient follow-up. In those who had stable disease, 4 had pain at baseline. In 1 patient there was stability of that pain. In 3 patient, 75 percent, the pain decreased.

Looking at all patients, a total of 41, including those with progressive disease obviously, had pain at baseline. 22 percent increased, 17 percent stable, 32 percent had decreased pain along with the mitoguazone, and in 29 percent we had insufficient follow-up. The patients were too ill and did not fill out those forms appropriately or at all.

Looking at the performance status, what we are looking at here is baseline versus the median performance status over the course of treatment. In those who had objective response, there was an improvement in performance status in 31 percent. The other patients maintained performance status. In those with stable disease, there was a maintenance of performance status in 62 percent, improvement in 15 percent, a decrease in 23 percent. Looking at all 90 patients, 54 percent maintained their performance status, 9 percent improved, 18 percent

declined, and insufficient follow-up in 19 percent.

The weight changes are listed here. Again, we're looking at baseline versus the median over study. In the objective responders, a total of 23 percent increased weight by 3 percent or more, 31 percent were stable, and 6 individuals had a decrease in weight. I'm going to come back to this in just one moment. In those with stable disease, 77 percent had stable weight over the course of study, 23 percent had decrease, and looking at all patients together, stability of weight in 54 percent, increase in weight in 7 percent.

Looking at the responding patients who had greater than 3 percent median weight loss over the course of mitoguazone, my point will be that there were extenuating circumstances in all 6 of these patients. 3 of them had opportunistic infections involving the GI tract at study entry that may have contributed to continuing weight loss. 1 had chronic pancreatitis and H. pylori. The other 3 had edema which resolved during the course of therapy.

The adverse drug reactions are listed on the next few slides. If we look at baseline parameters first, 82 percent of these patients came into the study with anemia, 92 percent had anemia while on mitoguazone. This included 4 percent grade 4 anemia, 23 percent grade 3

anemia.

Neutropenia was very important to us. 20 percent came on study with neutropenia, 56 percent neutropenic during the course of treatment. Grade 4 neutropenia in 2 percent at baseline, 7 percent during the course. Grade 3 neutropenia, 2 percent baseline, 11 percent during treatment.

Thrombocytopenia was present in 24 percent at study baseline, in 42 percent during treatment. Grade 3 went from 2 percent to 8 percent. Grade 4 went from 3 percent to 16 percent.

The clinical impact of these hematologic adverse events are described here. I just wanted to make two points. Number one, only 1 patient developed febrile neutropenia. This was grade 3 ANC. Furthermore, 18 percent of these individuals received Neupogen, 7 as prophylaxis, 9 as therapy. So, despite the fact that there was only 7 percent grade 4 neutropenia, in fact only 18 percent of these patients were on Neupogen.

Looking at the grade 3 and 4 non-hematologic adverse events, all grade 3, 12 percent; drug-related, 5. All grade 4 nonhematologic, 4 percent; drug-related, 2 percent. So, those adverse events that were possibly or probably related to drug, nonhematologic, 7 percent grade 3

or 4.

Just walking through those toxicities now, the most common toxicity of this drug is vasodilatation. It occurred in 57 percent of patients. What you see is facial flushing. Either the patient feels hot or flushed or you can actually see that. This occurs during the infusion. It goes away when the infusion is over. Grade 3 in 3 percent. No grade 4.

The second most common side effect of the drug is paresthesia, often perioral or in other places. This occurred in 61 percent. Only 1 had grade 3. Again, this occurs during the infusion. As soon as the infusion is over, that toxicity goes away.

About a third had nausea and vomiting on the drug. Only about half were actually treated prophylactically with antiemetics. No grade 4. 1 percent grade 3.

And then mucositis. This was obviously a concern of ours because this was a side effect when the drug was originally used at higher doses. Incidence of mucositis, 22 percent; grade 3 in 4 percent, grade 4 in 3 percent.

Other than this, the only real grade 4 toxicity, nonhematologic, was abdominal pain and elevated

SGOT in 1 patient, the same patient. This patient developed hepatitis and pancreatitis. Both of them resolved while still on study.

The reasons for discontinuing treatment with mitoguazone are listed here. 58 percent because of tumor progression, 14 percent because they refused further treatment. This was not necessarily because they felt so terrible. 2 patients refused treatment because they felt well. They went traveling to Hawaii and so forth.

Death not drug-related was a cause of discontinuation in 16 percent, and other toxicities as listed here or reasons.

As far as deaths on study, the investigators reported no death as possibly or probably related to mitoguazone. The FDA review concludes that patient on study 4, number 10, was highly suspicious of drug-related death. The patients 008 and 026 "might be drug-related." And there were also questions raised for another 4 patients. I'm not going to go through them all at this point. I'd be very happy to discuss them in the question and answer period.

I would conclude. Number one, mitoguazone at 600 milligram per meter squared days 1, 8, and every 2 weeks has demonstrated objective antitumor response,

lasting from 29 to over 675 days, in previously treated patients with AIDS-related lymphoma.

Number two, there was definite evidence of clinical benefit, particularly in responding and stable patients.

Number three, mitoguazone was well tolerated. There was only 7 percent drug-related grade 3 and 4 nonhematologic toxicity. Myelosuppression was of minimal consequence to the patients.

Number four, mitoguazone has a favorable safety to benefit ratio for previously treated patients with AIDS-related lymphoma.

I think you probably realize from your documents that there were some discrepancies in the response assessment between the independent review panel and the FDA review panel. In discussing these with the FDA by telephone last week, they suggested to us that we incorporate this information into our presentation. We thank them for that, and that's what I'd like to do over the next few moments.

A major issue I think again was this independent review group went back for months to get every single piece of data. The FDA has very nicely summarized this information for you in tabular form. It's on page 51

and 73 in your FDA document, and you also have these slides that I'm going to show right now.

Now, one of the issues was the issue of pathology, pathologic review. FDA reviewer comment states that 6 -- and I see now 7 -- did not have histologic biopsy confirmation of recurrent lymphoma prior to the initiation of mitoguazone. I'm going to go through these cases with you, but to summarize it quickly at this point, these patients were progressing in the specific sites of previously biopsied and pathologically documented lymphoma. They had known pathologic involvement of lymphoma. They relapsed in the exact sites of prior disease. We feel that it was not necessary to obtain another biopsy at that site that had already been biopsied and pathologically reviewed.

The second issue, according to the FDA reviewer who was absolutely correct, was that 4 of these biopsies of recurrent tumors were not reviewed by the reference pathologist by the time that the FDA review occurred. As soon as we realized that, we immediately got those slides, sent them to the independent review panel. All 4 have now been reviewed. 3 of them have definite high grade lymphoma. 1 has intermediate grade lymphoma.

So, this is an issue we can discuss, but I feel strongly that repeat biopsies over and over in the exact

same sites are not really necessary in this setting, and I'll give you the examples.

Now, walking through the other discrepancies here, on study 4, patient 005. The independent review committee called this a partial response. The FDA review called this nonevaluable. The reason was that chemotherapy, suramin, was given 8 days prior to mitoguazone. Therefore, the patient was nonevaluable. I should mention, by the way, that suramin was the fifth regimen of chemotherapy that this patient had had prior to mitoguazone.

Now, the suramin was given between 2/1 and 2/8/93. We have definite, clear evidence of progression while he was on suramin, and that's from a CT scan done 1/29, just before, and another CT scan done 2/10/93, immediately after suramin. There was definite increase in number and size of pulmonary nodules. There was definite increase in number and size of multiple lymph nodes both above and below the diaphragm.

We also believe this patient is eligible because he was past the hematologic nadir of suramin toxicity that is supposed to resolve within 8 days. This patient was treated at that point, not before.

This is another individual who did not have

histologic confirmation prior. He had an initial biopsy. He had a biopsy at relapse. The next relapse prior to mitoguazone was in the exact same sites.

The second issue was patient number 20. Our independent review committee said that was a CR. FDA said nonevaluable because, number one, prior treatment was 10 days before initiation of mitoguazone.

Now, the issue is as follows. The patient had a regimen of both chemotherapy and interferon. The chemo was given 25 days before the mitoguazone. It was the interferon that was given 10 days before. We believe this patient is still eligible because, number one, he has definite evidence of progression while on the chemotherapy and interferon, and number two, the protocol allowed biologic therapy within 7 days. This patient had interferon 10 days before.

The second issue was that the patient had cutaneous T cell lymphoma. He had 50 plus cutaneous lesions that were not all assessed according to FDA. The fact is that the patient did have 50 lesions. Every one of those lesions was counted at each visit and was listed on the sheet. In addition, five were considered signal lesions and they were also serially measured. All of the 50 lesions disappeared over the course of therapy, and

that's documented.

The other issue on our phone call with the FDA last week, the patient, quote, had other disease on the CT scan. That's true, and again it brings up how complicated these patients can be. This patient originally had a complete response to mBACOD. At the time that he was considered a complete responder, he had stable, small adenopathy on the CT scan. At that point, that adenopathy was unchanged over a 2-year period. He had three different CT scans before mitoguazone, each one of them showing the same small, stable adenopathy. He had no other progression in any of these sites, even though he had fulminant biopsy-proven progression on the skin.

Again, a problem of histologic confirmation of relapse prior to the mitoguazone. He had had biopsy of the disease. He had re-biopsy of the disease at relapse on skin. He did not have re-biopsy of the same skin lesion just before mitoguazone. I can get into more details later. He had another biopsy on study. It did show lymphoma and then another biopsy on study showed resolution of lymphoma. So, we don't believe that's an issue here.

In patient 027, the review committee says partial response. FDA says nonevaluable. The reason was that the patient had concomitant cutaneous KS on both legs

with inguinal adenopathy that was followed as putative lymphoma. He did have KS, but this was inactive during the entire course of therapy. This was eligible on the protocol.

The reviewer also states that the response was not confirmed 1 year later, and this was complicated in this case. Mitoguazone was begun on 8/2. He had axillary node. Actually that was removed by biopsy. He also had cervical and femoral nodes. He had right chest and left flank skin nodules. All of the skin nodules, all adenopathy resolved by 8/23, although he had shoddy cervical nodes that remained. This was confirmed, the resolution, by 9/6, other than the cervical nodes.

Then all skin nodules, all adenopathy still resolved on 9/20, but the examiner noted small bilateral axillary lymph nodes at that time. We did not know. I thought that that might be reactive. They were very small, or it could be the tumor flare and we were allowed to go further to see. We did and when he came back again on 10/5, the axillary nodes were gone with no new disease. The axillary nodes were still gone on 10/19/94, even thought at that point he progressed elsewhere. So, I believe we have confirmed this response for the required 1-month period.

On patient 029, the review committee said complete response. The FDA review says partial response based upon the fact that the patient had persistent periaortic and inguinal nodes. Just walking through this one, the patient had CT scans on 7/18 and 7/27 prior to mitoguazone. They showed small periaortic nodes and inguinal nodes. He then got mitoguazone on 8/19. CT scans on 10/14 and 11/16 showed, to quote the report, tiny periaortic nodes which had decreased in size and resolution of the inguinal nodes.

Now, in this case we had gallium scans, and it turns out the gallium before mitoguazone was positive in the periaortic area at the time that he had these small nodes, but after mitoguazone, when he had the tiny periaortic nodes, on 11/25 and again on 12/13, those gallium scans were negative. Again, I feel strongly that this is consistent with complete response.

On patient 28, the review committee said that was CR. FDA believes nonevaluable because the patient had prior chemotherapy, CHOP, 2 days before the initiation of mitoguazone. The patient was treated with MACOP on 7/27/95 and 8/10, two doses. His last dose of the chemo was on 8/10. He started mitoguazone on 8/24, 14 days later. What he did have was the residual of the tapering doses of

prednisone, and that was tapered down through 8/22. So, I think that's what the confusion was all about.

While he was on MACOP, he had definite disease progression. He had two perirectal masses at the onset. By the time that the second dose of MACOP was completed, he had three perirectal masses. The tumor mass went from 8 square centimeters to 11.25 centimeters squared. He had disease progression.

Now, the perirectal induration and three masses were measured on every visit. All of the masses resolved by 10/19. The induration was resolved by 10/30. He then went ahead and had biopsies on 9/23 and 10/26. Both of them showed no evidence of lymphoma.

We are very conservative in our statement of the duration of response. Our last skin biopsy on 10/26 gave us an objective 34 days duration of response. In fact, this patient was followed by the physician. He became ill later with Salmonella and so forth. He was followed at home, and up to 101 days after the institution of response, the patient still had a completely negative exam as it relates to the lymphomatous disease.

Again, the issue of histologic confirmation. He had had a biopsy of the rectal mass. He did not have a biopsy of the exact same rectal mass 2 months later.

Lastly, you don't have these two slides in your packets there. These were considered uncertain response status. We weren't that off, I didn't think, from the FDA review, but I quickly just want to say them now.

Our independent review committee says CR. FDA says CR of uncertain response status because in this case it was a gastric lymphoma with "inappropriate" follow-up method on the CT scan. Can you really get good measurable disease? And I totally agree. This is a difficult issue. I don't deny it.

But the data is this. Baseline CT scan 9/28/93 was read by the independent radiologist as a 3 by 3 centimeter soft tissue mass on cut 27 on the greater curvature in the exact same location as an abnormality on an upper GI. Mitoguazone was started on 10/8. There was disappearance of that mass on 12/15 and again on 2/17. The patient underwent endoscopies and biopsies. On 9/15/93 that showed high grade lymphoma. There was a small focus of low grade within the material. There is absolutely no question. The formal sign-out is high grade, and prognosis for the patient and treatment decisions are based on the highest grade of lymphoma within the specimen. This was signed out as high grade. In any event, he had the first biopsy, high grade.

He then had serial endoscopies and biopsies, 12/16/93, 2/18/94, 12/29/95. All of those showed no evidence of lymphoma. This is the mass that I believe is measurable on upper GI series. This is the CT scan, the 3 centimeter mass that was called by the independent review pathologist. This is the resolution of the mass on the CT scan. This is the original biopsy. It's totally infiltrated by high grade lymphoma. This is the biopsy after course 2, just residual reactive plasma cells. This is a biopsy after course 4. The patient remains alive. He remains without evidence of disease.

One last and then I'll leave you alone, and this is the last uncertain response status. Our independent review committee says CR. FDA says CR but esophageal lymphoma with imprecise follow-up method. Again, I agree. This is a difficult issue.

The patient was begun on mitoguazone 10/4. CT scan at baseline 9/22 showed measurable disease. There was a mass thickening measuring 4 by 4 centimeters in the AP and transverse diameter with thickened esophageal wall. Biopsy of the area was done. It was positive for lymphoma.

He then had a repeat CT scan 11/1/95. That showed a PR. The mass is documented. It's measured at 2 by 2 centimeters. In addition, the cardiophrenic node that

was present is now resolved.

He then has another CT scan on 12/4/95. It showed only minimal thickening of the distal esophagus, less than the 11/1/95, with disappearance of the mass. A scan 1/4/96 showed mild unchanged wall thickening, with repeat biopsy again showing no evidence of disease.

So, it's there on the CT scan, although it's difficult, and it's also there on the biopsies. It was interesting because the biopsies showed some inflammatory reaction and that was I believe the residual minimal thickening of that distal esophagus. Again, this was judged as CR by the review committee.

I would like to conclude simply by giving my perspective as a physician who treats patients with AIDS-related lymphoma.

Number one, as I'm sure you know, there are no approved or acceptable alternatives for these patients after they have received first-line therapy. This is an extremely difficult situation to be in both as a physician and as a patient.

Number two, although the response rate to mitoguazone is modest and while there may be a few differences in interpretation of the number of responders, mitoguazone clearly has demonstrated efficacy by both

reviews. These are individuals who would not have lived if it were not for this drug.

Number three, the incidence of severe toxicity with mitoguazone is very low, albeit it obviously not negligible. However, the agent does not cause significant problems for those patients who do not respond. In other words, you have not lost anything by giving it a try, and if it works, beautiful. If it doesn't, you can go on to try something else.

Lastly, I feel strongly the drug should be made available as part of our very limited armamentarium.

Thank you very much.

DR. DUTCHER: Thank you, Dr. Levine.

Do you have a statement you wanted to make?

DR. SANTABARBARA: Thank you, Dr. Levine.

As we have heard, the proposed indication is mitoguazone is indicated for the treatment of AIDS-related non-Hodgkin's lymphoma in patients who have received at least one prior potentially curative regimen.

As a part of the accelerated approval guidelines, the sponsor is committed to do a post-approval phase III trial. ILEX will have a meeting with FDA this Thursday, June 26th, to finalize the details of this trial's design.

Now, if there is a statement or another -- otherwise, I'll be happy to --

DR. DUTCHER: We have some questions, yes.

Dr. Abrams, do you want to start?

DR. ABRAMS: Sure.

The first question for Dan. Interesting the drug, developed or synthesized 99 years ago, has actually -- from the information we have through the NCI annual report and PDQ, there have been phase II studies in 33 previous malignancies and 7 phase III. Both of these did include patients with NHL and Hodgkin's disease. The data that you presented from the studies that were reported in the early 1980s with 24 to 46 percent response rates from Memorial and SWOG. I wonder whatever happened with that information. Why wasn't anything acted upon at that time?

DR. VON HOFF: Well, I think the good news was it was published, so we can reference it, that's for sure.

But I think because the drug was synthesized such a long time ago and of course was off patent, no one was interested in pursuing it. I think, as you know, people have put it in many combinations, MINE combinations and others, and they've seen activity, but there was not a lot of interest in pursuing it I think because it was synthesized so long ago. I believe that that's the number

one reason. Sorry I can't be more specific than that.

I know the NCI was giving it out for quite a long time, and thanks to their sponsorship, they kept it alive in some people's clinical investigation.

DR. ABRAMS: Dr. Levine, I have a question. Can you give me the distribution by sites of the CRs and PRs, the 6? Were they all localized in a few of the sites or were they disbursed evenly among the sites?

DR. LEVINE: If you can wait one moment, we will get the slide for you.

DR. SANTABARBARA: Do you mean by disease site or by investigational site?

DR. ABRAMS: Investigational. There you go.

DR. LEVINE: This is the data. Most of the responders were in those sites that enrolled most of the patients. So, I definitely can say that about it. Other than that, no real comment.

DR. ABRAMS: The CRs I guess because it's 6. That's study 4. How about --

DR. LEVINE: No, no. This is study 4 and the next slide please. That's study 7. So, again, the sites that tended to enroll the most tended to see more responders, but again you'll see responders in other sites as well, the small sites.

DR. ABRAMS: With regard to the 4 versus 7, what actually do you consider to be the difference between the two studies?

DR. LEVINE: The difference was really twofold. Number one, on number 7, there was a prospective attempt to get data as far as clinical benefit. So, as far as the design, that was the big difference.

The other difference was that the patients on the first study, on 004, were sicker. They had had more regimens of chemotherapy prior. The overall number of patients with one prior regimen of therapy was much greater on study 7 than on study 4. So, it was getting people who were a little bit less heavily pretreated, the second study.

DR. ABRAMS: But that was mandated by the protocol or was that --

DR. LEVINE: No. I think the word was out in the community the drug was there.

DR. ABRAMS: But I mean, in truth, the two protocols were really the same.

DR. LEVINE: Yes, they're the same protocol. One is my clinical sense of the patients and the other is the prospective clinical benefit data on 7.

DR. ABRAMS: This question about giving

patients drug within a 14-day period of receiving prior therapy, you mentioned in that last case that the patient might have still been on steroids and that might have been the effect. But certainly the response to treatment given within 14 days might be coming later obviously and that would obfuscate --

DR. LEVINE: Yes, it's true, no question. But that's why the cases that were coded as response had absolute objective data showing real progression during that period. It wasn't a subtlety of one-half centimeter in a lymph node. These were major progressions.

DR. ABRAMS: I thought it was very striking that of the complete responders, 5 out of 6 were CRs to their prior regimens, including their most recent one. So, doesn't this sort of predict that the biology of the tumor is very sensitive to whatever intervention?

DR. LEVINE: I would answer yes and no. Number one, of the 6 complete responders, 5 of them did have complete response to the prior, but the other had primary refractory disease, got that infusional CDE regimen, which is a good one, but had progressive disease, would have been lost if it were not for this drug. So, that was interesting to me.

On the partial responders, the same concept was

not true. So, of the 7 partial responders, 4 of them had progressive disease on the immediate regimen before mitoguazone.

So, I don't really agree with what you said. Kind of but not really.

DR. ABRAMS: Okay.

(Laughter.)

DR. ABRAMS: I notice also that 2 patients were reported to have developed squamous cell carcinoma during therapy. Were there any more cases of squamous cell carcinoma? Is there any idea of where this came from?

DR. LEVINE: No. I'm not aware of any other case. One was about the same rectal area in a patient who also had rectal lymphoma. As I'm sure you know, there appears to be an increasing incidence of squamous cell carcinomas in patients with HIV. So, I assume it's related to the HIV status and what we'll all learn in the months ahead.

DR. DUTCHER: I have a couple of questions.

Can you talk a little bit more about the pain syndrome? Because in non-AIDS lymphoma, that's not usually considered a clinical feature. Could you just talk about what you think the pain was from? Because you present very heavily that clinical benefit means pain relief.

DR. LEVINE: I wasn't saying that that was like a systemic B symptom of the lymphoma. The pain in each case was related to where that lymphoma was. So, for example, the patient who has the rectal masses would have complained of pain there. I showed patient number 6 on study 4 who was on IV morphine. He had extraordinary bone pain, and it was due to the bone marrow involvement just pressing on the periosteum. So, it wasn't in my view "lymphoma pain" in a nonspecific way. It was the site of lymphomatous disease causing the pain.

DR. DUTCHER: Can you also comment? There are several -- and I don't remember the exact number of patients -- that were responders but did not have improvement of B symptoms.

DR. LEVINE: Yes, they were partial responders. We thought the same. I was curious about it, but some of that was the weight and that was confusing. I expected that we would see maybe weight gain in all responders, but if you also have CMV esophagitis and Salmonella and so forth, there are other factors. So, it was really the weight that you did not see come back in some of those partial responders.

DR. DUTCHER: And could you also comment? When did the nonresponders come off study? How fast did they

grow through this?

DR. LEVINE: We have specific data. If you can tell me the exact time. I believe it was 40 days. It's about a month. I believe the specific was 40 days time to progression.

DR. SANTABARBARA: Per cycle.

DR. LEVINE: Per cycle, okay.

DR. DUTCHER: Does anybody else on the committee have questions? Richard?

DR. SCHILSKY: I have one question for you while you're there. I think one of the difficulties that I'm having in interpreting the data and I suspect others may have is the fact that there are many causes for adenopathy in these patients. So, it's a little bit hard to know when the lymph node shrinks whether it's shrinking because of regression of lymphoma or some other reason.

Now, you stressed the fact that many patients were progressing in sites of disease that had previously been biopsied and were known to have lymphoma at the time that they went on the therapy. I guess what I'd like to know is whether you can tell us if patients were regressing in sites that were previously known to have lymphoma because it seems to me that that's really the critical issue.

DR. LEVINE: I have to think about the 90 patients to be able to answer that, but let me start in another way.

88 percent of these patients had extranodal involvement. From the very beginning of the epidemic -- I agree with you -- I published early the importance of lymph node biopsy in gay men with lymphadenopathy. I completely agree with you.

But what we're talking about here is extranodal lymphomatous disease, and in that setting I can't prove that every single lymph node that was also there was lymphoma. What we do know is that in general, for example, in one of the cases that was questioned -- it was patient 005 -- he had on his previous treatment pulmonary involvement, multiple lung nodules, as well as nodes everywhere above and below the diaphragm. During the last treatment, he had progression, objective progression, everywhere in size and number of lung nodules and in size and number of lymph nodes.

So, on the one hand, I don't think it will ever be possible to prove in any kind of study of this sort that every single lymph node that's big is really lymphoma. I guess what I'm going to hang my hat on is that these patients had extranodal disease and most in fact, as you

know, do. So, I think that's the fairest way to answer.

MR. JOEL MARTINEZ: I have questions about the design.

The first one is how did you come up at this dose? It seems to me that it was done just with the PK studies and the half-life rather than any kind of efficacy.

DR. LEVINE: I'm going to answer a little bit and then Dr. Von Hoff perhaps.

We tried higher, 900 milligrams per meter squared. The bottom line is you can't get it in. Mucositis.

MR. JOEL MARTINEZ: How about lower?

DR. LEVINE: Lower we didn't really try because 600 seemed to be the way to go, but Dan can answer that with history that I don't have.

DR. VON HOFF: I guess I could answer that's how I got some of my gray hair because, as Dr. Abrams pointed out, we tested mitoguazone over the years -- since the early 1970s, we've had clinical experience with it -- and found that in Dr. Warrell's study in the Southwest Oncology Group with escalations of dose to 600, 600 was extremely well tolerated. But if you go to 900, as we demonstrated in this study, then you get the mucositis back. So, we wanted to use the most of the agent possible

with the least grade 3 and 4 side effects. So, that's what we were after.

There was one other target we were using. We knew that Raji cells, Burkitt's lymphoma growing in culture, that you need to have about 10 microgram per ml to have the cytotoxic and cytostatic effect against those Burkitt's lymphoma cells. The plasma concentrations that one can reach in the 600 milligrams per meter squared range anywhere from 7 to 40 micrograms per ml. And we were afraid to go below that so we could get below that 7 because we felt it would not be cytostatic or cytotoxic to the lymphoma cells. That's how we selected the dose.

MR. JOEL MARTINEZ: But never in patients, right? You've never given the lower dose in patients.

DR. VON HOFF: Oh, yes. In the initial Southwest Oncology Group phase I study, which we did in 1979, we started at 100 milligrams per meter squared and worked up.

MR. JOEL MARTINEZ: And the second question is why is this going for a second-line therapy instead of a first-line therapy? How was that decision made to pursue that rather than as a first-line?

DR. VON HOFF: Well, it was felt at the time of the design of the studies that, number one, the initial

patients that were treated under a National Cancer Institute study had progressed on first-line therapy. I would say all clinicians felt that we had some effective therapy for first-line treatment and it would be very tough to bring a single agent into a first-line situation where you knew that you had some patients who could achieve a complete response rate. The New England Journal article that just came out shows that with the mBACOD regimen, one can get complete remissions and we should keep that as at least the beginning in a disease.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: I assume, since you didn't say specifically, that there is no standard or approved drug or drug combination as first/second line therapy for AIDS-related non-Hodgkin's lymphoma. So, instead of pushing on that and the perhaps lack of trials that are this rigorous for other drugs or combinations, if you could just tell us what you think of as the standard first/second-line therapy for patients with a reasonable performance status who don't have other active malignancies or OIs in this disease.

DR. LEVINE: Your point is extremely well taken. There is very little data in the literature as far as any regimen for patients who have failed initial front-line therapy. You've said it but I just want to say this

out loud. There are two regimens in the literature.

One I mentioned by Tirelli in Italy, VP16, mitoxantrone, and prednimustine. That was tested in 19 evaluable patients. By definition they had had only one prior regimen of chemotherapy. The complete remission rate there was 26 percent. On the other hand, 42 percent had grade 4 neutropenia. The median survival was only 2 months. So, that's one study that we could use as an example.

Another is a study of high dose methotrexate and AZT. That was given in both patients with previously -- most of the patients had untreated disease. Only 8 patients had had previously treated disease. 2 of them had had very, what I would consider, noncurative therapy. One got vincristine/prednisone before and the other got alpha interferon as the only treatment before. So, that's 6 patients in the literature.

Dr. Kaplan, can you speak to that as well?

DR. KAPLAN: I'd just like to add that in our experience with second-line therapy in studies that we've done at San Francisco General using combinations of infusional ifosfamide and etoposide, the objective response rates are higher but the response durations in all cases and in all of the second-line therapeutic trials that Sandy

is talking about are really very short, on the order of about 3 months. So, we are dealing with a population where we really have pretty limited resources in terms of therapeutic options, and this is one that doesn't tend to make our patients sick and one that you can administer to patients who have poor hematologic reserve, as many of these patients do, particularly after they've gone through a variety of other combination regimens.

DR. LEVINE: So, to answer, you said what would my first choice be for second-line treatment. Forgive me, but it would be mitoxantrone -- mitoguazone. I'm sorry.

(Laughter.)

DR. LEVINE: I knew I was going to do that once. I picked the wrong time to do it.

(Laughter.)

DR. LEVINE: The bottom line, though, is that basically you don't burn a bridge there. You see right away the patient responds. It's fairly easy to tolerate and then you go on to something else if you have to.

DR. FORASTIERE: I was wondering if there's any data on change in urine spermine levels with the drug at this particular dose level and whether there was any thought to doing that as a correlative study.

DR. LEVINE: It's an excellent idea. We have

not done it and we were talking about it several weeks ago. We do have plasma stored on these patients and don't have urine stored, but we can go back and look at some of the plasma data and try to correlate with response. We did not do that originally.

DR. ABRAMS: Has anybody looked at Taxol?

DR. LEVINE: No. Judging from the people speaking earlier this morning, we should use it for everything.

(Laughter.)

DR. ABRAMS: I noticed that most of the patients in the two studies completed the trial prior to the advent of protease inhibitors being widely available. So, that's good.

DR. LEVINE: There were 3 patients on the trial who were on saquinovir. No other protease inhibitor was used, and in fact 39 of the 90 were on no anti-HIV drugs coming on to mitoguazone. There was no relationship between the use of antiretroviral drugs and the ability to respond or not. So, for example, of the 6 complete responders, 3 were not on antiretrovirals. Of the 7 partial responders, 3 were not on any antiretrovirals.

DR. ABRAMS: I also noticed that the patients were evaluated prior to the wide availability of HIV RNA

testing as well, but has there been any attempt to look to see if the drug itself had any impact on HIV RNA levels in patients?

DR. LEVINE: Yes, it did and we do have a slide on that. We've looked at 10 patients with serial HIV RNA levels, and we did not look over the long term, but we looked over the first week of therapy. As you may or may not be able to see when we find this slide, there was no substantive change in the HIV RNA levels.

I got them not because I was expecting that they would get higher, but the patients were living longer than I expected, like the stable disease. I wondered if it was doing something in a positive sense. I don't really think so, but median HIV RNA level at baseline, 21,000; 24 hours later, 21,978; 48 hours later, 16,000; 72 hours later, 10,000 as a median. And these are the ranges.

One of the interesting things to me is the range. Here's somebody coming on study with a viral load of 1,000, somebody else coming on study with a viral load of 1 million. So, there's a tremendous range in viral load in these individuals.

It certainly didn't make it worse. I don't think it made it better either.

DR. ABRAMS: Well, it's too bad you didn't

follow it for 3 weeks or something.

DR. LEVINE: Right, right.

DR. GELBER: Can I ask for a clarification on that?

DR. LEVINE: Yes.

DR. GELBER: Are those the same subjects in each one of those lines that are being followed?

DR. LEVINE: Yes.

DR. GELBER: Same patients.

DR. LEVINE: We had done pharmacokinetic work using plasma and we had all of that stored plasma and that, so we had specimens over those time lots on the same people.

DR. GELBER: Retrospectively evaluated.

DR. LEVINE: Yes, yes.

DR. GELBER: I have one question. We're being asked to look at phase II trial data as adequate and well-controlled evidence for effectiveness and safety. I'd like you to comment a little further about any other changes that might have taken place in the care or management of the subjects in these trials over time.

DR. LEVINE: The point is a very good one. If the two trials had gone into the time of widespread use of protease inhibitors, that would have been a very big deal.

I think that would have been a hit to the study. We couldn't have proved that they did better because of the drug. But in fact only 3 patients were on protease inhibitors. Other than that, other antiretrovirals and other reverse transcriptase inhibitors were licensed over the course of time, but again no relationship between use of those drugs and response.

DR. GELBER: I see, so that the patients, when they came into the trial, did not have any change in either their therapy for OIs, their antiretroviral therapies of any type, adding a second agent, changing other antiretroviral therapies. I'm not just talking about protease here.

DR. LEVINE: Right.

DR. GELBER: I'm talking about other interventions.

DR. LEVINE: Right. Well, just to start as one example, 26 percent of the patients came onto study with opportunistic infections. They were on all kinds of drugs as I kind of alluded, but ganciclovir and phoscarnate were commonly used and so forth. Those patients would have been on those drugs throughout. Basically we would not have stopped the treatment for atypical TB or for CMV.

6 percent developed opportunistic infections

while on treatment. To put that in context, in the ACTG 142 trial that was just in the New England Journal, 22 percent of those patients developed OIs on treatment.

So, here 6 percent did develop OIs, which wasn't all that bad to be honest. Those patients would have had additional therapy for those OIs, but other than that, there were no major changes there in the treatments they were getting. Pain medicines went away.

DR. GELBER: I guess my main concern is at the initiation of the trial time, rather than changes that might have happened over time in the trial.

DR. LEVINE: No. We did not change, and that's why, as an example, one of the eligibility criteria said that the patient could be on concomitant investigational antiretroviral drug or compassionate use antiretroviral drug. We didn't change. The only thing that we changed --

DR. GELBER: Nothing else changed at the initiation of the trial except for the study drug.

DR. LEVINE: No. Mitoguazone. No.

DR. OZOLS: Could you comment more about the correlation between the response to treatment and change in performance status? It looks like very few patients really had an improvement in performance status and some who actually progressed on treatment had improvement in

performance status.

DR. LEVINE: Yes.

DR. OZOLS: So, what's the net benefit?

DR. LEVINE: I think the net benefit -- it's difficult to get. I'm spending some time now on Karnofsky performance status. We used the Karnofsky scale as opposed to the SWOG scale simply because it has a wider splay and we thought we could get more subtleties there than just a 4-point base on the SWOG.

It's a difficult call because it's subjective. We're dealing with 18 different institutions. Somebody may call somebody an 80 percent, somebody else would call that a 90 percent. It's difficult to say.

We got the data and I think the most I can say about that performance data was that most of these patients did not fall to the ground. The issue is, in my view, that basically they did not become terribly ill because of the drug.

DR. OZOLS: But I mean, even the ones that responded, only 30 percent of the responders had an improvement in performance status.

DR. LEVINE: Right. As an example, there were several individuals who were coded on study as being 100 percent performance status. Now, in my own view that's not

compatible with a diagnosis of recurrent lymphoma, but that was seen. We got data back in that regard. So, it was confusing to me. It was difficult for me to evaluate that performance data. I guess that's the best I can say.

DR. SCHILSKY: This may seem like a minor point but it seems to me that when you have so few responses, it's important to look at every one of them carefully.

I'd like to go back to the patient who had previously received suramin prior to going on the study.

DR. LEVINE: Right.

DR. SCHILSKY: So, as I understand what you showed on the slide, the patient was demonstrated to have disease progression 2 days after completing the several-day course of suramin.

DR. LEVINE: Yes.

DR. SCHILSKY: That's being claimed as evidence of tumor progression while on suramin. Of course, suramin, as I recall, is a drug that previously has been reported to show some responses in patients with lymphoma and, of course, is a drug that has a half-life in the circulation of about 50 to 60 days.

DR. LEVINE: Right.

DR. SCHILSKY: So, one could anticipate that the suramin would be around for probably much of the

remaining lifetime of this particular patient.

DR. LEVINE: Yes.

DR. SCHILSKY: So, how can you conclude from that that the patient had objective progression while on suramin and that the suramin played no role in the response that the patient manifested?

DR. LEVINE: I understand your questions very well, and I'd make several points.

Number one, the patient came off suramin not because of disease progression. He came off suramin because he developed deep vein thrombosis. That was one of the complications of the drug and he was off. Now, while that occurred, we still had evidence of disease in lung, multiple lymph nodes, and so forth.

Next, the question was, now what are we going to do to treat the lymphoma? At that point we got repeat disease parameter assessments again and that's where we saw this definite progression.

Now, I realize that suramin has been associated with response in lymphoma, and the fact of the matter is that basically that was my patient that was reported. This is a very clearly different case. He has small cleaved follicular lymphoma. He was originally treated with suramin in May of 1985. He had a complete remission by

December of 1985 and has remained in complete remission since that time. He remains well. So, that is an amazing case.

We then opened a study in subsequent years looking at suramin. This was one patient. We've never again seen a response, unfortunately, to suramin. I'll make a joke. The patient is a minister. He was patient number 1 on our first trial in 1985. He was treated on Good Friday, and he believes that this was God. So, maybe it was God, maybe it was suramin, but I'm not used to thinking of suramin as a really effective agent, although your point is extremely well-taken. I understand.

DR. DUTCHER: I think we are going to have to end the discussion. We've gone a little bit over time, but that's okay. It's a good discussion. We're going to take a 15-minute break. We're going to meet back here at 10 minutes after 11:00 for the FDA presentation which will be allotted its full time. We're going to have to cut lunch short a little bit.

(Recess.)

DR. DUTCHER: Can we get started please? We'd like to proceed with the discussion and we'd like to have Dr. Albert Lin from the FDA present the FDA evaluation of the mitoguazone data.

DR. LIN: Good morning. Ladies and gentlemen, on behalf of the FDA review team, I will be presenting to you our review on this new drug application, NDA number 20-709, the application for Zyrkamine, which is mitoguazone and is also known as MGBG.

First, I would like to acknowledge my team members. The FDA review team includes the chemists, pharmacologists, statisticians, and medical oncologists, also other specialists in different disciplines. I would like to thank them for their support during the review process and in preparation for this presentation.

The proposed indication, as you heard earlier, is for treatment of AIDS-related non-Hodgkin's lymphoma in patients who have been previously treated with at least one potentially curative regimen.

My half-hour presentation will include introductory remarks followed by discussion of clinical trials, patient population, and results from clinical trials. I will spend most of my time focusing on the results from the clinical trials.

Published data on the treatment of relapsed and refractory AIDS-related non-Hodgkin's lymphoma are sparse. Two abstracts and one article deal with this subject using agents other than MGBG. Review of the literature reveals

two points. First, the response rate ranges from 0 percent to 33 percent. Second, the survival for the complete responders can be as long as 13 months.

A brief regulatory history of MGBG is shown on this slide. In late 1992, the National Cancer Institute began the first clinical trial, IDD004, on AIDS-related non-Hodgkin's lymphoma. Eventually the sponsorship would transfer to ILEX, the applicant for this NDA.

The second clinical study, IDD007, was initiated in 1994.

Toward the end of the first study, before the initiation of the second study, we met with the sponsor. The agency strongly recommended that a randomized controlled study or a dose-response study should be the next step for drug development. However, the sponsor declined our suggestion.

The NDA was submitted in October 1996. The ODAC meeting was planned for March 1997. However, the meeting was postponed at the applicant's request.

I'm going to skip the next few slides.

Two very similar phase II studies, IDD004 and 007, provided the basis of efficacy and safety data in this submission. When the primary endpoint in a study design, including the evaluation of efficacy and safety, are

compared, the similarity of these two clinical trials is apparent.

The only difference I would say is the way in which some of the efficacy parameters were collected. In the IDD004 study, the lymphoma-related symptoms/signs were collected retrospectively. In the IDD007 study, the information was collected prospectively. The pain VAS rating was not collected in the IDD004 study. However, these data were collected prospectively in the IDD007 study.

Twenty-two investigators from 21 study sites were involved in one or both studies. Six of them participated in both studies and enrolled 80 percent and 51 percent of patients in the IDD004 and 007 studies, respectively.

This slide shows the study site number in the first column, the number of patients enrolled at each site in the second column and the number of applicant's responders in the third column.

About one-third of patients were enrolled at study site number 1 and number 15. Both sites accounted for the majority of objective responders claimed by the applicant. No other sites had more than one responder.

The primary objective of this study was to

examine the efficacy and safety issues of MGBG in treating patients with AIDS-related non-Hodgkin's lymphoma. The second objective was to evaluate the quality of life among patients treated with MGBG.

The slide shows the eligibility criteria. The protocol calls for patients to have at least one prior potentially curative regimen at least 14 days prior to MGBG therapy and having bidimensionally measurable disease.

In addition, confirmation of pathology was required. Specifically the protocol calls for intermediate or high grade lymphoma.

This slide lists the exclusion criteria. Please note that primary CNS lymphoma is in the exclusion criteria.

This slide shows the dose and schedule for this protocol. I just wanted to mention that cycle 1 consisted of three treatments.

The definition for complete response is shown on this slide, and I just want to emphasize that the protocol calls for all measurable disease sites to be followed and measured.

This slide shows the definition for partial response. Again, I just want to emphasize that the protocol calls for all measurable disease-site lesions to

be measured, and the response should be durable for at least 1 month.

Let's look at the patient population for a second.

81 out of 90 patients had intermediate or high grade non-Hodgkin's lymphoma. Other histologic findings included mixed low and high grade non-Hodgkin's lymphoma, low grade and T cell non-Hodgkin's lymphoma. 1 patient had plasmacytoma. Another one had Hodgkin's disease. And the 2 other patients. One had unclassified lymphoma, 1 patient's diagnosis was uncertain.

It should be noted that of the 13 MGBG responders described in this submission, 7 did not have histologic confirmation of recurrence and 4 others had biopsies of recurrence but the biopsies were not reviewed by the reference pathologists, as you heard earlier.

In terms of the pathology review, 49 out of 90 patients had relapsed pathology materials. 25 of them were reviewed by the reference pathologist. 39 patients only had the original pathology reviewed. Neither the original or the relapsed pathology material was available in 2 patients.

A confirmed diagnosis of relapse in 8 patients is important. Because of altered immune systems, patients

with HIV infection have an increased risk for AIDS-defining malignancies shown on the left-hand side of the slide and non-AIDS-defining malignancies shown on the right-hand side of the slide.

At baseline 9 of 90 patients had KS. Again, 1 additional patient had Hodgkin's disease. Another one had plasmacytoma.

During study, at least one of the applicant's responders developed KS. Another one was diagnosed with squamous cell carcinoma. The importance of histologic confirmation of recurrence cannot be emphasized enough in this patient population at risk for opportunistic infection in a wide variety of malignancies.

This slide lists the prior therapy among the 90 patients. 88 patients received chemotherapy as prior therapy. 1 of them received MGBG on a compassionate protocol and this was the only chemotherapy the patient received. Among the other 2 patients who did not receive chemotherapy, 1 had primary CNS lymphoma. Another patient received radiation only for a localized cutaneous T cell lymphoma on the foot, and the pathology was not confirmed by the reference pathologist.

Response to prior chemotherapy is shown on this slide. 11 percent of them had complete response to prior

chemotherapy and relapsed afterwards.

Let's look at the results for a second. Before we look at specific response parameters, let me take a couple moments to go through some of the applicant's responders. In the interest of time, and as you heard earlier about the comments, I will briefly just comment on some of these patients.

Among 13 responders claimed by the applicant, the FDA assessment differs for 8 of them. The first patient was 4-002. We feel the response status on this patient was equivocal. The patient had two episodes of noncompliance lasting several weeks. As a result, the investigator changed the date of baseline assessment, which makes the patient's assessment equivocal.

You heard about the marginal zone B cell lymphoma on this patient.

I'm going to move on to the next patient. The second patient 4-005 was deemed nonevaluable because this patient received suramin 8 days prior to MGBG. The half-life, as you heard earlier, of suramin is up to 50-60 days. Now, for this patient, we did not receive any information prior to suramin therapy, and we were under the impression that the patient was off suramin because of DVT.

The next patient, the third patient, 4-009.

The response on this patient was equivocal because the pathology from this patient contained low grade non-Hodgkin's lymphoma. Second, the investigator used fluid collection as the site of the involvement to measure the gastric lymphoma. Concern was raised by our reviewers and by the applicant's independent reviewer that this patient was probably not eligible since there was no measurable disease at the study entry.

The next patient, 4-020, was deemed nonevaluable per our review, and this patient had 50 cutaneous lesions at baseline. This is taken from the patient's records at entry. Notice the patient had 50 cutaneous lesions. Five of them where chosen as index lesions. A 2-centimeter inguinal node was noted in the medical record. However, this one was not included as a measurable site.

More importantly, on this date, August 31, 1994, the patient was scored as CR. In fact, his record indicates the patient is stable PR and clinical CR.

The next patient, 4-027, was deemed nonevaluable because the patient had a KS lesion on both legs. An inguinal node was assessed as being involved with lymphoma. This was a case we felt the importance of having a biopsy to confirm the pathology. In addition, the

medical record indicates the patient's response did not last for 1 month.

The next patient, 4-029, had persistent periaortic and inguinal nodes. If one looks at just the inguinal nodes -- and from the medical record, the information indicates the patient did not have CR. So, this renders a PR instead of a CR.

The next patient, 7-028, had prior chemotherapy 2 days before MGBG. There was no clear documentation of disease progression after prior chemotherapy.

This slide shows the first record we have on this patient. At the date of entry, according to the record, there were three rectal masses on this patient. None of the tumor measurements matches with the information in the NDA submission.

The final patient, 7-032. The response was equivocal after review. The patient had esophageal lymphoma as shown on this CT scan indicating thickening of the esophagus. If one reviews this patient's chest CT films, one would conclude that there's an elongated lesion about 7 to 8 centimeters long. What the investigator did was arbitrarily choose two cuts as the measurements for the tumor sites and the esophagus continued to be thickened by CT scan, though clinically the patient was scored as a CR.

Let's look at the specific response parameters. Since both studies were similar, I will present the combined result.

The response rate. As I mentioned earlier, 4 patients were deemed nonevaluable in review. This renders the intent-to-treat response rate of 10 percent. The 95 percent confidence interval ranges from 3.8 percent to 16.2 percent. As you recall, response status from 3 patients was equivocal. If one removes the 3 patients, the intent-to-treat response rate would drop to 6.7 percent. The 95 percent confidence interval ranges from 1.5 to 11.9 percent.

One additional patient in whom we have a disagreement in assessment would change from CR to PR on review which does not affect the response rate.

Time to response. This slide shows a box plot of time to response with both the FDA and the applicant's assessments. The vertical axis is time by day. The median time to response was 49 days from our analysis, and the applicant's analysis was 53 days.

Two additional points need to be made here. First, notice that the patient 4-002 is an outlier. This is probably because of the fact that the patient had low grade non-Hodgkin's lymphoma.

Second, the applicant's assessment differs from FDA's assessment. This is because of the patient's noncompliance and the investigator's moving the date of baseline assessments.

Duration of response is shown on this slide, and this slide illustrates the Kaplan-Meier analysis of duration of response. The horizontal axis represents time by day. The vertical axis represents the probability. The red line represents FDA's assessment. The yellow line represents the applicant's analysis. The median duration of response was 113 days.

1 patient was censored. It was 4-009. Notice that there are two outliers, patient 4-002 and 4-009. As you recall, both have some low grade non-Hodgkin's lymphoma.

Time to tumor progression is shown on this slide. The green line represents the applicant's analysis and the red line represents FDA's analysis. The median time to tumor progression was 56 days from the intent-to-treat analysis.

2 patients were censored, 4-009 and 7-001. The second patient had plasmacytoma.

This slide illustrates the Kaplan-Meier analysis of survival with the intent-to-treat approach.

Again, the green line represents the applicant's analysis. The red line represents FDA's analysis. The median duration of survival was 83 days.

9 patients were censored in this analysis.

When prognostic factors, which are listed in the first column, were examined for responders versus nonresponders, one finds the response can be explained by the performance status in the applicant's analysis or the CD4 counts in FDA's analysis. 12 out of 13 of the applicant's responders had a performance status greater than 70 percent. In our analysis the median CD4 count was 169 for 9 responders and 44 for nonresponders.

Let's look at the clinical benefit next. We are uncertain of the significance of such evaluation in the NDA. The number of the cases was small. There was no comparator. The analyses were not prospectively defined and we have concerns about the statistical methodology.

In terms of response to the prior chemotherapy, I mentioned to you earlier that 11 percent, or 10 of 90 patients, had a CR in response to the prior chemotherapy. The applicant's assessments of MGBG efficacy is shown on the first column here. The FDA's analysis on the far right.

All 3 complete responders from the FDA's

analysis had prior CR, and 5 out of 6 applicant's complete responders had prior CR, as you heard earlier.

We now look at the safety issues. The most common high grade hematologic toxicity was anemia which occurred in 28 percent of patients during study. It was followed by thrombocytopenia and neutropenia. Note that 39 percent of patients received 48 red cell transfusions. 20 percent of the patients used growth factor during study. 7 percent of patients required 19 platelet transfusions during study, as you heard earlier.

Common nonhematologic toxicities are shown on this slide. Vasodilatation and paresthesia were the two most common nonhematologic toxicities. Two points to be made on this slide.

One is most of the nonhematologic toxicities were low grade and all of the events were reversible.

In terms of the opportunistic infections, 50 out of 90 intent-to-treat patients had opportunistic infection at baseline. 21 patients experienced 36 events of opportunistic infection during study. On the other hand, among those 40 patients who did not have opportunistic infection at baseline, 10 of them experienced 13 events during study.

Hospitalization. I apologize for the typo

here. This should be 29. 29 of 90 intent-to-treat patients required hospitalization. The adverse events for 12 out of those 29 patients were considered possibly or probably related to MGBG. 24 events were observed among those 12 patients.

Mucositis and neutropenia were the two most common events associated with hospitalization.

37 patients died within 30 days of the last MGBG treatment. Death of 7 patients were probably or possibly related to MGBG. We recognize that many causes, some of which are intertwined, played a role in the death of this patient population. The point here is the contribution of MGBG to these patients' deaths is unclear, and the possible link of drug to patients' demise is shown on this slide.

In summary, two studies were included in this NDA submission. 90 patients were enrolled in these two phase II studies.

The primary objective again was to examine the efficacy and safety of MGBG in treating patients with relapsed or refractory AIDS-related non-Hodgkin's lymphoma.

I reiterate that 4 out of the 13 applicant's responders were deemed nonevaluable on review, and this renders a response rate of 10 percent and the 95 percent

confidence interval ranges from 3.8 to 16.2. Response status on 3 patients was equivocal. If one removes the 3 patients as responders, then the response rate drops to 6.7 percent, again the 95 percent confidence interval ranges from 1.5 percent to 11.9 percent.

The duration of response in the corresponding group is shown in the bottom row here.

I should also add that 6 of those 8 patients where FDA disagreed in terms of the assessment were in the first study, IDD004, which was initiated as a pilot study and was not intended to be an NDA study.

The most common high grade hematologic toxicity was anemia, followed by thrombocytopenia and neutropenia.

Paresthesia and vasodilatation were the two most frequently observed nonhematologic toxicities.

This slide shows side by side the results from one published study using MVP regimen and the results from the MGBG treatment. Two points need to be made on this slide.

First, although there is no standard therapy for refractory AIDS-related lymphoma, it doesn't mean that there's no alternative therapy for such condition.

Second, the response rate is higher for the MVP regimen, which is about 33 percent, and the duration of

response for complete responders was comparable, up to 390 days.

The best way to determine if one therapy is better than the other one, is to do a randomized control study, and we believe the applicant agrees to this approach. They have submitted to the agency the drug protocols which support the concept for a randomized control study.

We conclude, first, the efficacy of MGBG in treating patients with relapsed AIDS-related lymphoma is uncertain. In terms of response, whether 6.7 percent, 10 percent, or 14 percent, the response rates are low.

Second, at the dose used, MGBG was not associated with severe adverse events in most patients. However, the risk associated with MGBG treatment is not negligible.

Thank you for your attention.

DR. DUTCHER: Thank you.

Are there questions for Dr. Lin?

DR. ABRAMS: Just on the basis of your second-to-the-last slide about the proposed phase III study, the agency feels comfortable with a trial of MGBG alone versus CHOP in previously untreated patients? You're recommending two different trials, one of MGBG alone versus --

DR. LIN: No. That's the applicant's proposal.

DR. ABRAMS: Oh, okay.

DR. LIN: That's not our recommendation.

DR. ABRAMS: I thought it was yours. Sorry.

DR. FORASTIERE: You went over exactly what you had in the materials before this session, and we heard from the sponsor a detailed response to some of the things that you raised as issues in the specific patients where you felt that their response should have been nonevaluable or something like that. I'm wondering if, after hearing their response, you had any thoughts about changing some of those points that you made.

For instance, let me give you an example. One is the one that just stuck in my mind, the patient that had the lesion in the esophagus that they said they had biopsied actually. They had looked at the serial CTs and, true, you can't really tell much from a serial CT. But they had biopsied and I think a path-negative biopsy.

You didn't mention that in your presentation. I'm wondering how you would interpret that now. Would that change your feeling about that particular patient and the response that was provided by the sponsor?

DR. LIN: On that particular patient who was diagnosed with esophageal lymphoma, as I mentioned, the way

the case was followed was using CT scan to look at the esophagus, and that measurement to me was imprecise. I mentioned earlier even when the patient was scored a CR, the esophagus continued to be thickened.

The question is whether or not the patient had bidimensionally measurable disease.

DR. FORASTIERE: Okay. So, your objection is the measurability and reproducibility of tumor measurements.

DR. LIN: Right.

DR. SCHILSKY: I had a couple of questions. One point I'd like some clarification on.

You showed a slide with respect to time to progression in which you showed the FDA's analysis and the sponsor's analysis. In that slide the median time to progression, according to the FDA, was 56 days and according to the sponsor was 57 days. The sponsor showed a slide in which the median time to progression was 40 days. So, what's the right number?

DR. LIN: 56 days.

(Laughter.)

DR. SCHILSKY: I don't believe you commented at all on the agency's thoughts with respect to issues of clinical benefit. Could you comment on the agency's

assessment of issues about performance status, weight gain, pain, et cetera that I think are important for us to consider?

DR. LIN: I believe I mentioned that in a slide. Well, in one of the slides I mentioned I think the bottom line is the analysis was not preplanned and the number of cases was small and there's no comparator arm. It's very hard to interpret.

DR. SCHILSKY: So, you don't feel that it's possible to draw any conclusions about clinical benefit.

DR. LIN: It's impossible to draw any conclusion specifically 3 percent weight gain was not defined and we don't know how they came up with this idea. Why 3 percent? Why not 5 percent or 10 percent or 20 percent? Those were not defined in the protocol initially.

DR. MARGOLIN: I guess I do need to ask a question to clarify whether the current application is being considered as a fast track, or whatever the correct term is, using surrogate markers of benefit such as objective response and that these phase III studies that are being proposed by the sponsor and will be presumably discussed further with the FDA will then be required to contain all the elements of a full approval such as well-defined and statistically prospectively defined

quality of life measurements and clinical benefit outcomes.

DR. DeLAP: Do you want a response on how we're looking at the application as far as regular approval versus accelerated approval standards and how those apply?

DR. MARGOLIN: Right.

DR. DeLAP: Well, the standards of course are that to get regular approval, we expect to see adequate evidence from adequate and well-controlled trials that demonstrate a meaningful clinical benefit for patients. The meaningful clinical benefit is generally regarded to be either a survival prolongation, which of course is very difficult if not impossible to assess in studies that lack a concurrent control group, or improvement in tumor-related symptoms. So, a significant palliative benefit.

So, in order to go with a regular approval, the recommendation of the committee would hopefully be based on some evidence that you've seen that you feel is reasonably -- well, is persuasive, that there is a clinical benefit of either the palliation of tumor-related symptoms or survival benefit.

The accelerated approval option could be based on response rate with the notion that subsequent definitive studies would be done to clarify and demonstrate the relationship between that response rate and meaningful

clinical benefits.

I just marked the page in the book on the accelerated approval regulation, and if I can just read from that what the standard is there. "This subpart applies to certain new drug and antibiotic products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses," which certainly this is, "and that provide meaningful therapeutic benefit to patients over existing treatments, e.g., ability to treat patients unresponsive to or intolerant of available therapy or improved patient response over available therapy." So, the operative phrase here would be "improved patient response over available therapy" and the surrogate endpoint would be the response rate.

So, if we had a recommendation from the committee for an accelerated approval action, it would be based on your assessment that this product provides an improved patient response over available therapy and that is likely, in your judgment, to correlate with clinical benefits when further studies are done.

So, you do have to take into account other therapies that are available for treating these patients, and your judgment then needs to be that in your opinion the response rate that you observed from these studies is

something that represents an improvement.

DR. DUTCHER: I don't want to open another general discussion, but I just would like to hear from someone, maybe Dr. Abrams, the impact of some of the antivirals on the ability to treat patients in subsequent relapses of lymphoma because certainly we've found they make it considerably easier to treat in first line, for example, the CDE study where we have a much higher response rate but we were also able to keep people relatively stable with antiviral agents. Is there a subsequent improved fallout of this when they relapse from their lymphoma and they are then retreated? Do you want to speak to that?

DR. ABRAMS: I don't personally have any experience in that situation. Dr. Kaplan. It would all be anecdote.

DR. DUTCHER: Dr. Kaplan?

DR. KAPLAN: I think there's very little experience so far. I think that so far, because we're really relatively early in the use of combination antiviral therapy, that there really isn't a whole lot of experience of combination antiviral therapy with second-line chemotherapy. Most of those patients, after they've gone through first-line therapy and some of them second and third-line therapy, are still going to be pretty severely

myelosuppressed.

DR. DUTCHER: Do you want to make a comment?

DR. LEVINE: I just wanted to bring up one other small point which is that this is being compared to VPM, and I'd just like to make the point that prednimustine is not licensed in this country. We can't get that drug in this country. I just wanted to say that.

DR. DUTCHER: Any other questions from the committee, comments? Dr. Von Hoff?

DR. VON HOFF: Thank you. I just want to clarify one point. We had gone through many other types of clinical trial designs, single agent mitoguazone versus another single agent chlorambucil or something else. But in these particular patients at this point in their disease, we could not get our investigators and our colleagues to randomize patients to another single agent because of the side effect profile of those agents.

We also tried a single agent versus an mBACOD or a CHOP and brought that up at least as a possibility, or second line, a combination versus single agent. Again, the investigators felt at that point in time that the current regimens were too myelosuppressive as opposed to mitoguazone.

The other one that we did try to do in this

particular trial is a dose-response effect because we felt that might be a good way to see if there's a difference even in time to tumor progression. So, we went from 600 to 900 but treated those first patients at 900 and they got severe mucositis. So, we felt that was not possible to do it. So, we were left with the phase II trial design.

DR. DUTCHER: Dr. Gelber.

DR. GELBER: One other follow-up on that. Have those conditions changed then to enable an alternative to the two trials, the phase III trials, that have been proposed for the future? Or do those conditions still apply so it would be very difficult or impossible to do any kind of phase III trial?

DR. LEVINE: The design that has been discussed and that will be discussed further with the FDA on Thursday is a design where patients would be treated first. It's a complicated thing but they would come on study as first-line treatment. They would be treated with attenuated dose CHOP for two cycles. They would then be reassessed. Patients who had a complete response would continue on with CHOP. Patients who had progressive disease would go to mitoxantrone. Shoot.

(Laughter.)

DR. LEVINE: MGBG. Patients who had PR or

stable disease would then be randomized to continue CHOP versus the MGBG. So, that is the design that we were going into to discuss with the FDA.

Oh, I'm sorry. Right. So, it was continued CHOP versus CHOP plus MGBG. I'm sorry -- in that PR and stable disease group.

DR. DeLAP: I just wanted to add one comment which is certainly not directed specifically at the current sponsor but is just a general, I guess, dissatisfaction on my part that we continue to have to struggle with deciding the merits of the drug based on very small numbers of observations. It's very troublesome to me that there are more people sitting around this table than there are responders, whoever's numbers you wish to use. It's a real problem I think and it would be so much easier if we could just get good, strong scientifically outstanding data so that we wouldn't have to grapple with these issues the way that we do each time.

Again, I don't direct that specifically at the sponsor here because I think we're speaking of a more general problem. Just in general it's very difficult to get patients in clinical trials in this country. I'm not quite sure what all the answers are, but I don't think we always do as much service as we would like for patients by

making decisions based on these very small numbers. There's a tremendous opportunity to make some major errors now and again, and it would be so much easier and more scientifically strong if we had the data.

So, I would appeal to the people in the efficacy communities -- that's a big part of the issue, at least for me, right now -- how do we do a better job of getting the science we need to make the decisions we're trying to make?

DR. DUTCHER: Let me just also, while you're getting up, please remind ILEX to provide us with the two overheads that weren't in the packet.

DR. LEVINE: I totally agree with what was just said and I would just make one point which is the largest trial that has ever been published in newly diagnosed AIDS lymphoma was the ACTG. That was 192. This trial was 90 patients in relapsed. So, it's a very small number and we feel the same way as you. On the other hand, if you look at what's out there, it's not all that crazy versus what has been published.

DR. DAVID JOHNSON: Let's make one correction. It's not a single trial that was done. It wasn't a trial of 90 patients.

DR. LEVINE: True.

DR. FORASTIERE: I guess I'd just like to make a further comment since I've been on this board for five years now and really our charge has been changing over that period of time. Now we're being asked to provide accelerated approval on the basis of phase II data. In this situation it's phase II data, two small studies with very marginal results and with clinical benefit data that's not very interpretable in my view.

So, I think that it is important that when we get these small studies to look at, that the studies are very clean, in other words, that whatever has been set up in the protocol requiring good tumor measurements, requiring tumor biopsies for histology and adhering to prior treatment requirements is done. Otherwise, it's very, very difficult.

DR. DUTCHER: I think we all concur with that.

Yes, Mr. Martinez?

MR. JOEL MARTINEZ: I just wanted to say from a patient's standpoint -- and I've been through my first-line and I hope that I don't have to go through a second-line therapy -- that this is very, very difficult to evaluate. I was reading the material with the hopes that I would find a good degree of certainty, not necessarily that the response rate was going to be tremendous but that the

response rate was going to be sure-footed somehow. I'm not sure that it was there, and that, more than anything, is disappointing.

I think that maybe this is directed a little bit at the applicants. I was a little bit disappointed too in the lack of rigor because, as a person who's looking forward to possibly having something that might save my life with a second-line therapy, I find myself uncertain.

DR. DUTCHER: Any other comments, questions?

(No response.)

DR. DUTCHER: Shall we address the questions from the FDA? They're in your blue folder. They're also in the agenda.

The first question. Patients with AIDS-related non-Hodgkin's lymphoma may develop enlarged lymph nodes or other abnormalities for reasons other than relapse of their NHL, e.g., infections or other cancers such as Kaposi's sarcoma. Is the committee satisfied that the lesions that responded to Zyrkamine treatment were NHL lesions? And should histologic reconfirmation of the diagnosis of NHL be an eligibility requirement for a study of a second-line drug such as Zyrkamine?

Would you like to discuss one or the other?

DR. ABRAMS: As Dr. Levine mentioned, I also

was somebody at the beginning of the epidemic who was very much involved in describing the syndrome of persistent generalized lymphadenopathy in patients with HIV, and we're now aware that lymphadenopathy per se is a response to infection with HIV. We used to biopsy many people's lymph nodes in 1981-82, and then I think as AIDS care providers, especially oncologists, we became rather familiar with the syndrome and are able, if you will, in a way to be able to distinguish between adenopathy that may be malignant and adenopathy that certainly might be benign.

In the clinical setting of a patient who has had a diagnosis of an AIDS-related non-Hodgkin's lymphoma, I think it might be very difficult for a patient to acquiesce and to consent to a second lymph node biopsy to be enrolled in a clinical trial. I think that if that were mandatory in these studies, that 90 patients perhaps would not have been able to be accrued.

Also in view of the fact that there's so much extranodal disease in patients and other things to follow besides the lymphadenopathy, I feel myself satisfied that the lesions that responded -- and again, I'm not convinced that there were that many responses, so it's a little easy -- may in fact have been NHL lesions and do not necessarily believe -- in the best of all possible worlds histologic

reconfirmation would be nice, but I don't think clinically that it's possible in the current environment. So, I think that this is okay.

DR. DUTCHER: I'd just like to comment that again in lymphoma, when it is recurrence in a site of previously biopsied and documented disease, I think we're all reasonably comfortable that that is the issue. I was a little concerned about the patient with liver lesions that were never biopsied that came and went. So, I don't know what that was. I agree that in the best of all possible worlds we would like a histologic confirmation. I think sometimes the bulk of the disease and the rate of growth gives us a clue if we're seeing progressive disease, not just stable adenopathy.

Dr. Gelber.

DR. GELBER: Don, is this true also of a situation where there are multiple centers where some of the centers might, in fact, enroll only one subject in a trial, therefore indicating a lower experience with the disease? Or are you speaking about from your experience, which is quite extensive?

DR. ABRAMS: Well, I think that most of those centers that were involved in the study are centers that I recognize as having experience, the people in AIDS

oncology. So, I would think that they would also have that ability.

DR. MARGOLIN: I guess I just have a question related to that answer which is that if you had a patient -- well, what would be the likelihood of this happening and then how would you address it? You have a patient who has recognized extranodal lesions and had previously been biopsied and is therefore eligible -- they're growing -- who also has modest adenopathy that seems to be stable. The patient responds to MGBG for this and then one or more of those nodes begins to grow. How would you address that?

DR. ABRAMS: It's sort of complicated. I think FNAs are useful and people don't like to make confirmatory diagnoses, but certainly with an FNA you can find KS. You can look for AFB. You can see Reed-Sternberg cells sometimes. So, you can get a clue.

Also, as was used, gallium scanning. Although many of my colleagues are not particularly fond of the nuclear medicine studies, I think that gallium scanning can be useful in such a situation as well.

DR. DUTCHER: Dr. Schilsky, do you want to comment?

DR. SCHILSKY: Well, I don't disagree with what has been said. I'm trying to look at the exact way the

question is worded, and it's sort of a matter of the precision of the language I think more than anything else. I'm certainly satisfied that many of the lesions that responded probably were non-Hodgkin's lymphoma. I don't know that I would be satisfied that every lesion that regressed was non-Hodgkin's lymphoma because I just think it's impossible to know that.

The issue about whether reconfirmation of the diagnosis should be necessary for study eligibility I also think is a difficult question because the likelihood is that most of the time I believe that if you have a patient in whom you know that they had a non-Hodgkin's lymphoma and who had clinical signs of progression, you would be able to biopsy a lesion and be able to confirm the diagnosis. So, I'm not so concerned about confirming the diagnosis for purposes of getting on the study.

Where I continue to have a problem is interpreting lesions that regress or even interpreting sort of any change in clinical status in what is an extremely complicated patient population. I think that most people know this, but it should be clear that I don't personally care for many of these patients. So, I'm not really speaking from personal experience, but it just seems to me that as an investigator, it's an extraordinarily complex

group of patients.

So, it's a little bit long-winded, but I don't know that I would necessarily feel that a confirmatory biopsy is required to get on study, but that still in my mind doesn't solve the problem of how you interpret what happens to the patient subsequently.

DR. DUTCHER: Dr. DeLap?

DR. DeLAP: I think at least the other thought in my mind behind this question is where do you decide that you know enough about an individual patient, particularly as you're getting to smaller numbers of patients and trying to make decisions. Should we really go to the level of documenting everything in each patient? If you get to very small numbers of patients, perhaps that's necessary.

On the other hand, I thought we heard some interesting discussion from Dr. Levine about how if you had previously biopsy-proven disease in a site and it comes back, do you really need to biopsy it again? That seems to be a very plausible argument.

DR. DUTCHER: Okay. So, let's start with 1b. Should histologic reconfirmation of the diagnosis of NHL be an eligibility requirement for a study of a second-line drug such as Zyrkamine? Or I suppose it could be modified to say if it is in the site of a previously biopsied

lesion. You could split the criteria certainly.

DR. DeLAP: We'd just like to have some guidance as we have other discussions with other sponsors down the road on this one.

DR. DUTCHER: So, do you want a formal vote or just a guideline? A vote?

DR. DAVID JOHNSON: Excuse me just a second, Dr. DeLap. Let me just make one clarification for me.

If the question is directed, as I think it is, for the situation in which we're being asked to assess this drug, i.e., a rapid or accelerated approval of a drug in a phase II setting, that's one issue -- I think that's what Rich is struggling with -- versus a situation where one is randomizing patients where the differences in "non-lymphomatous" lesions might even out and therefore would be less of an issue might be how one might interpret this question.

The second comment that I would just make actually Don has already made, and that is -- it goes further than this too -- what is histologic reconfirmation. So, for example, if one were to needle biopsy a site of prior known disease, that's an accepted and recognized way of confirming that in fact one is dealing with the disease. Now, we could argue whether that's necessary or not, but

the fact is that that's less than a lymph node biopsy and something to which patients may be more willing to consider subjecting themselves to as opposed to a full biopsy.

As is true of most questions in life, it becomes a matter of interpretation in how we look at this particular question.

DR. DUTCHER: So, how many feel that histologic reconfirmation of the diagnosis of NHL be an eligibility requirement for a study of second-line drugs such as Zyrkamine?

(A show of hands.)

DR. DUTCHER: How many do not feel it's necessary?

(A show of hands.)

DR. DUTCHER: So, six feel that it does and six feel that it doesn't. I guess that leads us up to Dr. Johnson's statement that it's a matter of interpretation.

(Laughter.)

DR. DUTCHER: Back to then 1a. Is the committee satisfied that the lesions that responded to Zyrkamine treatment were NHL lesions in the patients that were presented? Any discussion? Dr. Johnson?

DR. DAVID JOHNSON: Again, to pursue the interpretation theme, if we're being asked do we believe

that every case that responded was clearly and unequivocally an NHL, if that's the intent of the question, then I personally can answer that question. If the intent was do we think there was a sense that or a feeling that most were, I'll answer it but in a different way. So, I'd like some clarification from the FDA what specifically they're asking us. Are they asking in fact do we believe that all of the responses were NHL? That's the question I'm asking back to the FDA.

DR. DeLAP: I think it would be unfair for us to ask you to certify that every single one of these lesions was what it was said to be. That's a problem in every tumor study of any sort.

But I think we're asking a general reliability question here. Are you sufficiently satisfied that what we're looking at here in these patients is most of the time recurrent NHL and sufficiently so that you can rely on response rates?

DR. OZOLS: Our answer to 1b has got to answer 1a. I think it's the same thing. It's literally we don't know that they all are and nobody can tell, and we'd like that but in reality in this type of trial where you're dealing with so small numbers of patients who respond. Upon accelerated approval, yes, you'd like to see those.

But again, I think in a larger study where there's a higher response rate, we wouldn't be arguing about 4 or 5 patients which makes a big difference in this particular study. So, I don't think there is an absolute answer to that question.

DR. DUTCHER: So, I think that that's subject to interpretation.

(Laughter.)

DR. DeLAP: Well, the later questions are more critical I guess.

DR. DUTCHER: We'll table that one.

Number 2, studies that lack a concurrent control group may serve to characterize a product's acute toxicities and activity, response rate, in AIDS-related NHL, but may not identify other important drug effects, i.e., an increased rate of infectious complications or shortened survival due to immunosuppressive effects of drug treatment.

If only phase II data are generated, how many patients should be studied, and what tumor response rate and response duration should be required to support approval of Zyrkamine for treatment of AIDS-related NHL in patients who have failed first-line, potentially curative chemotherapy?

So, what is the n and what is the response

rate? I think the n is determined by the response rate. What response rate and response duration would you require for approval for patients who have failed first-line lymphoma therapy? Dr. Gelber, do you have any comment?

(Laughter.)

DR. GELBER: Unfortunately, I don't treat these patients. In fact, I'm not very familiar with the existing response rates. Ordinarily in phase II we talk about 20 percent, but that's just kind of rule of thumb. So, if asked for a number, excess of 20 percent.

DR. DUTCHER: I guess I'd just like to comment that the old MGBG data, in combination or even single agent, was around 37, 35 percent in phase II lymphoma patients that were probably -- I haven't looked at the raw data -- in much better condition than the patients that we saw presented here. I'm just concerned that the patients, although they needed to be treated, were in a performance status situation where they really compromised being able to look at a phase II drug. If you are looking for active agents, we've learned certainly the hard way in solid tumors that you need performance status and you need an ability to be able to treat the patient and see the outcome.

DR. MARGOLIN: I don't have the answer to 2a,

but I think that if we could analogize with, if there is such an answer, what response rate, duration of response in first-line therapy for AIDS lymphoma correlates or is felt to correlate with clinical benefit and is statistically associated with survival benefit to the group, if we knew the answers to those questions, we might be able to approach an answer to this question.

DR. ABRAMS: I would also say that I think we should use the same criteria that we use in the situation in patients without AIDS. Advances in treatment of HIV infection have offered new opportunities for people with HIV and I don't think that we should settle for anything less than the committee would use in patients without HIV infection at this point in time.

I was happy to hear 20 percent because that was sort of the figure that I wrote down as well, and I was going to ask the committee, who deals with this in other malignancies in patients without HIV infection, what your standards are because I would apply the same ones.

DR. DUTCHER: Dr. Ozols?

DR. OZOLS: Well, again, I think that response rate is hard, but I think if we look at the confidence limits, that may give us some clue perhaps. I have a hard time when we have response rates that have a confidence

limit, the lowest level of confidence limit being perhaps as low as 1.5 percent. Maybe if the lowest level was 10 percent, then I'd feel comfortable that we're actually dealing with an active agent because once you get down to response rates of less than 10 percent or 5 percent, you're almost talking background. I really have a hard time thinking that's an active agent.

DR. DUTCHER: Dr. Schilsky?

DR. SCHILSKY: I think that there are many ways to look at this, and I would agree with Kim's comments about looking carefully at the patient population also.

It seems to me actually one of the things that I think we have learned from the data that we've seen this morning so far is what types of patients might be most likely to respond to a therapy. In my mind those are patients who have a Karnofsky performance status of at least 70 percent, a CD4 count that is higher rather than lower, and patients who have previously responded to a therapy.

So, I think one of the things that needs to be considered in general in the design of trials in this type of patient population is whether the patient eligibility should be structured in such a way as to in a sense optimize the opportunity for response.

Now, obviously if you do that, you're also going to limit the number of patients who can be enrolled in the trial, which is going to potentially cause difficulties, but I think that has to be considered in the design of future trials.

With respect to what should be the level of response we should look at, we have some evidence of what this drug could potentially do from the older studies that have been done in patients with non-Hodgkin's lymphomas not in the AIDS setting. As you've pointed out, the drug seems to potentially be able to produce a higher level of response than certainly what we've seen this morning, albeit in a very different patient population.

Now, we do traditionally pick response rates like 20 percent, although there have been other drugs that have been approved in the last year or two by the accelerated mechanism with response rates lower than 20 percent in other diseases. So, I think that you do have to also consider what the alternatives are and the issues of clinical benefit and so on.

I also agree with Bob's point about trying to look at a lower level of the confidence interval that you feel comfortable with that you're actually seeing biological effect and not just random background noise.

DR. DUTCHER: Dr. Johnson?

DR. DAVID JOHNSON: I think I'll echo the things that have been said. With respect to lower response rates, Rich hit on it, and that is that in those circumstances, though, we had more convincing evidence of clinical benefit. I frankly don't care if the response rate is zero if we have some convincing evidence that the patient feels better in some way or is doing better. So, I don't know that we had that with the data we see here.

The other comment I would make, the area that I deal with more than this is lung cancer. It has been debated for a long time, for example, how best to study new drugs or to obtain evidence of activity in small cell, as an example. In some institutions, some cooperative groups use only chemo-naive patients, the idea being that they're a group of patients in whom front-line therapy is not terribly effective.

Others, however, have made a very persuasive argument to use refractory patients and in that setting have lowered the bar in terms of response rate from 20 percent to 10 percent and widened the confidence intervals from 95 to 90 percent and then went back and retrospectively analyzed all the so-called active drugs, which is perhaps an oxymoron or a non sequitur, but looked

at the active drugs and found that indeed if one had used those criteria, that one would have identified all of the so-called active drugs in that setting after the individual had received or recognized front-line therapy.

So, I think to answer the question would perhaps require some definition of the patient population, the expectations that one was looking for whether specifically solely drug activity or clinical benefit. I personally would accept a lower response rate in the face of what I would perceive as fairly clear-cut clinical benefit.

DR. DUTCHER: I just have to say in response to that, which I actually agree with, but in lymphoma in general, the response rates for second-line or third-line therapy are still reasonably good.

DR. DAVID JOHNSON: No, no. That's my point. It has to be disease-specific too. It clearly is not what one would get in lung cancer. See, we're happy with 15 percent as front-line therapy for lung cancer. So, who am I to talk about response rates. But the point is that it is, to some extent, disease-specific as well.

DR. DeLAP: Well, again, I think it would be unfair perhaps to ask you to vote on this, but we did want the discussion and we certainly will be able to use that as

we continue.

DR. DUTCHER: I think actually one of the crucial comments that was made by Dr. Abrams was that with the new modifications in treatment, the standard should be similar to non-AIDS lymphoma.

Do you want us to go on?

DR. DeLAP: Sure.

DR. DUTCHER: So, just to summarize question 2, the comments were that it's disease-specific but that there should be a response rate and a duration that is relevant to both AIDS lymphoma and non-AIDS lymphoma. We may lower the bar somewhat compared to first-line therapy, and if phase II study data is generated, it should be sufficient to answer the question either in terms of response rate or in terms of clinical benefit.

Dr. Krook.

DR. KROOK: I think what I'd like to say -- and I'll see if the committee agrees -- is that the response rate in second-line lymphoma, 35-40 percent. Now you lower the bar and then compare it here. Now, somebody may differ, but I think it's in that range. How much do you lower the bar?

DR. GELBER: Just one other comment on the number of patients. Again, this will be a matter of

opinion, but it should be sufficient so that we get some information about the clinical benefit out of the spectrum of patients that are treated. So, I think that that gets into the 100 range or thereabouts in order to be able to do that.

DR. DUTCHER: Moving on to question number 3, is this NDA approvable? Is there sufficient information presented today to approve this drug in an accelerated fashion for relapsed AIDS-related lymphoma?

DR. ABRAMS: I guess since I'm here as the expert, I would say not in my opinion.

DR. DUTCHER: Other comments? Dr. Schilsky?

DR. SCHILSKY: Well, I think we're all going to have to reveal our positions at some point.

(Laughter.)

DR. SCHILSKY: No reason to delay lunch.

Certainly not in my opinion either. I'm not persuaded that there's either a sufficient frequency of response or that the responses are of sufficient duration to be clinically meaningful, nor am I persuaded that there's really a very good relationship between whether patients respond and whether they feel better or not. Although the toxicities of the drug are not great, they are not negligible. So, I would agree that I don't believe

this is approvable.

DR. DUTCHER: Shall we vote? Okay.

All those who feel that this is approvable, please raise their hands.

(No response.)

DR. DUTCHER: There are no votes for approvable.

All those who would vote that it is not approvable at this time?

(A show of hands.)

DR. DUTCHER: It's unanimous. There are 12 voting no.

If it is felt not approvable, is there sufficient information presented that additional clinical studies would be helpful in further evaluating this drug for the indication of AIDS-related non-Hodgkin's lymphoma?

DR. KROOK: Jan?

DR. DUTCHER: Dr. Krook.

DR. KROOK: I think many of the things that have been said would be of great benefit. I was here for the pancreas cancer and the clinical benefit swayed us immensely, and I think that more attention has to be paid towards those performance statuses, weight loss, and to be done prospectively, as it was done otherwise. Obviously

it's great to have a larger study but dealing in clinical trials, that's sometimes hard. So, the larger the study would also be helpful.

DR. GELBER: If at all possible, I would urge some kind of a randomized trial of second-line therapy. I don't know the details of the proposals that are on the table, but I'm unclear as to how these studies, if they are done, will tell us any more about the role of this agent as second-line therapy. Following attenuated CHOP and so on seems very complex to conduct in this way, and I would rather see some kind of a randomized phase II with careful attention to clinical benefit or some kind of comparator study in this setting.

DR. ABRAMS: I personally would not feel comfortable evaluating this drug as a single agent, not in combination with other therapies at this point in time. That's why I asked if that second-to-the-last slide was an FDA recommendation that compared MGBG to CHOP. I think it needs to be looked at in connection with other agents which makes it even more complex to really tease out whether it's really having any effect, but I think from the data that I've seen here, I would not feel comfortable looking at it as a single agent.

DR. SCHILSKY: Just one other comment. I don't

think any of us are probably prepared to propose a study design, but it does seem to me that if there's going to be a randomized study in particular, that very careful thought has to be given to what the appropriate endpoint should be because while we customarily like to think about survival as an appropriate endpoint, it strikes me that this might be a very difficult patient population in which to evaluate survival as an endpoint because of all of the competing medical issues that might impact their survival. So, I'm not suggesting whether or not survival should be an endpoint but only pointing out that it seems to me that when the studies are constructed, that the appropriate endpoint needs to be very carefully thought about.

DR. DUTCHER: You made your comment. Do other people have similar feelings in terms of using this as a further evaluation as a single agent in this population? Dr. Margolin?

DR. MARGOLIN: I would hesitate to argue with the statistician about study design, but I would be very concerned about a randomized phase II because first of all, you just have two phase IIs, so you have to have a large study if you want to look for specific endpoints, and secondly, people will tend to compare even though they're not allowed to. So, I'm not clear on what one could get

out of a randomized phase II that one couldn't get out of a large well-designed phase II if that was how you chose to go.

DR. GELBER: The main advantage I would see in that is to provide some kind of comparator, if not direct, then at least in terms of the assessment of the endpoints under study, especially if you talk about clinical benefit endpoints. You always wonder in the phase II about other things that are going on in the care of these subjects. So, if you have some comparator so that you can get some sense that similar underlying approaches are being taken, that gives you more confidence that you're measuring the effectiveness or lack thereof of the test agent rather than a single sequence. That's the main reason for that design.

DR. DUTCHER: Any other comments? Suggestions?

(No response.)

DR. DUTCHER: Well, thank you very much. We will resume the afternoon session at 1:30.

(Whereupon, at 12:32 p.m., the committee was recessed, to reconvene at 1:30 p.m., this same day.)

AFTERNOON SESSION

(1:32 p.m.)

DR. DUTCHER: I'd like to just mention two things. One is that Michael Marco is joining us at the table as the patient representative.

And the other thing I would like to mention is that we're going to ask Mr. Peter Doherty to make his comments. He was delayed for the open public hearing because his welcome to Washington was that his briefcase was stolen at the airport. So, he has made the trip here and has a statement that he would like to read. So, we're going to do that quickly.

MR. DOHERTY: Good afternoon. My name is Peter Doherty. I'm 70 years old and I have prostate cancer.

I was diagnosed five and a half years ago, and as most men do, I opted for a prostatectomy. I was told I would live to be 100 after my prostatectomy after all the tests were in.

Two and a half years later, my PSA started to rise and then I took 38 radiation treatments. Late last year, my PSA started to rise again. I'm like the stock market, up and down, up and down.

But at any rate, now I'm on hormonal therapy, and the news for me is that again my PSA is starting to rise.

So, I am a prime person that is looking for what do I do after you've refracted. Where do you go next? As we all know, there isn't an awful lot of places to go after your principal therapies are done.

To deviate for just a minute, I helped to lead a group of over 400 men, all with prostate cancer, at the Morristown Memorial Hospital. This group is just slightly over three years old, and we've already buried seven men from our group. When I thought about coming and wanting to say to you, I go to these wakes and I see these men who most of them have died after being hormonal refracted, and I didn't recognize them. The doctors all tell us what a terrible death any cancer is, but the prostate, when it gets in your bones and the other place that it goes, it just must be terrible.

With that thought in mind, I want to ask you to very seriously consider this drug that Janssen is presenting because we really don't have anything. Those of us that are on the verge of having tried all the principal therapies, we need something else, and it's important to us that we can have this opportunity to have something else to look forward to.

We as a group now have in our prostate group at Morristown Memorial Hospital about 50 men that are working

on hormonal therapy, and some of them are going to fail probably. On behalf of them, I also want to urge you to make this decision.

I'd like to leave you with one last thought. In this 24-hour period that we're here today, 115 men will die of prostate cancer. That's a terrible statistic to think about, and it will be all very unpleasant deaths for all of them.

I want to thank each and every one of you for giving of your time to do what you're doing today. It's absolutely vital to us, anyone that's sick, to know the work that you all do, and I take back a message to Morristown. I'm very impressed with everything that you've done, I've heard this morning. In fact, I'm probably kind of lucky that I came late because I can sit and listen to some of the opportunity of what you went over.

Does anybody want to ask me a question or anything that I might have glossed over?

(No response.)

MR. DOHERTY: I guess not.

DR. DUTCHER: Thank you very much.

MR. DOHERTY: Thank you very much.

DR. DUTCHER: I appreciate your time.

All right, we'll move on then to the rest of

the afternoon. We'll begin with the sponsor's presentation on Taxol indicated for second-line treatment of AIDS-related KS.

DR. CANETTA: Good afternoon. I'm Renzo Canetta. I'm with the Pharmaceutical Research Institute of Bristol-Myers Squibb.

We present to you today the results of Taxol in the treatment of AIDS-related advanced Kaposi's sarcoma.

Dr. Susan Krown, who is a member of the ACTG and played an important role both in the definition of the staging and response criteria in this disease, will review the disease characteristics.

Then the principal investigators of the two pivotal trials, Dr. Robert Yarchoan from the National Cancer Institute and Dr. Parkash Gill from the University of Southern California will present the results of their own individual trials.

Finally, Dr. Benjamin Winograd, who's also with the Pharmaceutical Research Institute of Bristol-Myers Squibb, will present the integrated summary, the analysis of patient benefits, and the conclusion.

Taxol has been available since 1993 worldwide for the treatment of patients with advanced second-line ovarian and breast cancer. Lack of cross resistance with

active agents such as the platinums for ovarian cancer and the anthracyclines for breast cancer has been clinically proven. Today Taxol is widely used. The safety profile has been well characterized with a number of different dosages and schedules of administration.

The discovery of the high level of activity of Taxol in AIDS-related Kaposi's sarcoma occurred under a collaborative research and development agreement between the National Cancer Institute and Bristol-Myers Squibb. The discovery and the results have been rapidly reported in the literature.

The first trial, conducted by Dr. Yarchoan here in Bethesda, accrued patients between September of 1993 and January of 1995. An abstract was presented at ASCO as early as the spring of 1994. A paper was published in Lancet in early 1995.

A second study, which was sponsored by Bristol-Myers Squibb outside of the CRADA, independently confirmed these results and was conducted by the University of Southern California and the Harvard Medical School. I would acknowledge here the presence of Dr. Scadden who is the co-investigator for this trial.

This trial accrued between February of 1995 and December of 1995, and an abstract was presented at ASCO

last year in Philadelphia.

Given the importance of the results that we have observed with this compound in this disease, we have launched a comprehensive clinical plan. We are aware of the Taxol profile. We are aware of the change in paradigm of the treatment of HIV disease. We are aware of the fact that Kaposi's sarcoma is only part of this picture. Therefore, we launched a study to systemically investigate the potential for interaction between Taxol and the new class of protease inhibitors. That study is run by the Eastern Cooperative Oncology Group and was recently activated for accrual.

However, we are also aware of the fact that Taxol results historically got better as we treated patients with better characteristics, and also we were aware of the difficulties of designing a second-line randomized trial. So, we designed this first-line randomized trial which will compare Taxol with single-agent liposomal doxorubicin. This trial has been reviewed and approved in concept form both by the NCI and by Bristol-Myers Squibb, and the final protocol is in preparation.

I'd like to acknowledge the presence of Dr. Jamie von Roenn from ECOG who is the principal investigator of both trials and is also here today.

Today only two liposomal anthracyclines are approved for the advanced stage Kaposi's sarcoma. Unfortunately many patients still fail to respond to this treatment, and the duration of response, when a response occurred, is short.

We believe that effective novel therapies for AIDS-related Kaposi's sarcoma are needed and should be made rapidly available. This is why we recommend the approval of Taxol for the secondary treatment of patients with AIDS-related Kaposi's sarcoma.

We now give the podium to Dr. Krown who will review the disease.

DR. KROWN: Thank you and thank you, ladies and gentlemen.

This afternoon I'll be giving a very brief, I hope, overview of AIDS-associated KS and its treatment and evaluation that will serve as a background to the presentations on Taxol.

As you're all aware, Kaposi's sarcoma is the most common AIDS-associated malignancy. It most often presents with lesions on the skin that may be widely disseminated from the outset. Although the course of KS is quite variable, in many patients KS disseminates not only in the skin, but also to involve the oral cavity and

visceral organs, especially the lungs and gastrointestinal tract, and is often complicated by lymphedema of the extremities, the face, and the genitalia.

Depending upon its location and severity, KS can cause serious functional disability. KS lesions of the feet may be painful and limit mobility. Oral KS may cause difficulty eating and speaking. Edema may be associated with ulceration, infection, pain, and reduced mobility. GI KS may be associated with bleeding, pain, and obstruction, and pulmonary KS can cause respiratory insufficiency and death. Even in the absence of symptomatic visceral disease or edema, KS often impairs quality of life when it causes disfigurement, leads to social isolation, or serves as a visual reminder of an AIDS diagnosis.

KS usually presents multifocally without a defined primary lesion. So, staging according to a standard TNM classification is not appropriate.

In addition to tumor extent, immune status and the presence of systemic manifestations of HIV infection are relevant to prognosis in HIV-infected patients with KS. The most commonly applied staging classification for KS is the TIS system proposed in 1989 by the ACTG Oncology Committee. This staging system, which divides patients into good or poor risk groups for each of the variables,

was prospectively validated for survival in 294 consecutive patients entered onto eight ACTG KS treatment trials, and this analysis will be published in the September JCO.

In the subset of 111 KS patients included in this analysis who had a CD4 count below 50, which closely approximates the CD4 counts of patients in the Taxol trials that will be presented today, we saw a median survival of only 11 months. Furthermore, patients with untreated pulmonary KS have been reported to show a median survival only 2.1 months, making lung involvement an exceptionally poor risk feature for survival.

The potential impact of KS on patient function and quality of life is probably best illustrated by visual examples. This slide shows extensive lesions on the back and feet of a patient with KS and the foot lesions in this case were painful and immobilizing.

This slide shows extensive oral KS which caused difficulty eating and speaking.

This shows moderate but asymmetrical lower extremity edema that affected ambulation and also illustrates the difficulties encountered in reproducibly quantitating the number of KS lesions.

This shows ulcerated, infected KS in an edematous, previously radiated leg.

This shows extensive pulmonary infiltrates from KS.

Finally, this shows the extent of disfigurement that can be caused by facial KS and also illustrates the problem of quantitatively assessing facial edema.

Several treatment options are available for KS and their choice is dictated by the extent of disease, the rate of disease progression, and the presence and severity of symptoms affecting function and quality of life.

For limited, relatively slowly progressive disease without life-threatening organ involvement, local measures may be suitable in some cases. However, for more widespread symptomatic or rapidly progressive disease, systemic interferon or chemotherapy are more appropriate. Responses to interferon tend to occur slowly and are most reliably seen in the small proportion of patients with relatively high CD4 counts.

For the majority of patients with advanced or rapidly progressive KS, which causes medical or functional impairment, chemotherapy is indicated. The goals of such therapy are to induce durable regression of widespread disfiguring or disabling lesions, to control or reverse life-threatening visceral disease, to reduce functional impairment caused by edema or mucocutaneous disease, and to

achieve these benefits with agents that have an acceptable toxicity profile.

In addition, because the patients all have an underlying HIV infection that is generally quite advanced, chemotherapy should not interfere with delivery of treatment with antiretroviral drugs or treatment in prophylaxis for other opportunistic complications of AIDS.

In the past, studies of standard chemotherapeutic agents, including vincristine, vinblastine, doxorubicin, bleomycin, and etoposide, have demonstrated KS regression in a variable proportion of patients. However, disease control has been limited in part by cumulative toxicities from these agents. In general, combination therapy has induced higher response rates but at the expense of somewhat increased toxicity which often limited long-term use.

Nonetheless, by the early 1990s combination therapy was considered the standard of care, with the ABV regimen, which consists of doxorubicin, bleomycin, and vincristine, considered the most effective at least in this country.

The reported response rates and response durations for these single agents and combinations are difficult to interpret, however, since patient

characteristics and response definitions varied from study to study and the methods of disease documentation and response definitions were often ambiguous and inconsistently applied.

In the past two years, two liposomally encapsulated anthracyclines have been approved by the FDA for treatment of advanced AIDS-related KS. DaunoXome, a liposomally encapsulated daunorubicin, was approved as first-line treatment based on a prospective randomized comparison with a standard ABV regimen. Equivalent response rates of 23 and 30 percent of almost identical duration were observed in the two arms. Median survival was also similar but was less than 1 year in both arms. Significantly less neuropathy and alopecia were observed with single agent DaunoXome compared with ABV.

Doxil, a liposomally encapsulated doxorubicin preparation, was approved for treatment of AIDS-related KS after failure or intolerance of combination chemotherapy. Tumor response rates of 27 and 48 percent were reported, depending on whether a global investigator assessment was used as the response criterion or the response was based on changes in selected indicator lesions. The median response durations were 2.4 and 2.3 months from the time a partial response was recorded by these methods.

The previously cited inconsistencies in KS evaluation and response criteria were addressed by the ACTG Oncology Committee in recommendations published in 1989, and as experience with these recommendations grew, various minor modifications were made, but they were all consistent in requiring detailed quantitative documentation of the number, size, and character of skin lesions, qualitative descriptions of tumor-associated edema and oral and visceral KS, and a recommendation for photographic documentation when possible. This documentation was then used to evaluate the response to treatment.

Briefly a partial response was defined as a 50 percent or greater decrease in either the total number of lesions, the total number of raised lesions, or the indicator lesion surface area without new or increased visceral disease or tumor-associated edema.

Progression was defined as a 25 percent or greater increase in total lesion number, the number of raised lesions, or the indicator lesion surface area, the appearance of new or worsening visceral disease, or the development of symptomatic tumor-associated edema.

These criteria have been used in many of the recently published trials and have provided greater consistency in the evaluation of KS treatments.

The ACTG criteria do not specifically evaluate clinical benefits associated with tumor regression, however, and this deficiency is currently being addressed in a joint NCI, FDA, and AIDS Malignancy Consortium initiative.

So, in summary, extensive tumor burden, visceral and especially pulmonary KS, and a low CD4 count are all associated with a short survival in patients with AIDS-associated KS. Systemic chemotherapy is indicated for patients with rapidly progressive or symptomatic KS, and detailed documentation is required to fully assess the effects and benefits of such treatment.

Now, in the studies of Taxol that will be presented today, the following information was gathered prospectively to document tumor extent. In patients with less than 50 cutaneous lesions, all lesions were counted at each evaluation, whereas in those patients with over 50 lesions, the lesions on representative body areas were counted and each of the counted lesions was described as raised or flat.

In addition, 5 to 11 indicator lesions were selected in each patient and were serially measured in two dimensions and characterized as raised or flat.

Photographs were taken at baseline and

periodically thereafter to document response.

In addition, qualitative assessments were made of oral KS and edema, and visceral symptoms were investigated with appropriate diagnostic tests.

Each of the investigators assessed patient response as defined in the study protocols. Subsequently Dr. Jamie von Roenn of Northwestern University performed an independent assessment of response on the NCI study patients using the most recent ACTG criteria, and I performed the same assessment of the patients treated on the joint USC/Harvard trial. We reviewed all disease documentation and used this to assess overall response, efficacy by disease site, and the date and site of disease progression.

In addition, to provide a more global assessment of patient benefit, changes were documented in six areas that relate to functional status and quality of life in patients with KS. These included improvements in performance status in patients with a performance status at baseline, improvement of pain, and improvement or resolution of tumor-associated edema, and KS lesions located on the feet, face, and in the lungs.

With this as a background, Dr. Robert Yarchoan of the National Cancer Institute will now present the

results of the first study of Taxol in advanced KS.

DR. YARCHOAN: Thank you, Susan.

Chairman, members, and guests, over the next 10 minutes or so, I'll describe the initial phase II trial of Taxol for the treatment of Kaposi's sarcoma conducted in the intramural program of the National Cancer Institute. This study, which was initiated in September of 1993, was conducted primarily to address the question of whether Taxol had activity in HIV-associated KS.

I should note that I'm speaking here as part of my official duties as an employee of the National Cancer Institute and that the study was supported in part by a CRADA between Bristol-Myers Squibb and the NCI.

At the time we initiated the study, several pieces of evidence led us to hypothesize that Taxol would have activity in Kaposi's sarcoma. Vinca alkaloids were known to be active in KS, and Taxol affects the same cellular targets as the vinca alkaloids, although it causes irreversible polymerization rather than depolymerization.

Dr. Wayne Saville in my group had shown that Taxol had potent activity against a KS-derived spindle cell line in vitro, and further in vitro studies by Kim Duncan and Ed Sausville provided some evidence that it had antiangiogenesis activity.

Since the initiation of this study, evidence has emerged that Taxol can cause inactivation of bcl-2 by phosphorylation. This may provide another possible mechanism, especially as KSHV, a newly discovered herpes virus that's believed to be a pathogenic agent for KS, has recently been found to encode for a viral homolog of bcl-2.

The study was designed as a single center, nonrandomized phase II trial to evaluate the efficacy and safety of Taxol in AIDS-related KS. It utilized a two-stage design to reject a response rate of less than or equal to 30 percent.

The initial dose was chosen to be 135 milligrams per meter squared given over 3 hours every 3 weeks, giving an initial dose intensity of 45 milligrams per meter squared per week. This was then increased or decreased in each patient based on their tolerance.

Initially no hematopoietic growth factors were utilized unless these were medically indicated for another condition such as ganciclovir therapy for cytomegalovirus.

Taxol was to be given until progressive disease or unacceptable toxicity occurred. Retreatment was permitted for responders.

An amendment to the protocol permitted the use of G-CSF support for those patients whose disease had not

responded or had progressed in association with a lower dose of Taxol. A new baseline KS evaluation was established at the time the G-CSF regimen was added.

Patients who had advanced HIV-associated KS warranting systemic chemotherapy were eligible. However, patients who had substantially symptomatic or other acutely life-threatening KS were not eligible because when we started, we did not know whether Taxol had activity in KS. Patients could have had no more than one prior regimen of systemic cytotoxic chemotherapy and had to have a Karnofsky performance status of at least 70 percent. Concomitant antiretroviral therapy was allowed. This therapy was not changed unless a medical indication arose during Taxol therapy.

The study was conducted under an NCI IND, and I thank CTEP for their support in this. The protocol called for clinical evaluation of KS every course and photographic and radiologic evaluation every two courses. In all, 29 patients were accrued between September 1993 and January 1995. Presented here will be the follow-up on those patients through July 1996.

The patients who entered all had Karnofsky scores of 80 or 90. Overall the patients were quite immunosuppressed. The median CD4 count at entry was 15

cells per cubic millimeter, and 22 of the patients had a baseline CD4 count of less than 50 cells per cubic millimeter.

All the patients entered onto the study had at least two poor risk criteria. 97 percent had extensive KS with either edema, oral involvement, or visceral involvement. 90 percent had a CD4 count of less than 200, and all the patients had one of the manifestations of systemic illness.

Shown here is the KS involvement of various disease sites at entry. 28 of the 29 patients had some involvement of the skin. The remaining patient had pulmonary disease only. As seen here, the patients generally had extensive involvement with KS. In particular, 6 patients had visceral disease, 5 of the lung and 1 of the GI tract.

19 of the patients had had some prior systemic therapy, including 8 who had had systemic cytotoxic chemotherapy. Of those, 5 had received systemic anthracyclines, either DaunoXome or doxorubicin, as part of an ABV regimen.

Shown here is an analysis of the therapy actually received. The patients received from 2 to 39 courses of Taxol with a median of 10. The median dose

intensity received was 38 milligrams per meter squared per week. As of July 1996, 3 patients were still continuing on therapy after receiving Taxol for 20 to 30 months.

26 of the patients received antiretroviral therapy with nucleoside analogs. 2 also received protease inhibitors. In both of those cases, the protease inhibitors were started after the patient had achieved a partial response.

9 of the patients received G-CSF after having progressed on the initial phase of the study, while 9 received it for some other indication, most commonly concomitant ganciclovir therapy.

Shown here are the responses as assessed by Dr. Jamie von Roenn, the outside reviewer, on the initial 3-hour Taxol regimen without protocol-related G-CSF. 2 patients achieved a complete response, 1 of which was a clinical CR, and 18 patients achieved a partial response. Each of these responses agreed with the assessment of our protocol team. 8 patients were assessed as having stable disease and 1 had progressive disease. Overall 20 of the 29 patients responded, yielding a major response rate of 69 percent, with a 95 percent confidence interval from 49 to 85 percent.

The median duration of response from entry to

progression was 7 months, with a range from 3.5 to 29.2 months.

Shown here is an analysis of the improvement broken down by disease site. Overall 23 of the 28 patients had improvement in their cutaneous disease. It is worth noting that each of the 5 patients with pulmonary disease responded and that 16 of the 18 patients with edema had lessening of this disease manifestation.

To give a sense of the patient benefit achieved, shown here is a photograph of patient number 19 who had facial KS at entry, and shown here is the same patient after 10 months of treatment with Taxol.

Shown here is a CT scan of patient number 14 who had extensive pulmonary KS at entry. Shown here is a scan of the same patient taken approximately 8 weeks later, and as can be seen, there is dramatic improvement.

Shown here is the time from entry to disease progression in the group of patients. The median time to progression on this study was 5.5 months.

Shown here is the survival curve. The median survival of the patients was 14.1 months. As noted before, these patients were generally severely immunosuppressed at entry with 22 of the 29 having less than 50 CD4 cells. This survival is within the range expected at that time in

such patients even without Kaposi's sarcoma.

The most frequent dose-limiting toxicity seen was bone marrow suppression. All the patients had some neutropenia, and 76 percent had grade 4 neutropenia. 10 percent of the courses were associated with febrile neutropenia.

In all, 22 of the patients developed opportunistic infections during a total of 50 courses of therapy. This is within the expected range, given the degree of immunosuppression at entry. The most frequent OI seen was cytomegalovirus retinitis.

As seen here, the non-hematologic toxicity was generally similar to that found in other studies of Taxol. Hypersensitivity reactions, peripheral neuropathy, arthralgias, and alopecia were the most common seen. It should be pointed out that most of the patients had other causes for their neuropathy, especially their underlying HIV infection and nucleoside anti-HIV drugs, and it was hard to separate out the contribution of Taxol.

In addition to what is shown here, 2 black patients on the study developed elevated creatinines. This is often a complication of HIV infection, however, in this population. 1 of these patients also developed severe and eventually lethal cardiomyopathy which was found on autopsy

to be related to thrombotic thrombocytopenic purpura.

In summary, this study first established the activity of Taxol in patients with AIDS-related Kaposi's sarcoma. All patients had poor risk, extensive KS, warranting systemic chemotherapy. Taxol induced an overall response rate of 69 percent with a median duration of 7 months. All 5 patients with pulmonary KS responded. Therapy was relatively well tolerated with a median of 10 Taxol courses administered.

Finally I want to acknowledge some of the collaborators who contributed to this project. I should especially mention Dr. Wayne Saville who first spearheaded the project with me, Dr. Lauri Wells, and Jill Lietzau, the principal research nurse.

I would now like to turn the podium over to Dr. Parkash Gill who will describe the joint study done at USC and Harvard Medical School.

DR. GILL: Thank you very much, Bob. I'd like to thank the Chairman, ladies and gentlemen.

This study 281 was designed based on preclinical evaluation of Taxol in Kaposi's sarcoma cell lines showing that IC50 was just over 1 nanomol and far below the plasma concentrations achieved with standard dose Taxol. We hypothesized that lower peak levels of Taxol

should be active.

This trial therefore adopted a dosage of 100 milligrams per meter squared as a 3-hour infusion and was the first effort to explore that possibility. This phase II nonrandomized trial was designed to evaluate the efficacy and safety of Taxol in patients with advanced KS.

Patients were accrued in two strata based on their prior history of systemic chemotherapy. The study was designed with the intent to treat 25 patients per stratum, with an expected response rate of 40 percent or better in each stratum.

Patients were eligible for this study if they had advanced KS, defined by symptomatic visceral disease, edema, or extensive mucocutaneous disease. The Karnofsky performance status of 60 or above was required, and the use of concomitant antiretroviral therapy and hematopoietic growth factors were also allowed.

An investigator-initiated IND was submitted in November of 1994 and exempted by the FDA since Taxol was commercially available and no new toxicities were expected at this dosage. KS evaluations were planned every two cycles. Evaluation of patients with visceral KS was planned with endoscopy and radiographic evaluation at baseline and at the time of maximal response.

Detailed disease evaluations were performed prior to every other cycle and recorded on standardized forms. In addition, photographic documentation of the indicator lesions and selected areas of disease, such as facial KS, tumor-associated edema, and tumor ulceration, were performed as indicated.

Overall 56 patients were accrued, 2 were women. 13 patients were accrued in Boston and 43 in Los Angeles. 16 of the patients were Hispanic and 6 were black.

Karnofsky performance status was available in 43 patients. Several patients had missing data. However, 46 percent of all patients had a KPS of 70 or less.

Patients had far advanced AIDS, with a median CD4 count of 20 cells per cubic millimeter. 39 of the 56 patients had a CD4 count below 50.

Similarly patients accrued in this study had widespread disease. 39 patients had tumor-associated edema, and 32 had oral KS. 24 of all patients had visceral disease. 1 of the patients had both pulmonary and GI disease. In general, overall KS was seen in 29 percent of patients in the lungs and 16 percent in the GI tract. Only 9 patients of this study had KS limited to the skin.

Application of TIS staging criteria were applied to all patients, and all patients had one or more

indicators of poor risk disease. In fact, 68 percent of all patients had three poor risk categories. 91 percent of patients had advanced tumor defined by either tumor-associated edema or extensive oral or visceral disease. 88 percent of the patients had a CD4 count less than 200, and 86 percent of all patients had B symptoms, KPS less than 70, a history of opportunistic infections.

The majority of the patients were heavily pretreated. 40 patients had received systemic therapy prior to study entry. 36 had received chemotherapy, of which 33 had received anthracycline. Notably 18 patients had received liposomal anthracyclines as well. Of the 40 patients with prior systemic therapy, 16 had received 1 prior regimen, whereas 24 patients had received between 2 and 6 prior regimens.

Looking at Taxol therapy in all study patients, the median number of courses given was 10, with a range of 1 to 35. The median dose intensity in this study was 39 milligrams per meter squared per week. This analysis took into account all treatment delays and dose modifications. At the time of this analysis, 19 patients were still on therapy 7 to 17 months after study entry.

The majority of the patients also received specific antiretroviral therapy. 37 patients received one

or more nucleoside analogs, and 20 patients received a protease inhibitor. Only 3 patients received protease inhibitors prior to the documentation of response. The majority of the patients were not started on protease inhibitors until after 11 courses of therapy.

G-CSF was given to 77 percent of the patients. 28 patients received G-CSF from the start of study due to neutropenia at baseline. 15 patients were started on G-CSF sometime during the study. 13 patients never received G-CSF during this trial.

The overall response rate in this study population of advanced KS applying the ACTG criteria was 59 percent, with complete remission in 1 patient and partial in 32. Notably 9 of 18 patients -- that's 50 percent -- who had previously been treated with liposomal anthracyclines, also showed response. These response rates represent the independent assessment by Dr. Susan Krown.

Responses in this patient population were durable, with a median of 10.4 months, ranging from 2.8 to 18 months.

Efficacy was also assessed by disease site. Decrease or resolution of KS at various sites was based on case records and serial photographs when necessary. Taxol had a significant impact on reduction or resolution of KS

lesions in most locations. Even for patients with pulmonary KS, 7 of 16 patients showed improvement either by radiographic findings or by pulmonary symptoms. I'd like to show some examples of responses in this trial.

The first example is of a patient with facial KS who showed marked and durable response. The second picture is cycle 11 several months later.

A female patient with extensive oral KS at baseline and difficulty eating. The oral KS resolved completely and the response persisted over a year. There is some residual pigmentation at the disease site.

This patient had confluent and ulcerated KS on the lower extremity associated with pain. This disease developed after previous failure to ABV and DaunoXome. After 1 month of therapy, the ulcer had healed with improvement of the area of KS confluency.

This patient had previously been treated with liposomal daunorubicin, ABV, and etoposide. He had extensive lower extremity edema and KS of the feet. He responded to Taxol with near complete resolution of KS and improvement of edema.

This patient with a history of prior cytotoxic chemotherapy developed progressive, symptomatic pulmonary KS. The baseline CT scan in November 1995, compared to

repeat study 3 months later, showed marked response. A bronchoscopy and biopsy in May 1996 showed no evidence of pulmonary disease. The patient remains alive and on study.

Looking at time to progression, time to first treatment failure was also assessed applying the ACTG criteria for disease progression. The median time to progression for the whole patient population was 6.9 months. In this analysis, 17 patients were censored for the following reasons. 9 had not yet progressed. 4 received secondary therapy without prior assessment of progression, and 4 patients were lost to follow-up.

At the time of this analysis, 33 patients were still alive and the median survival in this poorest population was estimated at 13.7 months.

Patients in this study were also asked to complete the Heidelberg quality of life questionnaire. I should note that only a few of the questions directly address the symptoms related to KS. This graph represents the median change from baseline in the global score. For the patients who completed the questionnaire, these changes suggest an improvement in quality of life.

Overall Taxol therapy was well tolerated in these severely immune suppressed patients. Neutropenia of grade 4 severity was observed in only 35 percent of the

patients. Furthermore, only 9 percent of the patients, or 1 percent of the courses, were associated with neutropenic fever. Opportunistic infections were observed in 31 patients and the rate was 12.8 per 100 patient-months.

None of the patients experienced severe hypersensitivity reaction. Grade 1 and 2 neuropathy was reported in 46 percent of the cases and grade 3 in 1 case. Neuropathy may in part be secondary to underlying HIV infection, prior use of vinca alkaloids, and concomitant use of neurotoxic agents such as ddI, ddC, or d4d. 16 percent of the patients experienced severe arthralgia or myalgia at some time during the trial. Alopecia was common.

11 patients showed disease progression. Another 11 patients died during the trial, 2 of them as a result of Taxol-induced neutropenic sepsis. 5 patients discontinued Taxol therapy due to adverse events, 2 for prolonged myelosuppression, 2 for alopecia, and 1 for malaise.

In summary, patients in this study had extensive symptomatic and progressive KS. All patients had poor risk disease, and the majority had previously received systemic therapy. Taxol achieved an overall response rate of 59 percent with a median duration of 10.4 months.

Therapy was well tolerated with a median of 10 Taxol courses given.

On a personal note, Dr. Scadden and I, after having treated several hundred patients, find that Taxol is one of the safest drugs in treatment of Kaposi's sarcoma at this dosage and schedule. Furthermore, it's one of the most active agents in patients who have failed prior therapy that is used commonly in patients with advanced disease.

Dr. Benjamin Winograd will now present the integrated summary of both trials. Thank you.

DR. WINOGRAD: Chairman, ladies and gentlemen, I would like to summarize the efficacy and safety of Taxol in AIDS-related Kaposi's sarcoma and compare the safety data in KS patients with what is known in patients with ovarian and breast cancer. I will summarize all data from these phase II studies for the three patient populations, considering all 85 patients. 59 of these had previously received systemic therapy, and 38 among those had previously received an anthracycline.

The great majority of patients had become resistant or were intolerant to their prior therapy, specifically 50 out of the 59 who had received systemic therapy, and 34 out of the 38 who had received

anthracycline containing therapy. Note that the majority had become resistant, 43 and 29 patients, respectively.

The overall response rate, as assessed by independent reviewers and using the ACTG criteria in these three cohorts, was 62 percent considering all patients, 63 percent considering the patients with prior systemic therapy, and 53 percent for those who had previously received anthracyclines.

The median duration of response, using the WHO criteria, was quite similar, between 8.2 and 10.4 months.

Similar efficacy results were seen in the subset of patients resistant to prior therapy or resistant to prior anthracyclines with response rates in excess of 50 percent and prolonged response duration.

Time to progression, as analyzed for all patients, was quite similar in the respective patient populations of all of previously treated patients, with 5.6 to 6.5 months.

Also survival was analyzed for the three populations. It should be noted here that this data is quite mature with a median follow-up for survivors of 11.8 months. Median survival was similar and exceeded 1 year in all three populations.

Our retrospective analysis of patient benefit

was possible because of detailed, well-documented, and prospective data collection in both studies. This included more than 12,000 pictures for documentation. We evaluated the improvement and duration of improvement of symptoms and parameters which are typical for Kaposi's sarcoma and affect quality of life.

A total of 57 patients presented with KS-related edema of the legs, face, or scrotum. The status of edema was recorded prospectively in the patient charts. Based on these records in total, 83 percent of patients had an improvement of their edema, including complete resolution in 44 percent of the patients. This benefit was seen in all patient populations and was durable.

In this picture -- and the patient agreed to show these photos -- you see a patient whose KS facial edema interfered with his vision. Two weeks later you see partial resolution occurred, and this benefit is maintained as of today.

KS lesions on the feet were documented on baseline by photographs in a total of 19 patients. Serial photographs were reviewed and compared to any additional case notes. A decrease in disease on study was assessed for 84 percent of all patients.

This patient had previously received three

regimens of chemotherapy. The baseline photo shows widespread lesions on his right foot. A marked improvement occurred within 5 weeks.

Facial KS lesions were documented at baseline in a total of 34 patients. Sequential evaluations of marker lesions as raised or flat and photographers were available. Based on these evaluations, 65 percent of all patients improved. This improvement was maintained for a median of 13.1 to 14.1 months.

This female patient -- and again the patient agreed to show these photos -- had multiple lesions which continued to be cleared about 1 year later.

There were overall 26 patients who started Taxol protocol with a Karnofsky performance status of 70 or less. 17 patients, or 65 percent, had an improvement of at least 10 points on study, and this improvement lasted for a median of 4.6 months.

A total of 31 patients had pain related to KS at baseline. For 7 patients, an improvement of at least 1 CTC grade was documented in the case notes. For many other patients, the documentation was not comprehensive.

A total of 21 patients had biopsy-proven pulmonary KS at baseline which often was symptomatic. Of these, 57 percent had an improvement on study. For 1

patient, disease resolved completely, and for the other 11, or 52 percent, a decrease in disease volume was documented radiologically. The duration of improvement lasted for a median of 7.4 months for all three populations.

This is a response in the anthracycline pretreated patients after 2 months of Taxol therapy.

My last few slides will deal with safety. We are going to compare safety in this population to our vast database, and particularly to data that the agency has previously reviewed at the time of our submission for second-line ovarian and breast cancer.

We will use safety for Taxol at the presently recommended dose of 175 milligrams per square meter as one comparison. 181 patients had received a median of 6 treatment courses.

The other comparison stems from a patient population who received Taxol at lower than the recommended dosage and a dose intensity similar to what the KS population had received. This population received a median of 5 treatment courses.

Due to the similarity in planned and actual delivered dose intensity for Taxol in the two KS studies, we have pooled the safety data for this comparison.

Myelosuppression in this severely

immunosuppressed population was more severe than in patients with solid tumors. The incidence of grade 4 neutropenia was higher and febrile neutropenia occurred in 25 percent of patients and 5 percent of courses. This increase of myelosuppression has to be judged in view of the underlying HIV disease, the high number of cumulative treatment courses, and in view of prior and concomitant myelosuppressive medications.

Despite the increased number of courses for patients with KS, the incidence and severity of typical nonhematologic Taxol toxicities was similar.

In summary, Taxol achieved higher response rates of 59 percent and 69 percent verified by independent reviewers in two trials in patients with advanced Kaposi's sarcoma.

Taxol induced lasting improvement of parameters associated with patients' function and quality of life: edema, foot or facial KS, low Karnofsky performance status, pain and pulmonary KS.

The high efficacy of Taxol was observed in patients who received prior systemic therapy prior anthracyclines or who were resistant or intolerant to prior therapy.

Prolonged therapy with Taxol was tolerated in

these immunosuppressed, heavily pretreated patients with advanced stage Kaposi's sarcoma.

The safety profile was comparable to that of patients with previously treated carcinomas of the ovary and of the breast.

In view of the large existing safety database, a dosage of 135 milligrams per square meter every 3 weeks can be recommended.

In conclusion, the efficacy and safety of Taxol previously documented in cancer patients who had received or failed on prior therapy, including anthracyclines, are confirmed in patients with AIDS-related Kaposi's sarcoma. Therefore, we propose Taxol is recommended for the secondary treatment of patients with AIDS-related Kaposi's sarcoma.

Thank you and I'm happy to address any questions.

DR. DUTCHER: Are there questions from members of the committee for the company?

DR. ABRAMS: We're focusing on secondary treatment, and I noted that in Dr. Gill's study it was planned to have 25 patients without prior therapy and 25 with. It appears that 40 patients had prior therapy I guess and 16 didn't. Is there any information on response

rates in the 16 patients who were receiving Taxol as their first-line therapy?

DR. WINOGRAD: Basically what you have seen is that the response rate stays in the order between 50 and 60 percent no matter whether you analyze all patients, you go down to those who have received systemic therapy, those who have received anthracycline or were resistant. So, I don't have the exact number right now. Somebody is going to look it up. However, it is going to be between the 50 and 60 percent.

DR. ABRAMS: Is there a reason why 25 patients were not accrued who are naive to therapy?

DR. GILL: It was simply because the patients coming in had previously failed other therapies and tended to accrue more patients into previously treated categories. So, we had planned that way but the outcome is different than what we had planned.

DR. KROOK: One of the things that this morning we commented on, since we're dealing with AIDS, was that the people who had complete responses to second-line therapy had had a prior response to a prior therapy. The point was made, and I was just curious what the response to the prior therapy was. Was it similar?

DR. WINOGRAD: Yes. When we collected the

data, we looked at what was available as far as best response to previous therapy as well as why did the patient come off therapy. Information on best response to prior therapy was submitted in the original study reports and we could cite you those numbers from there. Is it that number that you want to see?

Marion, could you please cite the best response to prior therapy for the 281 study?

Again, we are looking at all the treatment regimens that those patients have received. So, I think in study 281 there were a total of 92 treatment regimens received, so the numbers you hear refer to 92 regimens because we looked for each regimen separately.

Best response to prior systemic therapy. 55 percent of the 92 regimens had a response.

However, if you look in our analysis of resistant or intolerant, a patient that had as best response a progression or progressed after at least 3 courses was considered resistant. So, this is an analysis where each patient was only considered once.

DR. KROOK: As I recall in the document that I reviewed, there was a difference between intolerant, which means I don't want anymore -- there was toxicity -- and then resistant. There were probably some people who were

intolerant who said I no longer want to take this. I rarely in non-AIDS have people refuse therapy for alopecia, and here it's a different population.

DR. WINOGRAD: Yes, but you have to look at the intolerant in the patient population I guess. The majority of patients in fact, as I showed, were resistant to prior therapy and a small number also were only intolerant.

DR. KROOK: My second question you might have answered is that as the two studies went on, there were patients who received G-CSF. Was there a different response rate as the doses were escalated? In some people G-CSF was added and the dose was escalated, if I remember right.

DR. WINOGRAD: Yes. The design of the two studies was a little bit different in that in the NCI study every patient started without G-CSF and the aim was to give the highest possible dose. So, if patients tolerated, patients were escalated without G-CSF.

In the study at USC in Boston, the dose was always kept at 100 milligrams per square meter. The patient could or could not have G-CSF up front.

The response that is analyzed in both studies is for that first segment. Then there was a second segment only in the NCI study where a patient after initial dose

reduction and progression could go on to receive Taxol plus G-CSF and come back with the originally planned dose. But the efficacy analysis, as we showed today and as it's reported in the reports, refers to the first segment of the study.

DR. KROOK: Did you see responses when the G-CSF was added back?

DR. WINOGRAD: It's best for Dr. Yarchoan to address.

DR. YARCHOAN: We had I think about 8 patients where they in general had responses but then, because of neutropenia, we had to lower the dose of Taxol, and we then introduced G-CSF. As I recall, 2 of them then went and had a subsequent response. We reset the baseline when they restarted on G-CSF. So, we did have those people who were responding a second time, but no new responses were introduced as a result of the G-CSF addition, as I recall.

DR. DUTCHER: Dr. Schilsky?

DR. SCHILSKY: I have a couple of questions.

Can someone just summarize for us what the Taxol premeds that were used for these studies were?

DR. WINOGRAD: The Taxol premed was pretty much the three-drug combination as is used in solid tumors. However, there was the intent to use less dexamethasone.

Specifically I believe in the NCI study, the dose was 10 milligrams of oral dexamethasone. In the USC and Boston study, they tended to reduce the dose of dexamethasone as they went from course to course and saw that the patient didn't have a significant hypersensitivity reaction with the reduced dose of dexamethasone.

DR. SCHILSKY: Is there any data on dexamethasone activity in KS?

DR. GILL: There's actually published data that the use of steroids, glucocorticoids, enhance tumor growth and withdrawal leads to tumor progression, and the mechanisms of that have been also studied.

DR. SCHILSKY: Another question relates to what happened to the CD4 counts in the patients during the time that they were receiving Taxol?

DR. WINOGRAD: Could we go to section L and you could flip just through patient by patient and give a few examples of CD4 counts over time?

DR. CANETTA: As we found the results, we can give you the answer to the question of efficacy in previously untreated patients. The response was 11 out of 16, or 69 percent.

DR. WINOGRAD: This first slide shows you a patient that started roughly with a CD4 count of 4,

achieved a partial response, and continued with a low CD4 count.

Next, this is a patient that starts with a CD4 count of 45 to 60 and goes down, achieves a partial response here.

Next, a patient that starts with a CD4 count of 14, and I'm just going patient by patient for the NCI study.

Go to the next patient please. A CD4 count of 15, partial response, and this is the continuous CD4 counts.

CD4 count of 0 and stayed 0.

CD4 count of 100, 75. The patient achieves a partial response, has a reduction in CD4 count.

CD4 count of 10, partial response.

Baseline CD4 count of 50.

DR. SCHILSKY: I think I've seen enough. Thank you.

(Laughter.)

DR. SCHILSKY: I have one other question if I might, and that is do you have any data on the percent of patients who actually received the intended dose intensity in the studies? Because in both studies, the delivered dose intensity was just under 40 milligrams per meter

squared per week. Although when you look at the range of the delivered dose intensity in both studies, the range extended above 45 to 50 milligram per meter squared. So, I'm curious to know about what percent of patients actually got the intended dose intensity.

DR. WINOGRAD: Okay. The fact why patients could have a higher than intended dose intensity comes from the NCI study where a patient, as I said, could be escalated.

Could I please have slide E29? That will give you the dose intensity and the proportion of patients versus the intended dose intensity. This shows you relative dose intensity, more than 80 percent of planned dose or less than 80 percent of planned dose. If you look in the total population, roughly half of the patients received more than 80 percent of planned dose intensity and the other half of patients received less than 80 percent of the planned dose intensity. Is that what you were asking for?

DR. SCHILSKY: That will be fine. Thanks.

DR. WINOGRAD: Okay. And if you go over to the subpopulation of the prior systemic or prior anthracycline, it's roughly the same.

DR. DUTCHER: Dr. Swain?

DR. SWAIN: Could you comment on your choice of a recommended dose of 135 every 3 weeks since you seem to have less toxicity on the 100 every 2 weeks?

DR. WINOGRAD: Why the choice?

DR. SWAIN: Yes.

DR. WINOGRAD: It's basically what I had in the summary slide. We feel that our vast safety experience for the drug comes from a dose given every 3 weeks. The experience with the lower dose every 2 weeks is from this one study and the database is growing. As you have seen, the two studies that ECOG is planning or the one that has just started both use the lower dose every 2 weeks.

We feel that at the present time with the large safety database that we have overall for the drug, we feel more comfortable recommending that dose. That doesn't exclude that at the point that, for instance, the data on the randomized study is available. That could be switched.

DR. SWAIN: Because the febrile neutropenia level was very high for the KS patients in the first study.

DR. WINOGRAD: Yes, but again remember that the design of the study is not entirely similar. A, in the USC study the patient who seemed to need G-CSF up front got G-CSF up front. The patient in the NCI study, on the other hand, was sort of dosed to reach toxicity, then got the

dose reduced, and only at the point of progression or if there was another reason, G-CSF was only added at that point. So, this design asked for a higher incidence of neutropenia and neutropenic fever. Again, the reason is the experience with the drug at the present dose schedule.

DR. SWAIN: I had one other question. Do you have any idea what the effect of protease inhibitors would be on the duration of response?

DR. WINOGRAD: On the duration of response, that is obviously difficult to address. What we have is we have analyzed at what point the patients start on protease inhibitors. Again, both of the studies started at an area that the protease inhibitors were not available.

Could I have, please, slide section D and slide 17?

This analyzes the use and the start of protease inhibitors for study 281. In fact, in that study 20 patients received protease inhibitors during any time of study. The other two patients in the whole population Dr. Yarchoan described when he described his study presentation. 20 patients received protease inhibitors at any time. The onset of protease inhibitors was a median at course 11, and the start ranged between course 1 or course 22 that the protease inhibitor was started.

18 of the 20 patients were responders according to the ACTG criteria. 3 of the 18 got the protease inhibitor prior to the assessment of a response. 15 received the protease inhibitor after the assessment of a response. In fact, 5 of those 15 received a protease inhibitor only at the point they had already progressed, using the ACTG criteria. So, I think the time period that these studies were done, if the patient received a protease inhibitor, they received them relatively late.

The question as to what is the impact on duration I can't really exactly answer.

DR. ABRAMS: Also relevant, I note that the P450 isoenzyme CYP2C8 and CYP3A4 are involved in the metabolism. Have there been any studies done or have you checked on any of the levels of the protease inhibitors?

DR. WINOGRAD: Yes. What we have analyzed in the present population for the 22 patients who got protease inhibitors to see whether it interferes with metabolism of Taxol, the first thing that you would see most likely is an increase in the dose-limiting hematologic toxicity. In our analysis, there were similar rates of myelosuppression whether a patient received or a patient didn't receive protease inhibitors.

As was mentioned in the introduction by Dr.

Canetta, ECOG is presently conducting a prospective study where patients receive constant protease inhibitors and Taxol. There are four different strata for 6 patients each to assess plasma levels of Taxol and of the protease inhibitors and prospectively study that. So, this is ongoing.

DR. ABRAMS: I guess the surrogate endpoint of that would have been if you saw any changes in HIV viral load in patients in this study that would have suggested that maybe you were losing the impact of the protease inhibitor activity.

DR. WINOGRAD: Is there anything you could say to that point, Dr. Gill?

DR. GILL: No.

MR. MARCO: Also, don't you think that most of these patients started with saquinovir? And they were probably doing saquinovir monotherapy. This was a few years ago when we didn't know how to use these drugs. So, they were having inadequate antiretroviral therapy.

DR. DUTCHER: Do you have a question?

MR. MARCO: I do. I have two questions.

My first was about the pulmonary KS. The response rates seemed impressive, especially for the 5 of 5 patients from the NCI study. Do you know, in the

literature, other response rates for pulmonary KS or at least for, say, Doxil or DaunoXome?

DR. WINOGRAD: Dr. Gill, do you want to comment on that?

DR. GILL: Yes. The literature goes back 10, 15 years. So, you have to consider all the changes in therapy. But the response rate with combination chemotherapy in pulmonary KS is quite high, in the range of 50-60 percent.

There is a recent study of DaunoXome in pulmonary KS alone at a higher dose of 60 milligram per meter squared. That is first line in patients who have not previously been treated with chemo. The response rate is around 50 percent.

MR. MARCO: What about the survival? I think it's 7.4 months in this, in the combined studies. Do you know what the survival was?

DR. GILL: Yes. Survival in patients with pulmonary KS who have no treatment is about 2 months. Those who have treatment, first line is around 7 to 8 months. Patients who have pleural effusion along with pulmonary KS and have chemotherapy have a dismal outcome of about 2 and a half months. So, in general, the outcome is very poor, far below 7 months, and that is first-line

treatment.

DR. WINOGRAD: You mentioned the survival. I didn't show the survival for patients with visceral disease, but as you mentioned it, the survival in the pooled analysis in the patients in this study is 13.7 months for the 31 patients with visceral disease. So, it's pretty much the same as the overall population.

MR. MARCO: Also my last question was about access to therapies because basically I think 50 of the prior systemic therapy patients were resistant or intolerant. Did they have any other treatment options? Do you know if the anthracyclines were available to them at that time?

DR. WINOGRAD: Well, 19 of the patients who went into these two studies had already received one of the two liposomal anthracyclines and were resistant to the respective liposomal anthracycline. So, 19 patients --

MR. MARCO: Right. Weren't those from Dr. Gill and Dr. Scadden mostly because they were already on the studies, but were the drugs approved? Were there any other treatment options for these patients? That was my question.

DR. WINOGRAD: At the time that these studies were conducted?

MR. MARCO: Exactly.

DR. WINOGRAD: I think that's better for the investigators to address.

DR. GILL: No. DaunoXome wasn't approved and I think Doxil was approved very late, actually not during the NCI trial but during the second trial, the later part of the second trial. So, those drugs actually were not available. So, the reason we had several patients on who had previously been treated with liposome therapy were because they were on those trials at the time.

DR. DUTCHER: Dr. Schilsky?

DR. SCHILSKY: I'd like to come back to the question of the dosing for a moment because I guess I'm a little concerned about the proposed dose. You have two studies and the proposed dose is from the study that has half the number of patients that the other study has. So, you're proposing the dose from the study with the more limited clinical experience.

Although I recognize that you've got this large database at that dose level, when you look at, for example, the febrile neutropenia that occurs, when you lump it all together, you're integrated analysis showed that you had febrile neutropenia in 25 percent of the KS patients compared with only 3 percent of the patients at that dose

level of 135 with solid tumors.

However, when you look at the USC results, there's febrile neutropenia in only 9 percent of patients which in my mind compares more favorably with the solid tumor results than when you lump everything together.

So, I'm wondering again about the selection of the dose and why you would choose the dose that comes from the more limited clinical experience in this patient population and appears to be associated with a higher degree of febrile neutropenia.

DR. WINOGRAD: Again, you have said what is the reason that we are proposing at present that dosage and regimen, and that is based on the large experience in solid tumor and the similarity of the nonhematologic toxicities in those. Again, the experience in the every 2 weeks 100 milligrams per square meter is 56 patients at that point, and that's why we feel maybe less comfortable.

Again, I would really like that you remember the differences in design in that those patients who seemed to have myelosuppression up front got G-CSF immediately in the USC study, and in the NCI study, they were treated and dosed according to myelosuppression and tolerability. And in the major part, only at the point they progressed and had gone down with a dose well below the 135, then they got

G-CSF and started at 135 per meter squared again.

I see your point and obviously we had this discussion internally. If you want, we could run through some of the safety comparisons more than what you had seen maybe. If you want, we can do that. We have examples.

DR. SCHILSKY: Let me just ask you what is your proposal with respect to how G-CSF should be used if this application would be approved?

DR. WINOGRAD: That's a very good question and obviously this would build in on the experience between the two studies and the experience of a relatively high incidence of neutropenic fever if you give G-CSF late. I think our policy would be to suggest supportive therapy should be given as needed and that would include G-CSF. So, the recommendation would be probably -- the proposition would be to use G-CSF more liberal than what you maybe originally did in your study.

DR. YARCHOAN: Just maybe one clarification that may be useful. We initially elected not to use G-CSF largely because we didn't know whether Taxol was going to work and we didn't want to push a drug that we didn't know was working with bone marrow support.

The other thing, just as background, is that what is called febrile neutropenia here really means a

patient who's neutropenic and had a fever. A lot of these patients have almost no CD4 cells, and a lot of time the fever is due to cytomegalovirus disease or something else. So, it's a little bit confusing in terms of sorting those things out.

DR. WINOGRAD: But obviously we are not hooked to that dosage and regimen. This is our proposal.

DR. DUTCHER: Dr. Williams?

DR. WILLIAMS: I'd like to ask why you think you can give this to low performance status patients, on the basis of what data, or why you think it's okay to give it to low performance status patients because all the patients that received the higher dose were high performance status patients.

DR. WINOGRAD: I'm not sure I followed exactly.

DR. WILLIAMS: Well, the NCI trial was in patients with good performance status. The other trial was low performance status, but despite that fact, there's more toxicity in the good performance status patients with the 135 dose. So, what's going to be the toxicity in low performance status patients? Do you have any data or is it just going to be --

DR. WINOGRAD: Again, I think this is something for the -- we don't have more data, if you just look at the

performance status, in the regimen that we are proposing. However, part of the Karnofsky performance status is also driven by the underlying disease rather than what you are used to from solid tumor patients where Karnofsky -- like if a patient has swollen feet and can't walk, this immediately impacts on your low Karnofsky performance status. Is that a fair interpretation of the low Karnofsky performance status?

DR. CANETTA: (Inaudible.)

DR. WILLIAMS: So, you're saying you don't think performance status in AIDS Kaposi's -- that it's not related to your tendency to myelosuppression. Is that what the literature --

DR. WINOGRAD: I don't think that we can say it as hard as that, but as Dr. Canetta said, there's no difference in nonhematologic toxicity between the patients with low performance status and high performance status, i.e., between the two different studies.

DR. DUTCHER: Dr. Krook.

DR. KROOK: I was going to comment on Grant's question. A 10 percent difference on a Karnofsky scale, one study took down to 60 and the other to 70. That's not quite the same as a level on the other scales. If I read my notes right, there were 46 percent of that second study

that were between 60 and 70. So, I don't think there's a big difference between the two. That really becomes subjective whether they're 60 or 70 in my mind.

DR. DUTCHER: We need to take a 10-minute break -- thank you very much. I think we're going to finish this discussion at the end of the meeting -- to allow the FDA to set up and we've got a couple of people who need to try to catch airplanes. So, we're going to try to move along quickly. So, we'll take a break now, but please be back here in 10 minutes.

(Recess.)

DR. DUTCHER: Okay. We're going to move on now with the FDA presentation. Dr. Chico is the reviewer and Dr. Williams is the team leader. Dr. Chico.

DR. CHICO: Good afternoon. Dr. Dutcher, Dr. Abrams, members of the advisory committee, Drs. Justice and DeLap, my colleagues at the FDA, ladies and gentlemen, today I'm presenting the FDA review of clinical studies on the two pivotal trials for the efficacy supplement 20-262 on Taxol.

Before I proceed, I'd like to acknowledge the members of the FDA review team: Dr. Grant Williams, our medical team leader; Drs. Clare Gnecco and George Chi from biostatistics; Drs. Mishina and Rahman from

Biopharmacology; Drs. Brower and Paul Andrews from Pharmacology; Drs. Jee and Wood from Chemistry; Dr. Turner from DSI; and our project manager, Dianne Spillman and Dotti Pease, team leader.

This application seeks approval to market Taxol in the United States for the second-line systemic chemotherapy of patients with AIDS-related Kaposi's sarcoma.

The proposed dosing schedule is 135 milligrams per meter squared given as a 3-hour infusion every 3 weeks.

The primary endpoint of the studies in this application is objective tumor response. Additional clinical benefit is being sought from the retrospectively collected data on six domains of clinical benefit. This in addition to cutaneous tumor response is being presented to obtain full approval of Taxol for this indication.

Between September 1993 and January 1995, the first study was undertaken in order to assess the efficacy of Taxol in AIDS-related KS. This study was performed at the NCI, National Institutes of Health, in Bethesda, Maryland, and designated as BMS139-174.

Between February 1995 and December 1995, the second study was initiated in order to confirm the findings of the first study. This trial was conducted at two study

sites, the Kenneth Norris Cancer Hospital and County Hospital in Los Angeles, California, and at the New England Deaconess Hospital and Massachusetts General Hospital in Boston, Massachusetts. This study was designated as BMS139-281.

Both are open label phase II studies with tumor response as the primary efficacy endpoint. The secondary efficacy endpoints for study 174 were not defined in the protocol, while for study 281 they were defined as time to tumor response, duration of response, and survival.

Two different dosing regimens were utilized. For study 174, patients received 135 milligrams per meter squared as a 3-hour infusion every 3 weeks, while patients from study 281 received 100 milligrams per meter squared as a 3-hour infusion every 2 weeks.

A total of 85 patients were enrolled in both studies. However, there were only 59 patients who were previously treated, 40 from study 281 and 19 from study 174. The emphasis of the efficacy review will be on these 59 previously treated patients.

The applicant met with the agency on October 9, 1996 to discuss a proposal to submit an efficacy supplement under the accelerated approval mechanism in the treatment of patients with AIDS-related KS. The data will be based

on the two phase II studies.

Full approval was thought possible if, in addition to tumor response, evidence of clinical benefit such as amelioration of tumor-associated symptoms or prolongation of response or survival was shown.

During the meeting, the following additional concerns were expressed: first, that the difference in dosing regimens between the two studies may pose difficulties in interpreting data, as well as providing dosing guidelines for labeling.

Secondly, with 85 patients enrolled in the phase II studies, the FDA review may show that the claimed responders may be less.

Thirdly, the sponsor was also advised by Biopharmaceutics to capture pharmacokinetic data in patients with KS, especially data related to concomitant medications which may interact with Taxol.

This supplemental NDA was submitted on February 4 of 1997.

Except for a difference in performance status, the patient demographics were similar in both studies, showing that patients enrolled were those with KS at poor risk for survival as defined by ACTG or features of advanced AIDS. Among the 85 patients enrolled, 59, or 69

percent, received prior systemic chemotherapy. 38, or 64 percent, of the patients who had previously received chemotherapy had received at least one anthracycline containing regimen.

The cutaneous response analysis focused on all the patients who responded to Taxol regardless of prior treatment history, and this was accomplished by reviewing and making queries from the electronic data listings, looking at case report forms, reviewing patient case summaries and photographs. For my presentation, I will just be using photographs of patients who were previously treated.

A comparison of the sponsor's and the FDA response analyses was done. The list of patients with differences in the determination of cutaneous tumor response was transmitted to the sponsor who agreed that 1 of the 3 patients with differences in their response analyses may not be considered as a true response according to ACTG criteria. However, the final FDA position is to exclude 2 patients from the list of responders.

Patient 1 from study 281 had less than 50 lesions at baseline, and the response assessment was based on lesions from certain target areas and not on all the lesions. There was concurrence between the FDA and the

applicant that this patient does not qualify as a response.

Patient 12 from study 281 was noted to have new edema and a new lesion on the foot 1 week after being declared a partial response. The sponsors reviewed the source documents and determined that the edema was temporary and may have been due to other therapies. The single new lesion on the foot was outside the target area for response assessment. There was concurrence between the FDA and the applicant that this patient should be retained as a response.

Patient 24 from study 174 was noted to have lesions on the scalp and right toe on the day of being declared a partial response. 2 weeks later he had new lesions on his chest. Since the patient had more than 50 lesions, only the right and left arms were being monitored as target sites. The appearance of several lesions in several areas of the body within a short period of time speaks against chance occurrence and cannot be overlooked despite being outside the target areas. We believe that this patient should not be considered as a response.

The following table summarizes the final position of the FDA regarding response rates in the two studies on both patient groups. Two patients were eliminated from the original 37 patients who responded to

treatment. As a result, the new response rate is 35 out of 59, or 59 percent. The 2 patients who were eliminated both had prior systemic chemotherapy, therefore affecting only the responders in this group.

Among the group of 35, there were 2 patients from study 174 who had a complete response to treatment. A majority of the partial responses, however, were due to flattening of more than 50 percent of previously raised lesions.

The Kaposi's sarcoma symptom complex analysis was performed by the applicant in response to the advice by the agency during the pre-NDA meeting that there should be evidence of efficacy or clinical benefit other than that from cutaneous tumor response. Except for Karnofsky performance status assessments in edema, data from each of the following dimensions were collected by the sponsor retrospectively: KS of the foot, face, lung, and KS-related pain.

Kaposi's sarcoma of the foot was documented by photographs at baseline for 19 patients, 8 patients in study 174 and 11 in study 281. The BMS medical team evaluated these photographs and described the lesions on the feet as either absent, stable, increased or decreased during the intervals that the photos were taken. Only 12

of the 19 patients received prior systemic chemotherapy. Photographs of all 19 patients with foot lesions were evaluated by the FDA done with the reviewer blinded to the sponsor's foot and cutaneous disease response assessments.

Among patients with prior chemotherapy, improvement in foot lesions were seen by the FDA reviewer in 7 patients and there was a difference in opinion between the sponsor and the FDA in 4 patients. 6 patients had both foot and cutaneous disease responses, and 3 patients had simultaneous remarkable improvement in the foot lesions and foot KS-related symptoms.

Patient 8 from study 174 is a 33-year-old white male who was previously treated with chemotherapy and had a biopsy-confirmed complete response to Taxol. He stopped taking morphine for foot pain. Notice that there was also a decrease in edema during treatment.

Patient 26 from study 281 with lesions on the plantar surface of the foot was able to stand up again.

This is the same patient showing a decrease in leg edema.

Patient 34 from study 281 stopped taking morphine for foot pain and there was resolution of infected KS lesions.

Similarly data on facial Kaposi's sarcoma were

collected retrospectively by examining photos of lesions on the face in 34 patients. Only 19 of these 34 patients, or 56 percent, had received prior systemic chemotherapy. The BMS reviewers described the lesions on the face as either absent, stable, increased, or decreased. The FDA reviewer evaluated the photographs independently and described the lesions as improved or not improved. Facial KS responses were correlated with overall cutaneous responses.

Photographs of the 19 previously treated patients with facial lesions were evaluated by the FDA with the reviewer blinded to the sponsor's facial and cutaneous disease response estimates. Among patients with prior chemotherapy, improvement in facial lesions was seen by the FDA reviewer in 10 patients, and there was a difference in opinion between the sponsor and the FDA in 7 patients. 10 patients had both facial and cutaneous disease responses.

Again, this is a 26-year-old gentleman who had received two prior systemic chemotherapies. He achieved partial response of cutaneous lesions at course 5 with improvement in pulmonary and facial disease according to the applicant. The facial lesions were noted to have decreased significantly from baseline. This patient's overall duration of response was 4.5 months.

This is a 36-year-old previously treated male

who received a total of 10 cycles of Taxol. This patient achieved a partial response of cutaneous disease but continued until he achieved a biopsy-negative complete response. The lesion on the tip of his nose was noted to have decreased significantly.

During the course of reviewing the patient's photographs, other facial changes were noticeable. Although these patients were assessed by the sponsor as having an improvement in the status of facial lesions, it is apparent that alopecia from treatment resulted in other changes. Although some lesions may have turned lighter in color, some have become more apparent from alopecia caused by the treatment itself.

The design of studies looking at Kaposi's sarcoma lesions of the face in the future should take into consideration the patient's evaluation of changes in facial lesions which reflect overall satisfaction, feelings regarding self-image, and functional changes.

Extremity and facial edema were noted at baseline and at regular intervals and described by the applicant as either absent, stable, increased, decreased, not assessed, or new in the case report forms. The investigators, however, did not provide additional information on objective findings such as change in limb

girth, skin integrity, or range of motion.

Only the available entries in the case report forms and photographs were used by the FDA reviewer to confirm the status of edema. Queries from the electronic data were generated to compare observations of the status of edema and cutaneous disease.

For patients with prior chemotherapy, there was a decrease in edema while on treatment with Taxol in 36 of the 59, or 61 percent, of patients. However, there is no strong correlation between cutaneous tumor response and objective improvements in edema.

Photographs were helpful to the reviewer in confirming change in the status of edema. However, subtle changes in edema were not apparent in the examination of the photos. 16 patients who had received prior chemotherapy showed changes in edema that were obvious from the photos, while in the other 20 patients, who were evaluated by the sponsor as having a decrease in edema, had changes that were not apparent to the reviewer or the photographs were not adequate to make an assessment.

This is a 42-year-old white gentlemen who had received 5 regimens of chemotherapy prior to treatment with Taxol. This patient did not meet the criteria for partial response due to the absence of a confirmatory evaluation

after 4 weeks. Lesions in the face and large confluent areas of the inner thighs were noted by the sponsor to have flattened. Edema of the scrotum and extremities decreased, and the patient was able to walk from being wheelchair bound.

As previously stated, patient photographs were helpful in confirming the applicant's assessment of edema. However, in some cases, changes may not be apparent from the photos. These are photographs taken 2 and a half months apart during treatment with Taxol in a patient who was assessed by the applicant to have a decrease in edema during treatment.

The extent of pulmonary disease was assessed by radiologic exams at baseline in at least once every 2 cycles in study 174. For study 281, chest x-ray was done at baseline and only those with abnormal results were repeated every 4 weeks. An external reviewer assessed Taxol efficacy separately for the pulmonary disease using the overall criteria of resolved, stable, increased, or decreased as compared to baseline. For the FDA review, queries were made on the electronic data to show all procedures done to document pulmonary disease and the sponsor's assessments. For patients with adequate documentation of pulmonary disease, individual patient

narratives and common sections of case report forms were reviewed. Confirmation of pulmonary KS response was done by reviewing radiology reports and bronchoscopy reports and by examining the radiographs.

Of the 29 patients in study 174, 5 patients were found by the applicant to have radiographic evidence of pulmonary KS at baseline. However, among these 5 patients, only 2 were previously treated with systemic chemotherapy, and according to the sponsor, both showed evidence of a decrease in lung KS.

On the other hand, there were 8 of 16 patients who received prior chemotherapy in study 281 who had a decrease in pulmonary tumor volume. The FDA review, however, only confirmed a decrease in pulmonary KS in 1 patient from study 174 and 2 patients from study 281.

Patient 2 from study 174 had a confirmed decrease in pulmonary disease for at least 2 courses. This patient had a partial response of cutaneous disease and the pulmonary lesion response lasted for 79 days.

Patient 20 from study 281 was still on active treatment as of final report. He had documentation of resolution of disease by bronchoscopy.

Patient 33 had evidence of decrease in pulmonary KS by chest x-ray and CT scan. However, the

radiology reports were not submitted.

FDA review of the follow-up chest x-rays showed that there was a decrease in bibasilar nodular infiltrates. The rest of the patients reviewed did not have adequate documentation to confirm baseline lung KS status or disease responses.

Performance status was collected prospectively at regular time intervals in both studies and the patients from each study presented with different patterns of performance status at baseline. All patients in study 174 presented with a Karnofsky performance status of 80 or better, and only patients with a performance status of 70 or less at baseline were considered by the sponsor in their analysis. Note that this patient group represents only 40 percent of the patients in study 281, with 30 percent of patients having no baseline assessment. During the whole duration of treatment, there were missing values in 50, or 89 percent, of the patients.

I will just briefly highlight some of the relevant safety issues for this particular group of patients, and that includes deaths within 30 days of treatment, hospitalizations, occurrence of infections, and the more common hematologic and nonhematologic toxicities.

Individual patient narratives and case report

forms were reviewed for patients who died within 30 days of treatment. 10 of 59 patients, or 17 percent, who previously received systemic chemotherapy died within 30 days. Generally these patients had multiple problems that include inherent immunosuppression, rapidly progressing Kaposi's sarcoma, possible adverse effects from polypharmacy, side effects from chemotherapy, undisclosed emotional and social issues, et cetera. During our analysis, it was difficult to determine whether death was a result of one particular cause or a combination of several different causes.

Data on the frequency of hospitalizations during treatment was collected from case report forms and the electronic data. In study 174, 21, or 72 percent, of the 29 patients enrolled were hospitalized at least once during the treatment with Taxol, while in study 281, 35 of the 56 patients, or 61 percent, were hospitalized at least once.

Of the 374 courses of treatment given in study 174, 76, or 20 percent, were associated with hospital admissions, while this was seen in 63 of the 605 courses, or 10 percent, for treatment in study 281.

The reasons for hospitalizations were mostly infections and febrile neutropenia. The most common

documented infections are PCP, pneumonia, sinusitis, CMV retinitis, and catheter related sepsis.

The study report by the applicant, however, mentions more episodes of opportunistic infections than that that was counted by the FDA. According to the applicant, there were 65 episodes of opportunistic infections in study 174 and 48 episodes in study 281. This probably includes infections that did not require hospitalization.

15 of the 139 or 11 percent of admissions to the hospital were due to febrile neutropenia. Note that despite a relatively higher performance status at baseline, there are more patient hospitalizations for febrile neutropenia and infections in patients in study 174. Hospitalizations for other reasons may be for diagnostic workup or management of certain symptoms that may or may not have been related to Taxol treatment.

The following table shows only grades 3 and 4 hematologic toxicities from treatment with Taxol. In general, despite higher baseline performance status, there are more grade 3 and 4 hematologic toxicities in the group of patients treated at the NCI in study 174. The whole population seems to reflect the grades 3 and 4 hematologic toxicities that were seen in the group of patients with

prior systemic chemotherapy. Severe neutropenia was experienced by 43, or 74 percent, of the patients, of which 30 patients had grade 4. Grades 3 and 4 thrombocytopenia and anemia was experienced by 10 and 33 percent of patients, respectively.

Most of the blood transfusions on study were red cell transfusions. In study 174, 17 patients, or 68 percent, were given 92 transfusions, while in study 281, 26 patients, or 46 percent, received 54 transfusions. More patients received blood transfusions in study 174 compared to patients in study 281. However, there seem to be more patients needing blood transfusions than those who actually experienced severe anemia. This may mean that not all data on severe anemia was captured or simply the fact that this group of patients have several reasons, other than myelosuppression from chemotherapy, to be transfused.

Overall incidence of common nonhematologic toxicities were comparable in the pretreated in the total patient groups. All grades of alopecia were experienced by 91 percent of patients. The other more common severe toxicity is asthenia, which is experienced by 26 percent of patients, followed by diarrhea, arthralgia and myalgia in 15 percent, and nausea and vomiting in 11 percent. Note that grades 3 and 4 renal toxicity was experienced by 5

patients, all of whom were previously treated.

In conclusion, the submitted phase II studies of Taxol in patients with previously treated Kaposi's sarcoma should be considered adequate and well-controlled studies of objective tumor response. The objective response of Taxol in this patient population may be a clear demonstration that antitumor activity with the comparator in this case being the known natural history that the tumors do not shrink without treatment.

The objective tumor response was well-documented in 59 percent of the patients, with a median duration of response of 9.1 months using the WHO definition which starts at the beginning of treatment rather than the first date of response.

Considering the limited treatment options available for patients who have received prior systemic chemotherapy for AIDS-related Kaposi's sarcoma, the 59 percent objective response rate in cutaneous tumors represents a notable level of antitumor activity. However, the population sample for this conclusion is small.

Patient benefit was evaluated retrospectively by assessing the six dimensions of clinical benefit. The criteria used by the sponsor to describe changes in foot, facial KS, and edema were not identified and there was a

large amount of missing data in the analyses of lung KS, KS-related pain, and Karnofsky performance status.

Since information was collected retrospectively in these studies, it is of concern that the assessments were not blinded and that the sample sizes for such parameters were small. The methodology likely underestimated the true incidence of symptoms at baseline in these patients. However, despite these flaws in design, there were notably similar trends in the cutaneous tumor responses versus improvements in facial and foot KS lesions.

There were also individual patients who may or may not have had cutaneous tumor response who had remarkable improvements in foot, facial KS, edema, and lung KS lesions.

In regard to the secondary endpoints, particularly time to progression and survival, the studies were not adequately controlled. The secondary efficacy endpoints were only defined prospectively for study 281. Randomized controlled trials would be necessary to adequately assess the effects of Taxol on these secondary endpoints.

The phase II studies provided sufficient information to assess the potential toxicities of Taxol in

patients with AIDS-related Kaposi's sarcoma. The sponsor presented a review of toxicities from Taxol in patients with AIDS KS compared to patients with other tumors treated with Taxol that showed a higher risk for more frequent and severe hematologic toxicities.

However, there seems to be a difference in the patterns and incidence of toxicity between the two studies where different regimens of Taxol were used. In study 174 where Taxol was given at the higher dose less frequently, there seemed to be more severe hematologic toxicities. Clinically there are more dose reductions, more use of cytokines, and more requirements for blood transfusions, and hospitalizations for infections and febrile neutropenia on study 174.

On the other hand, there are more treatment delays associated with study 281 where a lower dose of Taxol was given more frequently. Tumor response with Taxol in previously treated patients was 14 out of 19, or 73 percent, in study 174 and 21 out of 40, or 52 percent, in study 281.

The applicant proposes that the approved dose and schedule be that which was used in study 174, that is, 135 milligrams per meter squared every 3 weeks. Clearly a discussion of the optimal dose for this indication is

warranted.

Whether one recommends approval of this NDA supplement should depend primarily upon whether one considers the sample size represented by these trials as large enough to support approval for this indication and whether the evidence of patient benefit documented in photographs and recorded symptoms, imperfect as they may be, adequately support the objective data on response rates. One must then consider, in view of the documented toxicity of Taxol in this setting, whether the overall therapeutic ratio of Taxol therapy was acceptable in these trials and population of patients with previously treated Kaposi's sarcoma.

Thank you very much.

DR. DUTCHER: Thank you.

Are there questions for Dr. Chico? Dr. Gelber.

DR. GELBER: Yes. The response rates are rather impressive either from the sponsor or from your review.

DR. CHICO: The sponsor's review showed a response rate in previously treated patients of 63 percent. My review showed 59 percent.

DR. GELBER: So, both rather close.

DR. CHICO: Very close.

DR. GELBER: The question I have is, did you do an investigation of any changes at the beginning of the phase II studies in therapeutic approaches that might have explained some of the responders? Were other things being changed in the course of the treatment for these patients that might have contributed to some of the responses? Obviously not all of them, but some of them.

DR. CHICO: Could you please be more specific?

DR. GELBER: Yes. For example, were the same antiretroviral therapies, same therapies for OIs being used prior to enrollment in the phase II trials?

DR. CHICO: No. Study 174 was initiated earlier, and the patients enrolled in the study mostly were on AZT and ddI, while approximately 45 percent of the patients in study 281 were on the newer antiretrovirals.

DR. GELBER: And at the time the KS was evaluated at baseline and the patients were enrolled in this study, those therapies were maintained for all of the responders?

DR. CHICO: I didn't have data regarding when the antiretrovirals were started in these patients, so I wasn't able to determine that.

DR. GELBER: So, that kind of assessment wasn't done.

DR. CHICO: By me, no.

DR. ABRAMS: We heard that most of the patients who started protease inhibitors had already achieved a response prior to that.

DR. GELBER: Yes. I'm really not specifically concerned about the protease. I'm really concerned about the issue of the findings saying Taxol achieved X response. So, my question was Taxol was initiated. I'm convinced that there were responses related to the initiation of Taxol. The question was a response rate of 60 percent roughly. Is that response rate related to the initiation of Taxol, or in this very limited number of patients that we're looking at, were there some other changes in their therapy, at or around the time of initiating the phase II Taxol, that might have contributed to some kind of favorable response in some of the patients recorded as responders? Is it fair to attribute all of the response rate to Taxol? That's the question.

DR. CHICO: I think we have to look at especially patients who were treated on the newer antiretrovirals in study 281 more especially and look at when they responded and make a correlation. But I don't believe that I was able to look at that data.

MR. MARCO: But there's also really no data

that is conclusive that would say that a change in antiretroviral therapy that is really impressive is going to markedly change a response rate. So, even if you did show that, it's not like we have historical data.

DR. GELBER: Yes. If we're asked to look at 35 patients who responded, it would be nice to have a review that addresses the question in how many of those 35 patients was the treatment, prior to starting Taxol and immediately after starting Taxol, the same, and in how many of those 35 were there other changes in management. Then we could at least debate the issue.

MR. MARCO: No. I understand. I would love that too, but it's a problem when you have underlying disease.

DR. WILLIAMS: But the point is I don't think that any of the treatments that we know of we would expect to cause a response in Kaposi's other than perhaps the newer antiretrovirals. Isn't that correct?

DR. ABRAMS: Right, and there were no real other treatment advances during the time that these studies were conducted except for the introduction of protease inhibitors which came in December of 1995 and then again in May of 1996.

DR. MARGOLIN: This may be rhetorical. Maybe

Dr. Abrams knows the answer to that, but it seems to me that the demonstration of the lack of a favorable CD4 response in those samples that were shown would also argue against a general immuno-improvement in these patients contributing in large part to the regression of their KS lesions.

DR. SCHILSKY: A question again with respect to dosing. Your analysis shows that there are some differences between the two regimens that were used with respect to toxicity and also with respect to response rate, that is, that 135 every 3 weeks produces a somewhat higher response rate compared to 100 every 2 weeks. I'm curious to know if you did any further analysis trying to dissect out the impact of dose any further.

For example, I'd be curious to know whether there was a difference in the median dose intensity received by responding patients versus that received by patients who didn't respond to the treatment.

DR. CHICO: No. I didn't do such analyses. Maybe the sponsor has.

DR. ABRAMS: Do the confidence intervals for those response rates overlap, the 70 and the 59 or whatever? With the small numbers, they're likely to be the same response rate.

DR. CHICO: Actually the response rates in study 174 were higher, but again these are a much smaller group of patients.

DR. WILLIAMS: And also the fact that these are different performance status patients. So, it's a very different comparison.

DR. CHICO: Actually in addition to that, as far as inclusion criteria, study 174 only allowed treatment with one previous systemic chemotherapy, while in study 281 they allowed more chemotherapies.

DR. KROOK: I guess what I'd like to go back to is the review of the lung Kaposi's. In the one study there were six differences between the sponsor's and the FDA. What were the differences? Was it on films? Was it on CT?

DR. CHICO: Yes.

DR. KROOK: That's 75 percent --

DR. CHICO: Correct. For study 174, there were only 2 patients who were previously treated, and I was able to confirm only 1 patient with a decrease in lung KS. In the other patient, they documented improvement of a patient's clinical symptoms, but there was actually no improvement by radiology of disease. All the radiology reports showed a stabilization of pulmonary KS.

For study 281, there were 16 patients at

baseline with pulmonary KS, 2 of which I confirmed as 2 responders. There were 4 patients where there was no documentation of pulmonary KS either by radiology reports or films, while in the other 9 patients there were no follow-up radiographs or radiology reports that I received from the sponsor, so I wasn't able to confirm those.

DR. KROOK: So, the difference is probably related to what was presumed by the investigator to be clinically improved but not documented.

DR. CHICO: I'm not really sure because there were radiographs that the applicants showed that I didn't see. So, it's probably that not all the films were submitted. I'm not sure. Maybe the applicant could answer more.

DR. YARCHOAN: Maybe I could make one comment about the NCI study. The clinical center radiologist, Irwin Fuersten, developed a methodology of loading the electronic data from the CT scans into a three-dimensional imaging. And each of our responses was able in this way to find a greater than 50 percent decrease that was called for. In fact, most of them were greater than 75 percent. I don't know which one there's some discussion.

We did have 1 patient where most of the lesions decreased but one lesion increased. That second lesion was

biopsied and was found to be a concomitant pulmonary lymphoma.

DR. CHICO: Was this patient previously treated, Bob?

DR. YARCHOAN: I'm sorry. I just don't know.

DR. CHICO: The thing is I only focused my analysis on the 2 patients who were previously treated.

DR. YARCHOAN: But anyway, that was the procedure that we used in the clinical center. I don't know if anyone can comment on the other stuff.

DR. DUTCHER: We have to change the order just a little bit because Dr. Abrams has to leave. So, what we're going to do is just ask him to make a few comments. Is that all right with you, Dr. DeLap, about the questions?

DR. CANETTA: On the piece of information that was asked for the dose intensity for responders was 37.55 milligrams per square meter per week. The dose intensity for nonresponders was 38.95 milligrams per square meter per week.

DR. SCHILSKY: So, it's the same. Thank you.

DR. OZOLS: Can you elaborate on your concern about the possible not supporting the clinical benefit? From what we heard this morning and from what you showed and what the sponsor showed, I think the edema benefit was

quite substantial and some of the others as well, but you seem to have some concerns about that.

DR. CHICO: The main concern with the analysis of clinical benefit really is the way that it was collected retrospectively, especially for foot KS, facial KS, and KS-related pain. But actually for edema and performance status, these were collected prospectively.

Now, first, the other concern is the fact that the sample sizes were very small and that the studies were just open-label, one-arm studies, so there are no comparator arms. Actually beyond progression of cutaneous disease, both protocols did not have any specification on how to follow up the other clinical benefit parameters. So, they're really largely uncontrolled. So, those are just mainly my concerns regarding the analysis.

But again I have to emphasize there were a few patients who had marked, impressive improvements in each of the clinical benefit parameters.

DR. DUTCHER: Dr. Abrams?

Thank you.

DR. ABRAMS: Yes. Sorry that I do need to catch this flight.

This was a unique experience for me. In my previous experience on the Antiviral Advisory Committee, we

never had the opportunity to look at a drug that has already been marketed, licensed, and available for a different indication.

I utilized the document that I received with my packet on FDA approval of new cancer treatment uses for marketed drug and biological products where it stated -- and these are draft guidelines that are not yet implemented, but it recommends that if a product already has been shown to be acceptably safe and effective in treatment of patients with a given type of solid tumor malignancy in advanced, refractory stages, then a single adequate and well-controlled multi-center study in patients with another type of advanced, refractory solid tumor with a response rate endpoint and enrollment of sufficient patients to estimate response rate with adequate precision may be sufficient to support approval for treatment of this additional type of tumor.

So, in contrast to our experience this morning, I feel that the data presented here in my opinion does demonstrate reliable evidence supporting the efficacy of the drug in this group of patients.

I must say that that was augmented significantly by the comments that we heard from the individuals during the open mike session this morning where

a picture is worth a thousand words. I've been treating patients with AIDS-related KS since 1981 and really I have never seen such dramatic improvements as we've heard about and also I've heard from my other colleagues who've used the drug in these patients.

With regards to whether or not we have adequate and well-controlled studies, I think that's something that people will have more to say about. A sample size of 59 patients, is that adequate? In the MGBG documents that I reviewed, it had been suggested to the sponsor that 50 to 100 patients should be at least evaluated in the two phase II studies that they were presenting. So, here we do have 59, so it puts it into that number that would be considered to be adequate.

With regards to the dose, I think that there is going to need to be continued debate. On the Antiviral Advisory Committee, we used to leave that to the FDA, but I understand this committee likes to have more direct recommendations. Obviously, it's a tradeoff. I think the response rates probably are the same, although it looked better in the NCI study. Certainly with regards to quality of life, patients receiving infusions every 3 weeks would be superior to patients receiving every 2 weeks, but that needs to be balanced by increased hospitalization for

neutropenia, fever, and the other toxicities. So, I think that that is something that needs to be further evaluated with regards to what the appropriate dose is.

I guess I was asked not to say what I thought about approval, but I think it should be clear from my comments that I'm impressed with this agent. I would personally not see any benefit of accelerated approval as the drug is licensed and available and is being utilized. In treatment of patients with AIDS-related diseases, once something is available, as we see with all of our protease inhibitors, I'll tell you the opportunity to study it in the controlled clinical fashion disappears. So, I think the window of opportunity to expect that there's going to be really meaningful subsequent studies of this agent that may allow accelerated to move to full has probably closed, and I think again my opinion, on the basis of the strength of the data that we see here, would suggest that -- I'm not supposed to comment on what --

(Laughter.)

MR. MARCO: We'll finish it for you.

DR. ABRAMS: Yes. You all vote and somebody will let me know, but I need to go home.

DR. DUTCHER: Thank you very much for your participation and your comments. I appreciate it.

Now, back to the discussion of dose. You wanted to see additional toxicity data regarding the two dose levels in patients with KS. Is it possible to make a switch of some of the audiovisual equipment so that they can present that?

DR. WINOGRAD: Again, I will show data to compare the two studies and compare it to solid tumors. Again, I wanted to remind of the difference in study design, but I also want to mention that we are open to have all the data disclosed in a possible package insert, meaning the one and the other dose schedule. At the time that we wrote the proposed indication, this is what we felt most comfortable with, but again we are open to any suggestions.

What we are showing here -- and this is how the slides are built up -- you have the NCI study, the USC study, the total patient population, and the total patient population that had received prior systemic therapy. The incidence of fever and febrile neutropenia is broken down, percent of patients and percent of courses.

If you look, indeed febrile neutropenia was seen in 55 percent of the patients and 9 percent of the patients in the two studies respectively, 10 percent and 1 percent of the courses.

Could you go to the next slide please?

If you compare that to what is the experience in solid tumors, again that is the buildup of the slide. You have here the 135 milligrams per square meter dose in solid tumors, the 175 milligrams per square meter dose, the total KS patient population, and all KS patients with prior systemic therapy. The overall incidence of patients with febrile neutropenia is 25 percent or 24 percent as compared to 3 and 4. If you go down to the incidence by courses, it's 5 percent of the courses or 4 percent of the courses in the KS population as compared to 1 percent in the solid tumor patients.

DR. SCHILSKY: It would have been helpful to put on that slide the 55 percent incidence of febrile neutropenia in the KS patients who got 135, just to put it in perspective.

DR. WINOGRAD: Oh, you wanted to merge the two slides.

DR. SCHILSKY: Well, no, the problem is that the total data for the KS population is heavily skewed by the fact that there are twice as many patients who got the 100 per meter squared every 2 weeks.

DR. WINOGRAD: No. I agree. You would want to have the six columns on one slide, but it's sort of

difficult to present. You had seen the one study and then the other study and then the summary. Yes.

Is there any other area of safety that you want to look at? All the safety is broken down in that type of analysis.

DR. DUTCHER: Dr. Swain, did you have another?

DR. SWAIN: No. That's all right.

Was there any difference in the neurologic toxicity at all between the two?

DR. WINOGRAD: Could we go to slide number 14?

The incidence of any grade of neuropathy, 79 percent of patients in the NCI study, 46 percent of patients in the USC study, with an incidence of 10 percent grade 3 and 2 percent grade 3, with an overall 5 percent and 58 percent.

Can you go to the next slide please?

When you compare that to the experience in solid tumors, it's 58 percent in the KS population as compared to 48 for the low dose Taxol and 64 percent incidence in the high dose Taxol. Again, remember, these patients have received 10 courses versus a median of 5 or 6 courses. Plus, those patients have a high number of prior vinca alkaloids.

DR. DUTCHER: Could you go back to the previous

one?

DR. WINOGRAD: Yes. Can you go back one please?

DR. DUTCHER: Other issues with respect to toxicity?

DR. WINOGRAD: With this respect, we could also show you the data of neurotoxicity prior to study start for the two studies, if you want, and concomitant neurotoxic nucleoside analogs.

If you go to file number C, slide 20. This is peripheral neuropathy in the NCI study. 15 patients had grade 1 at worst, 4 patients grade 2, 3 patients grade 3. For 1 patient the grade is unknown. 13 patients reported PNS prior to start of Taxol therapy, and 15 of those 23 patients with PNS received concomitantly didanosine, zalcitabine, and/or stavudine.

And equivalent, the slide for study 281, file D, slide 31. 12 patients had at worst grade 1 neuropathy, 6 grade 2, 1 grade 3. For 7 patients the grade is unknown. 7 patients reported PNS prior to Taxol including 5 who previously received vinca alkaloids. 19 of these 26 patients with peripheral neuropathy received concomitantly ddI, zalcitabine, or stavudine.

DR. DUTCHER: Thank you very much. I

appreciate it.

Anything else? Any other questions?

(No response.)

DR. DUTCHER: Thank you.

Discussion on either issues raised by the FDA or the company?

MR. MARCO: I would like to talk about the clinical benefit and sort of looking at a history of how the division has tried to judge clinical benefit in previous KS studies. Maybe, Dr. DeLap, you can talk about projects that you're involved with with the NCI right now in actually trying to validate a clinical benefit in KS studies and case report forms, and then also how that reflects to this study.

DR. DeLAP: Well, of course, we've had a great deal of difficulty over the years with evaluations of clinical benefit by tools such as performance status measures and various questionnaires looking at quality of life. Those have been very difficult for us. There are a number of quality of life scales that are available in different types of malignancies, many of which are said to be validated. Of course, what that generally means is that if the same patient takes the same test twice, then you'll get the same kind of result. It's a little harder to say

what it means in terms of is it really measuring something that's meaningful to the patient.

We've historically put more stock in things that looked to be clearly related to the tumor, symptoms the tumor is causing, symptoms that get better when the tumor is controlled. So, if it's bone pain related to bone metastases from a tumor or if it's ability to breathe if you've got pulmonary Kaposi's, if suddenly you're able to walk around the block again whereas before you were confined to your apartment, those kinds of things are very meaningful.

Of course, those are difficult really. It's hard to find 100 patients with any given thing that you can measure that then you can treat them with the drug and then see what happened.

So, the direction that this seems to need to move in as far as relief of tumor-related symptoms is to develop some kind of a package of symptoms that are associated with a particular kind of tumor and say you're looking for a patient with one or more of these symptoms, problems that are fairly clearly related to the tumor, and then seeing if that gets better with the treatment. There is some effort going on along those lines that involves us and NCI and some of your colleagues.

So, I think that's very important and I hope that in the next few years that we won't be stuck with kind of looking at what happened in patients and trying to see if we've got a reasonably impressive series of anecdotes, that we can go to a more systematic and scientifically persuasive way of looking at these things. We're still very much in what I'll call the Gestalt mode of how many do you have and how many does it take to really be impressed. I'd hope that we can move away from that and get to something that's a little more clinical science.

But certainly you can see things that are impressive in individual patients and for right now I think it's real important to look at those and to take those for what they're worth certainly.

DR. DUTCHER: Shall we move on to the questions? Okay.

The questions are a little bit lengthy. So, I think you should read them yourselves.

(Laughter.)

DR. DUTCHER: We'll skip to the italics. So, hopefully you've had a chance to look at some of this, but on question number 1, just read the preamble. The question that's being asked is, do the above analyses by the applicant and FDA reviewer provide reliable evidence

supporting the efficacy of paclitaxel in this group of patients?

Dr. Krook.

DR. KROOK: I would answer the question yes. I believe that it does after reviewing the documents and the presentations that I've heard. So, my reply to that is yes.

DR. DUTCHER: Other comments?

(No response.)

DR. DUTCHER: All those who would support yes as an answer to question number 1, please raise your hand.

(A show of hands.)

DR. DUTCHER: Eleven, and Dr. Abrams voted yes.

Dr. Gelber, are you voting no or abstaining?

DR. GELBER: I'm going to abstain on that because I still have a lot of questions about the clinical benefit. I'm prepared to accept the response, although I'm not sure that the 60 percent really can be associated with Taxol. It might be something less depending on what changed. So, I'm going to abstain on that.

DR. DUTCHER: Okay.

Question number 2, is the sample size of 59 patients from the two phase II studies adequate for an efficacy supplement in this indication?

Who would like to start with that?

DR. WILLIAMS: I'd like to encourage that the advisory committee maybe also discuss the facts of what the response rate is in this case and whether adequacy would depend upon response rate.

DR. DUTCHER: In terms of numbers.

DR. WILLIAMS: Right.

DR. DeLAP: I would just add to that that when we were discussing this, to expand a little bit on what Dr. Chico said I believe, when we were discussing the possibility of this supplement with the sponsor, we did have a concern that the response rates would decline more substantially as more experience was gained and as we reviewed the cases and disallowed some of them in our analyses. So, we had encouraged the sponsor to come in with a significantly larger application I would say than what we saw.

But again, you have to look at the results you got. So, I think that's what Dr. Williams just said. We'll look at the results we got in the 59 patients that we received.

DR. DUTCHER: Dr. Gelber, do you want to comment on the number?

DR. GELBER: Here I'm not prepared to abstain.

Here I would say no. I'm looking at some of the information on the longitudinal measures of benefit and I'm very happy you raised the issue before about benefit. There was one assessment of a global score of quality of life which showed improvements on the screen. 30 patients started out. By 2 months, there were 12 patients assessed that showed a spike in quality of life and by 6 months, the positive effects of treatment were based on 3 patients out of the 30. So, on the basis of that, in order to track and get a good handle as to what the true clinical benefit is for a population, I think you do need more than the 59 we've seen.

MR. MARCO: But I think as far as response rate, you do have at least all the patients evaluable. In other NDAs that I've seen here, especially the first one, for a liposomal anthracycline, half the patients were thrown out. So, at least since all these patients were at least evaluable and only some of the responses were questionable, I think it at least gets us enough to go on, as far as at least tumor response. I think the clinical benefit, what we got from the sponsor, is a given since it's the first time it's been done.

DR. GELBER: I don't remember what the number is. Do we know what the lower confidence band was on the

study that involved two centers for the previously treated patients?

DR. SCHILSKY: In the sponsor's application anyway, it was 45 percent. I was going to bring that up also. It seems to me with respect to this particular application and response rate as an endpoint, at least I'm satisfied that even if the true response rate was actually the lowest end of the confidence interval, it's still an impressive response rate.

I think one of the points that you're making, though, that I think is important to consider in future trials is that generally speaking the sample size in these types of clinical trials is driven by what the anticipated response rate is and trying to have appropriate confidence intervals around that. There's usually not much consideration given to other clinical parameters and how having an adequate estimation of those parameters might drive the sample size.

So, for example, it might also be appropriate in designing a trial to say that we're looking for some percentage of improvement in some parameter of clinical benefit and to have adequate numbers of patients in the trial to reliably estimate whether or not that improvement occurs. That type of thing is not usually taken into

consideration in developing the sample size. That's why we often end up in this quandary of wondering whether we have enough patients to adequately determine clinical benefit even though we may have enough patients to be comfortable with response rate.

DR. GELBER: Exactly. Right.

DR. MARGOLIN: I think as an addendum to that, the fact that we try and identify after the study predictive factors for this, that, or the other and end up saying such and such a factor was not correlated with response, it's more likely because there weren't enough responses, there wasn't a high enough power to detect that, but people go away interpreting it as meaning there's no connection between the two and that's the end of the story, which may well not be the case.

DR. DUTCHER: Dr. Ozols.

DR. OZOLS: Well, I guess if we're looking at response, I'm not sure another 20 patients or 30 would really help me in this. So, if the question is asked was it an adequate phase II study for response, I would disagree with Rich and I'd say it was adequate. With the number that we saw, I would vote opposite.

DR. GELBER: Yes, I did make a preliminary statement that I wasn't speaking about the response rate in

my answer to no. The way I read the question, adequate number of patients to address all of the issues for a non-accelerated approval. I think that it's too slight in that. If you ask me about a response rate specifically in this case, to rule out a response rate, say, lower than 35 percent, 40 percent, then the data because of the high observed response rate would suggest that that's been done.

DR. WILLIAMS: Dr. Gelber, I think we would totally agree in terms of performance status, those sort of longitudinal analyses that this is inadequate, and I don't think that really is the question. I believe our feeling is that those endpoints -- in Dr. Chico's review, he certainly felt that the whole design wasn't even adequate to look at those.

But the question would be in totality all the anecdotes, all of the evaluations of photographs, is in totality this enough efficacy data. Is this sample size large enough to make a consideration for full approval here I guess. It's not just response rates, though.

DR. GELBER: Response rates, yes. Other evidence, I still have questions.

DR. DUTCHER: You may want to refer to the beginning paragraph of the questions which defines the criteria for full approval and accelerated approval just to

refresh the committee in terms of the things that you're looking at.

DR. KROOK: Jan, I don't think this question asked which approval, does it? Is that the question we're asking?

DR. WILLIAMS: I think you should answer it as for full approval.

DR. DUTCHER: All right. Shall we vote? Other comments?

DR. KROOK: I guess my only comment as the other reviewer, since Don left, is that I agree with Dr. Gelber. 59 patients is a small number, and I would vote no on this one if yes means indication for full approval.

DR. DUTCHER: Other comments?

DR. SCHILSKY: One of the things that I guess I'm impressed with, even though the numbers are low, is that there's a fair amount of consistency across the two studies. Two different patient populations, two different ways of giving the drug, studies done at two different points in time in different institutions, and yet there's a remarkable consistency in both the response rates and the evidences of clinical benefit across the two studies. I'm not sure that if we had another 100 patients we would really come to any different conclusions.

DR. DUTCHER: Dr. Margolin?

DR. MARGOLIN: I guess the other question is I think I took pretty seriously what Don Abrams said about the concern that since this is already a marketed drug, that providing accelerated approval may lead to the inability to get the post-marketing studies completed the way the FDA might want that to happen since the drug is out there and available to all treating physicians. I don't know what the FDA's stance on that would be.

DR. DUTCHER: Do we think that's true?

DR. KROOK: Except didn't I hear that there were at least two ongoing ECOG trials using Taxol as one of the -- so, there are trials that are going on.

DR. SCHILSKY: One just activated and one being planned.

MR. MARCO: The one being planned is first-line. This is second-line, but second-line studies are very hard to accrue too, especially with the new liposomal anthracyclines. Accrual is very poor.

DR. DeLAP: Well, I think we're very sensitive to these issues of what's doable versus what's not doable for a follow-up study for an accelerated approval. Certainly we've struggled with some of our prior actions as to how one does a meaningful follow-up study. Certainly a

follow-up study that's front line can be done even though the accelerated approval is for second-line use. You can certainly use a front-line study in the same indication as satisfying that requirement.

That's an important consideration but I wouldn't regard that as the determining consideration. I think the data either speak to approval or to accelerated approval or to whatever they speak to, and we can grapple with what's doable and what's not doable as a follow-up study but that shouldn't dictate your vote on an accelerated approval versus regular approval question.

DR. DUTCHER: Arlene?

DR. FORASTIERE: Just maybe another point of clarification. If we talk for approval, if that's what you're asking us for, not the accelerated, then this criteria is for a controlled clinical trial. By definition I don't know how we can vote for that.

DR. WILLIAMS: We would consider this to be a historically controlled trial.

DR. FORASTIERE: Historically controlled trial, okay.

DR. WILLIAMS: Well, a patient is his own control I guess is the way we would put it.

DR. DeLAP: That has been the philosophy in the

past when products have occasionally been approved based on phase II data.

DR. FORASTIERE: I just want it clarified.

DR. DUTCHER: All right. Well, then we really actually have two. We have question number 2 and then we have question number 4 and 5. Is the sample size of 59 patients for the two phase II studies adequate for an efficacy supplement in this indication for full approval? All those who would vote yes?

(A show of hands.)

DR. DUTCHER: Eight yes.

All those who vote no?

(A show of hands.)

DR. DUTCHER: Three. It actually should be nine yes because Dr. Abrams voted yes.

Now, we'll take up the issue of dose. Do you agree with the proposed dose of 135 milligrams per meter squared every 3 weeks? Comments on dose. Dr. Swain.

DR. SWAIN: Well, I would say no based on what we've seen just because the toxicity seemed much less with the 100 and also because I guess the two new studies that we heard about are using 100. So, it's a little incongruous to approve it for one dose and have two large studies using 100.

DR. DUTCHER: Dr. Johnson.

DR. DAVID JOHNSON: Is it necessary to settle on one of those two doses? Why not have, as was suggested, if we approve the agent, the results of both studies in the package insert, and it may come down to a clinical judgment issue.

As I understood the first study, the NIH study, there was some dose alteration. I don't know what other term to use. Is that right? That point kept being made.

DR. SWAIN: Well, that makes even less data available then.

DR. DAVID JOHNSON: That's right.

DR. YARCHOAN: There seems to be some misunderstanding. The patients were started at 135 and then were pushed up to a maximum of 175 --

DR. DAVID JOHNSON: That's my point.

DR. YARCHOAN: -- unless they got grade 3 toxicity, were de-escalated for grade 4. Actually the study was designed to push people until they got toxicity.

DR. DAVID JOHNSON: But, see, I think that's all the more reason to go with Sandy's recommendation because in essence we really don't know what happens at 135. There were a lot of modifications. It seems to me a more prudent course would be to put both sets of data in

the package insert and have the clinician make that decision.

DR. DUTCHER: Okay, we'll modify question number 3. Would you recommend this be approved putting both doses and the data for each study in the package insert versus deciding on a specific dose?

DR. KROOK: That's two questions.

DR. DUTCHER: That's two questions. Well, it's a versus.

DR. FORASTIERE: Can we clarify also the G-CSF because that will go hand in hand?

DR. DUTCHER: Well, that's right. The original proposal was they would propose the 135 dose with a requirement for G-CSF -- or recommendation for G-CSF.

DR. SWAIN: And also if they want to include the 135 data, they need to -- we really haven't seen which patients actually got 135 and what the toxicities were for those patients. It might have only been 5 patients.

DR. WILLIAMS: I think we get the sense of your vote that we do something other than what's here. Then I think we can grapple with it.

DR. GELBER: But everyone did start at 135. Is that right? So, everyone got one dose at least at that level, and then some of them might have had that toxicity

you reported at even the higher dose.

DR. DUTCHER: Right. So, it may have been at the higher dose rather the 135.

DR. GELBER: So, you really don't know what the dose relationship to toxicity is from the data that have been presented. It needs further discussion outside of this committee.

DR. DAVID JOHNSON: Except for the second study I think where the dose was kept constant. Right? That was not changed. There the toxicity data are fairly modest. I think that's why the recommendation came to look specifically at that. But I still think one could be a little bit flexible on this.

DR. DUTCHER: Okay. The FDA gets the sense of the committee's discussion. Thank you.

All right, question number 4. Should Taxol be approved for second-line systemic chemotherapy of Kaposi's sarcoma? Full approval. Comments?

(No response.)

DR. DUTCHER: Shall we vote? All those in favor of full approval, please raise your hand.

(A show of hands.)

DR. DUTCHER: Seven.

All those not in favor?

(A show of hands.)

DR. DUTCHER: Four.

Anybody on either vote want to make a comment? The comments were that they didn't think the post-approval studies would be feasible. Comments for those that voted no? Sandy?

DR. SWAIN: Well, I guess one reason I voted no is because I think the mechanism of accelerated approval is to get the drugs out more quickly, but unfortunately with that, you don't have a lot of the toxicity data and it's a small number of patients and we're also arguing about the dose here too. So, I'm a little concerned about that and I would prefer to see another study done or the data at least from the studies that have been started.

MR. MARCO: For the approval vote, I completely agree with Donald Abrams, but it's also important to know that the response rates for this drug are double that of most other either single agent or combination chemotherapy. The clinical benefit, while at times it's marginal or it's not on all patients, is obvious. So, here we have excellent tumor response and we do see some signs of clinical benefit. So, I think that can equal efficacy.

DR. DUTCHER: I think my concerns are related to the fact that there was significant toxicity at the

higher dose, and as we've just discussed, we don't know what dose actually that was. As was pointed out, they were better performance status patients. This will be used in a variety of patients and we may well see considerably more toxicity. So, I think the toxicity part of this is still to be determined and really needs further careful analysis.

I'm not saying that the response rate isn't there. I think we all agree, but I think that the outcome data still needs to be evaluated.

DR. KROOK: Jan, my vote was not for disapproval. It was simply the same as you said. Additional studies and some studies are going to go on. The ECOG study -- you're going to see what toxicity is probably in there and elsewhere. So, just to be sure that the FDA looks at other studies. So, it was not a vote of disapproval for me.

DR. GELBER: Yes, and I would support accelerated approval. I'm optimistic essentially based on what you said. I would like to see more information about the clinical benefit to get a handle on what that really is.

Also, it's interesting. I note the studies that were presented. One of them completed accrual almost two and a half years ago, and another one about 18 months

ago. I also heard that hundreds of patients have been treated with Taxol. Somehow this committee has had the benefit of seeing a selected group of 59 in this category. If the data are out there, then it should be put together and presented to us so that we could move more rapidly toward a full approval. I'm a little concerned, although enthusiastic, about the anecdotal nature as opposed to seeing the hard data that might in fact be there already, but unless it's presented to us, it's very difficult for me to vote a full approval at this time, as much as I would like to do so.

MR. MARCO: Because you don't see the clinical benefit clean and everything.

DR. GELBER: Well, that's exaggerating, but I would like to have seen more information relating to the clinical benefit to the response rates that we saw. It's probably there.

MR. MARCO: Well, in two or three years from now, that will be a valid statement, but it's not what these drugs, two years ago when these studies were done, when clinical benefit wasn't being recorded, when it was never really an issue.

DR. DUTCHER: So, the four people who voted no on question 4 were voting for accelerated approval. So, we

have eight in favor of full approval and four in favor of accelerated approval.

DR. GELBER: Yes.

DR. DeLAP: Did Dr. Abrams leave his vote on that then before he left? You said eight to four.

DR. DUTCHER: He said for.

Any other questions, discussion?

(No response.)

DR. DUTCHER: Thank you very much. We will adjourn and reconvene tomorrow morning at 8:30.

(Whereupon, at 4:32 p.m., the committee was recessed, to reconvene at 8:30 a.m., Tuesday, June 24, 1997.)