ORIGINAL

TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

58TH MEETING

Pages 1 thru 300

Bethesda, Maryland
September 1, 1998

MILLER REPORTING COMPANY, INC.
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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58TH MEETING

Tuesday, September 1, 1998

8:30 a.m.

Holiday Inn Bethesda
Versailles I, II, III
8120 Wisconsin Avenue
Bethesda, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
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PARTICIPANTS

Janice Dutcher, M.D., Chairperson
Karen Templeton-Somers, Executive Secretary

MEMBERS

Kathy S. Albain, M.D.
James Anderson, Patient Representative (a.m.)
E. Carolyn Beaman, Consumer Representative
David H. Johnson, M.D.
Kim A. Margolin, M.D.
Robert Ozols, M.D.
Richard L. Schilsky, M.D.
Col James Schultz, Patient Representative, (p.m.)
Richard Simon, D.Sc.
Derek Raghavan, M.D., Ph.D.

CONSULTANTS

Howard Scher, M.D., (p.m.)
George Sledge, M.D. (p.m.)

FDA

Rachel Behrman, M.D., M.P.H.
Judy Chiao, M.D. (a.m.)
John Johnson, M.D. (a.m.)
Robert Justice, M.D.
Wole Odujinrin, M.D. (p.m.)
Grant Williams, M.D. (p.m.)

C O N T E N T S

C O N T E N T S

P R O C E E D I N G S

Call to Order and Introductions

DR. DUTCHER: Good morning. In case you are in the wrong room, this is the Oncologic Drugs Advisory Committee. We are going to start a three-day meeting. Two of our committee members were unable to make it here because they live in cities that are served only by Northwest Airlines, Drs. Krook and Santana. They send their regards.

We will start, I guess, by introducing the committee. I am Janice Dutcher from Albert Einstein in New York.

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

DR. CHIAO: Judy Chiao, Medical Reviewer, FDA.

DR. J. JOHNSON: John Johnson, Clinical Team Leader.

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

DR. OZOLS: Bob Ozols, Fox Chase Cancer Center, Philadelphia.

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

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

DR. D. JOHNSON: David Johnson, Vanderbilt

University.

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

DR. SIMON: Richard Simon, National Cancer Institute.

MS. BEAMAN: Carolyn Beaman, consumer advocate, Sisters Breast Cancer.

DR. SCHILSKY: Richard Schilsky, University of Chicago.

DR. DUTCHER: Thank you.

Before we get started with the meeting, Dr. Templeton-Somers needs to read a conflict of interest statement.

Conflict of Interest Statement

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

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

Dr. Howard Scher is excluded from participating in today's discussion and vote concerning Metaret. In addition, Dr. Richard Schilsky and Dr. Derek Raghavan have been granted waivers which permit them to participate fully in all matters concerning Metaret.

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

In addition, we would like to disclose for the record that Dr. Robert Ozols' employer has interests which do not constitute a financial interest in the particular matter within the meaning of 18 U.S.C. 208, but which could create the appearance of a conflict.

The Agency has determined notwithstanding these interests that the interest of the Government and Dr. Ozols' participation outweigh the concern that the integrity of the Agency's programs and operations may be questioned. Therefore, Dr. Ozols may participate fully in today's discussion and vote concerning Metaret.

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

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

Thank you.

Open Public Hearing

DR. DUTCHER: We are now going to proceed with the open public hearing.

DR. TEMPLETON-SOMERS: For our open public hearing we do have a video which was submitted by Michael Miller of Juneau, Alaska, who is not attending for obvious reasons. We have shortened the video a little bit because it was quite lengthy and so I ask the committee members to please refer to his patient history and advocacy experience in the Letters from the Public section of your blue folder.

For the audience, the Letters from the Public will be available for you to view at the registration desk. They are in a notebook there.

MR. MILLER: (By video) Good morning or afternoon. My name is Michael H. Miller. I have been requested to give a video in regards to the evaluation of the suramin drug that is being reviewed at this present time by the Food and Drug Administration Oncologic Drugs Advisory Committee.

Per JoAnn Minor's instructions, I have attached a

profile page plus two reference items, and I wish to thank JoAnn Minor for obtaining permission for my video presentation. I would like to allow the committee members to know that a professional did not produce the video, however, today, we have Steve Nelson, Governor Tony Knowles's videographer, assisting Juneau-Douglas High School health teacher Nancy Seamount with the production.

Hopefully, the format is acceptable and it closely matches the profile page submitted. However, before we get to the profile page, I would like to inform you that I was diagnosed with metastatic prostate cancer on January 17, 1996, at the age of 43. My staging classification is at the D-2 level, a Gleason Score of 9. My PSA count is 26.6.

My cancer has metastasized to the bone on the skull region and C-6/7 region of my neck.

DR. TEMPLETON-SOMERS: The entire patient history is in the folder. In the interest of time, we are going to go past his professional experience a little bit. It is in the folder.

MR. MILLER: As stated before, I was diagnosed on January 17, 1996 with metastatic prostate cancer, and my survival rate according to Dr. Lowe was 17 to 35 months. However, I was originally diagnosed here in Juneau, Alaska, by Dr. Mark McConn, and I would like to let everybody know that he is a very wonderful man and was right on target with

the diagnosis.

I became involved with the South West Oncology 9205 program, and there were only 20 of us currently in the U.S. at the time to participate in this clinical trial program. I chose to do this program because I really believed in the fact that it was beneficial for me to pull out all the stops according to what Dr. Lowe had given me.

He allowed me one week to make my decision. He felt that it was in my best interests to get going as quickly as possible because, as all of you are well aware of, with advanced prostate cancer it moves swiftly with younger men.

I truly believe that I made the right choice of the six choices that I was given. It was my choice on a shared responsibility between Dr. Bruce Lowe and myself, and I really believe that between the medical treatment and the change of my diet of going to a low fat diet, I am working on going to a Mediterranean style type of a diet, and I started exercising on June 13th, 1996.

At that time it took me to go through a 17-station program with a Cybex weight program, it took me four and a half hours to go through the first time. To give you an example, with a leg press machine I was only able to press 20 pounds at that time. Today, I can push 130 pounds.

So, I really believe that through medical

treatment, through lowering your fat intake or your diet, watching your diet, as well as exercising to help boost your immune system, it makes a win/win situation for the patient.

Shortly after being diagnosed, I began giving talks with a local high school here in Juneau, Juneau-Douglas High School, to share my story and increase awareness about prostate cancer, a disease if caught early, while still localized, in the localized stages, all of you are well aware of, has a 99 to 100 percent success rate according to the American Cancer Society.

Since my first talk at Juneau-Douglas High School government class and health classes, I have spoken with 1,885 students and 630 teachers in Juneau. We were able to get the students involved in Prostate Cancer Coalition in the National Prostate Cancer Coalition signature drive and was instrumental in getting state politicians behind the signature drive as well as spearheading the passage of House Joint Resolution 29, supporting an increase in federal funding for prostate cancer research, which today is the only state in the nation to pass such a resolution with our legislative body.

I have also spoken to 10,235 people in Alaska, California, Oregon, and Washington State about preventative disease which includes students, Rotary groups, Chambers of Commerce, and businesses.

In Alaska, specifically Juneau, I have spoken to 4,260 people, which is an average of 179 people per month, and in Alaska, I have spoken to 9,340 people, which is an average of 210 people per month. As I stated before, I have talked to 10,235 people, which is an average of 428 people per month about this particular cause.

Since 1997, I have spoken as a "starter" and speaker at prostate cancer runs in Anchorage and Juneau, and most recently chaired and was a panelist in two panel discussions at the North West Prostate Cancer Forum. There, I was honored to be on the same panel of which I had chaired a specific panel on Saturday, August the 8th, with Dr. Hiram Ira and many other well-known North West oncology radiology doctors.

I have also been a panelist in the 1997 Oregon State Prostate Cancer Conference, as well as currently serving as a member of the American Cancer Society Western Pacific Division Prostate Cancer Task Force Committee, which serves Alaska, Oregon, and Washington State.

I want to help educate the public, especially men, that men's health care is vital and that one in five men will possibly develop prostate cancer in their lifetime. However, as we all know, it is encouraging that if detected early through non-invasive screenings, men can increase their chances of being classified in the curable status.

Through my public outreach efforts, I hope to encourage men to take the initiative towards good health and help those diagnosed to make good choices for themselves and their families.

Speaking of families, I have been married to my lovely wife, Judy, which we celebrate our 25th year of marriage on August 25th, 1998, and we have three fantastic children, Michael Todd Miller, who is 21 years of age, and he is my hero and my inspiration, because Michael Todd in 1989 was hit by a truck carrying a boat at 45 miles an hour, and had a 2 percent chance to live when he was med evac'd out of Juneau. Today, he is walking, and they told him at the time that he would never walk and he would be on a ventilator the rest of his life, so he is my hero and my inspiration, and another big, integral part of why I am where I am at today.

My youngest son is Christopher Scott Miller. He is 18 and will be attending the Art Institute of Seattle in October. My daughter, Jena Brianna Miller, is 14, and is attending Dzantik'i Heeni Middle School here in Juneau.

Now, I would like to leave you all with something that you can think about and that I hope can be of value to you. I would like to thank the Food and Drug Administration for allowing me to do this video.

I would like to read a creed to live by. Don't

undermine your worth by comparing yourself with others. It is because we are different that each of us are special. Don't set your goals by what other people deem important. Only you know what is best for you. Don't take for granted the things closest to your heart. Cling to them as you would life, for without them life is meaningless. Don't let your life slip through your fingers by living in the past. By living your life one day at a time, you will live it to the fullest. Don't give up when you still have something to give. Nothing is really over until the moment you stop trying. Don't be afraid to admit you are less than perfect. Don't be afraid to encounter risk. It is by taking chances that we learn to be brave. Don't dismiss your dreams; to be without dreams is to be without hope, and to be without hope is to be without purpose.

I truly can tell all you folks on this committee that if I did not take the risk, and if the Food and Drug Administration were not giving patients like myself hope through clinical trials, I would not be where I am today.

So, I really believe even though that I have the side effects, and as I stated before, that this drug at the stage where I understand that it is at, can be of value to future patients, and I hope the Food and Drug Administration approves this drug.

Thank you very much.

DR. TEMPLETON-SOMERS: We have also received a letter from Verne E. Roby of Decatur, Illinois, that I would like to read into the record.

My name is Verne E. Roby. I am 76 years of age and reside at 141 Delmar in Decatur, Illinois.

I was diagnosed with prostate cancer which had metastasized to my bones in January of 1991. I was treated with chemotherapy by Dr. James Wade of Cancer Care Specialists of Central Illinois from January of 1991 to June of 1992. At that time Dr. Wade indicated he had gone as far as he could with me and suggested that we see if I could be admitted to a study at the University of Chicago involving the investigative drug suramin.

I interviewed Dr. Retain and some of his associates and was admitted to the program in July of 1992. My PSA at that point was 720. The protocol provided for the administration of suramin four times in a two-week period preceded and followed by a week of observation. Thus, we made six trips a month to Chicago which is 180 miles distance from our home in Decatur.

After four rounds or courses of suramin from July to October 1992, my PSA increased to 1,034 and I had concern about the drug and its effectiveness, however, from October of 1992 to October of 1993, my PSA dropped dramatically from 1,034 to 0.2 and my 16 rounds or courses of suramin were

terminated. The only side effect I had from suramin was a 5-second period of nausea on my way home after the first administration in July of 1992.

My PSA gradually increased from 0.2 in October of 1993 to October of 1996, at which time the PSA level was 118. I was then out on a protocol of suramin calling for suramin once a month for three months, and my PSA by March of 1997 decreased to 2.6. My PSA again reflected increases until January of 1998, when it reached 173. I was again put on a three-month protocol of suramin. My PSA decreased and as of July of this year was at a 20.8 level.

I firmly believe that suramin has permitted me to enjoy some years of life that I undoubtedly would not have enjoyed otherwise. My quality of life and longevity have been very good. I am aware that there are others who have not had my success, but I am an example of what suramin can do. My quality of life is good and I keep busy with both paid and volunteer work.

Speaking for myself, I would trust that the availability of suramin to others would give them the opportunity to have the success that I have had.

DR. TEMPLETON-SOMERS: This letter is in the folders of all the committee members and again is available in the notebook at the registration desk if anybody else would like to read it.

DR. DUTCHER: We have two spontaneous requests also for participation. I believe there is a person in the audience who would like to make a comment, who notified Dr. Templeton. If so, please identify yourself and any potential support from the sponsor.

MR. ZEPHIR: Hi. I am Buford Zephir. I was diagnosed with prostate cancer in 1986. First, my urologist said not to worry, that he would treat it with radiation, however, he found out very shortly that the cancer was already out of the prostate and in the lymph nodes, and could not be treated with radiation.

My urologist then called the Cancer Center at the University of Maryland Medical Center where Dr. Eisenberger was at the time and told them that he had a patient in pretty good health otherwise, but wanted to know how he could treat me for my prostate cancer.

They told the urologist to perform an orchiectomy to prevent testosterone production and reduce or slow the cancerous growth. This operation was effective for about two years, but then my PSA began to double every month or so. This was in the summer of 1989, and my urologist told me there was nothing more he could do for me and that I could be dead by Christmas.

However, the urologist did say that he had heard about a study the University of Maryland Oncology Center was

conducting on a grant from the National Institutes of Health. This was the drug suramin which was an experiment on its effectiveness on prostate cancer that was being conducted by Dr. Mario Eisenberger.

I met with Dr. Eisenberger on June 5, 1990, and after some various blood tests and exams, he accepted me into the program, and I began receiving suramin on July 23, 1990. At this time, my PSA was 73. They informed me of many possible side effects, some of which were very serious. I had to sign a waiver sheet not holding the hospital responsible for any ill effects.

My reasoning was that I didn't have too many or any other alternatives. I was one of the first ones in the program, and at that time the protocol was that you went into the hospital for five days, received daily injections of suramin, and after the first week, you returned to the hospital as an outpatient for either three or two treatments for several weeks and then for one treatment for a week.

With the treatment method, I would like to tell you how my PSA reacted. As I said earlier, I started treatments on July 23rd, and my PSA was 73. On July 30th, the PSA was 43. On August the 6th, it was 21. On August the 13th, it was 12.1. On August the 20th, it was 6, and on August the 27th, it was 3.7. I didn't keep any records of my PSAs after August 27th, but I received chemo through the

last week of September, and my PSAs were well below normal.

I did have some side effects from the suramin, such as tingling in my fingers and feet, I had a rash for a short time, and the most significant one was the loss of appetite which eventually made me lose 30 pounds.

I was readmitted to the hospital in December 1990 where they discovered that the suramin had destroyed my adrenal glands. The doctor gave me large doses of hydrocortisone and by that evening I was eating dinner when the doctor came in.

I would just like to say that the suramin drug gave me eight years of life that I never expected to have and that these have been quality years. If any others might have results such as mine from the treatment of cancer with suramin, I urge you gentlemen to approve it for them.

Thank you.

DR. TEMPLETON-SOMERS: Thank you.

We have a letter that appeared today. This letter is dated August 27th, but Dr. Dutcher just received it today. It is from William B. Nance of Troy, Michigan and Fort Myers, Florida.

Dr. Dutcher. I am pleased and excited to have this opportunity to testify in behalf of the suramin program for the treatment of prostate cancer. I developed prostate cancer in late 1990 when I was 68 years old, and it had

progressed to an emergency state before I became aware of the problem.

By the time it was diagnosed in April 1991, my PSA was at 211. My doctor recommended an orchiectomy that was performed immediately. Remission of the cancer occurred within days. The remission lasted for approximately one year. In April and May of 1992, I went to three oncologists for a diagnosis and advice, and each of them gave me the same answer. There was nothing they could do for me and my life expectancy was nine to 12 months.

One of the doctors told me of the suramin program that was being administered by Dr. Mario Eisenberger at the University of Maryland Cancer Center in Baltimore, Maryland. He assisted me in getting an appointment with Dr. Eisenberger as they were professional colleagues.

Fortunately, I was accepted for the program and began treatments in July 1992. My PSA began to recede almost immediately and by the middle of September it was at zero. I continued the treatments until November 1992.

My PSA remained at or near zero for over five years until December 1997. Without a doubt, those were the best five years of my life. I felt as good as I had ever felt in my life and the only medication that I took all those years was 30 mg of hydrocortisone each day and with no side effects. How could one person be so fortunate.

In December 1997, my PSA began to rise for the first time since 1992, and I was admitted for a second round of suramin treatment in February 1998. My PSA got down to a low of 3 after two months of treatment, but I must say I don't worry about it as I have been so fortunate to get these extra six-plus years of life. I can handle the possibility of death much easier now, and for now my quality is life is excellent.

I am now 76 years old. These extra years of life have given me time to put my house in order, to spend more time with my family and friends that I was unable to do during my business career. Perhaps the most important thing has been that it gave me the opportunity to get to know my children better, as well as my nine grandchildren who were very young in 1992.

In 1997, I began a program to take each of my seven grandsons on a world tour of their choice beginning with the oldest and working down by age. One of the reasons I was unable to appear in person at this hearing was that I had just returned Sunday from a Pacific tour with my second oldest grandson. It is difficult, if not impossible, to explain what this means to me, spending one-on-one quality time for an extended period with these young teenagers.

Perhaps I have given too much of this presentation to personal things, but to me that is what the suramin

program is all about. It gives one the opportunity and time to do those things that they never got done during their life and to get things in order.

I know that many of the suramin patients weren't as fortunate as I to get six-plus extra years of life, but getting even one additional year is tremendously valuable to anyone in this condition. Therefore, I hope that you and others responsible for approving the suramin program do not judge the success of this treatment on the basis of how long the patients live, but rather on the extra days of life that it has provided to these families.

Having lived through this, I can assure you that even one year is like a lifetime. In addition, it has worked extremely well for me and others, and I am confident that eventually the key to making it more successful for many will be discovered. Also, what do you have to lose by giving it a broader test? I can think of none. The gains can be tremendous. The tough decisions in life take courage and foresight.

Through these years I have gotten to know Dr. Eisenberger and Vickie Sinibaldi very well. They are two of the most capable and dedicated people that I have met during my lifetime and Dr. Mario Eisenberger has dedicated his entire working career to research in prostate cancer. Let's keep him busy with all of this expertise.

I regret very much that I am unable to be here in person, however, if there is additional information I can provide, or if I can help this process in any way, please let me know. Thanks for listening and I shall be awaiting your favorable response. William B. Nance.

Unfortunately, because we just received this letter, it will not be in the notebook quite yet. Thank you.

DR. DUTCHER: Thank you. We have two additional people who have joined us at the table. If you could introduce yourselves.

MR. ANDERSON: Jim Anderson.

DR. DUTCHER: Patient rep.

MR. ANDERSON: Patient rep. Survivor.

DR. BEHRMAN: Rachel Behrman, Deputy Director, Office of Drug Evaluation I, FDA.

DR. DUTCHER: Thank you.

DR. TEMPLETON-SOMERS: There is another public speaker.

MR. ROE: I am the last speaker who is not going to use slides this morning, so get your rest while you can.

My name is Terry Roe. I am 73-year-old prostate cancer survivor of about 7 1/2 years. I was diagnosed I believe in 1991 with a 77 PSA.

I opted for surgery on the assumption, based on

the primitive tools at the time, that the cancer was contained in my prostate. Unfortunately, it wasn't and after a partial operation, the surgery was aborted, I went on to seven weeks of radiation, external beam, and then went on Lupron and Eulixin, at that time supposedly for the rest of my life.

Lupron is a very devastating therapy, at least I found it so. Besides the aesthetic things of losing body hair and muscle mass, which you have built up all your life, you develop a set of breasts, you lose a great deal of pep and energy, and you become somewhat depressed from that last symptom.

Later, I went a physician at Columbia Presbyterian who was conducting a trial in intermittent hormonal therapy, which I agreed to participate in. I have been on the trial now for 2 1/2 years, as an anecdotal patient I might add, and my PSA is 0.1. I consider myself extremely, extremely lucky.

The other gentleman who spoke, as well as the letters that were sent in, as well as the TV presentation, I feel a closeness to these men that you can't believe. Prostate cancer strikes one in five men, so you gentlemen on my left or you gentlemen in the audience, look around you. Look around to your left and your right, look at the man in front of you and look at the man behind you, one of you will

be coming down with prostate cancer in your lifetime.

It is a family disease, too. It affects the family of the man perhaps more so. It ruptures a lot of your relationship between a husband and wife as sexual problems may develop from treatment. The son of prostate cancer survivor has a 50 percent better chance of contracting the disease in his lifetime. It truly is a family disease.

I was going to talk today about my situation and how it affects me, but I have written a small article in one of the institute communications about a gentleman in Boston named Tom Largey, who at the age of 39, with a 37-year-old beautiful wife, and three-month-old beautiful child was struck with prostate cancer.

He underwent a radical prostatectomy. The disease had spread to his seminal vesicles. As a result he was impotent. Fortunately, he had frozen sperm, and I am happy to say his wife is today pregnant with a set of twin boys.

The reason I mention him -- and this is the honest truth -- I received a fax in my hotel room last night, and it is apropos to that same gentleman. It was from a young man in Texas, Cornrow, Texas, it seems, who had seen the article and he wanted to get in touch with Tom Largey, and I will just read you part of it.

He said I just got caught up in my Us, Too

backreading regarding your story with a great deal of interest. It really parallels our own challenge. I was 40 with a two-month-old daughter in September 1995, when a PCA diagnosis was made. Now, almost three years out post-radical prostatectomy, we have got a great outlook and a six-month-old lad, much thanks to a supportive urologist who pushed sperm banking.

We found that the issues facing people of our age were entirely different from most "customers," with a different decisionmaking employed, however, we were truly positive and looking forward to the best years of our lives.

Here is a young man of 39 who is looking forward to the best years of his life. It says something about the power of the spirit. It also says something about why we are here today, because a man as young as him can look forward to enhanced treatments in the future.

I meet a lot of people with prostate cancer as a volunteer with Us, Too, a support group network of 550 chapters with some 250,000 members. I am continually amazed at the spirit these men have, and one of the primary reasons is that we have left the dark ages of prostate cancer treatment just 7 1/2 years ago when I was treated.

Today, we are looking at things like suramin, which I myself on intermittent hormonal, realized that at some point in my life, intermittent hormonal therapy will no

longer work for me. I can grasp at Lupron again with all its problems, but that is a medicine which becomes refractory after a while. Now, I and thousands and thousands of patients in my same point of view can look forward to a better lifestyle as we go into our waning years.

The gentleman who wrote the letter said it beautifully. I used to look at my family, I have five children, nine grandchildren, one great-grandchild almost as furniture. They were there, I loved them truly, but they were there. Now, as that gentleman said, I view every moment with them as precious and every day I live is a moment to enjoy life to the fullest.

I strongly support the palliative effects of suramin, the pain-resistant qualities of that drug. It is a hope for men who are coming down the road of treatments that are failing them.

You know, Us, Too, helps patients. They are sort of like the patients themselves, and you ladies and gentlemen on the advisory panel are sort of like doctors. You help cure the patient, you do help cure them, but we in Us, Too teach patients to heal themselves.

They Say U.S. is a very success-oriented society, and I suppose it is. We have the Forbes 500 of millionaires. We think any man who has received several

million dollars a year is a success. Let me tell you this. The true successes in the world are people like the scientists at Parke-Davis who bring help and hope to survivors, and people like you ladies and gentlemen on the FDA panel who give further hope to those people. God bless you.

Thank you.

DR. DUTCHER: Thank you.

We will now proceed with the sponsor's presentation.

NDA 20-893 Metaret (suramin hexasodium for injection)

Parke-Davis Pharmaceutical Research

Sponsor Presentation

Introduction

DR. MARTIN: Thank you, Dr. Dutcher.

I am Irwin Martin from Parke-Davis, Regulatory Affairs. On behalf of Parke-Davis/Warner Lambert, I would like to thank the Division of Oncology Drug Products for the opportunity to present to the committee today an overview of our NDA for Metaret (suramin hexasodium).

For the committee's convenience we have provided at your seats a copy of all these slides which will be used in this morning's presentation.

[Slide.]

You will hear today of the data which support the

use of suramin in the treatment of hormone-refractory prostate cancer. First, however, I would like to provide some historical perspective to this NDA.

[Slide.]

Suramin was introduced in the 1920's by Bayer AG to the German market. Bayer marketed suramin from 1923 to 1995 as an antiparasitic agent. Suramin is available today in a limited number of countries on request. Suramin has never been marketed in the U.S., but is available from the U.S. CDC under an IND for the treatment of parasitic infections.

NCI studies in the 1980's showed that suramin might have a unique antitumor activity. Clinical testing by NCI began in 1987. In 1990, the NCI conducted a study in prostate cancer at the University of Maryland. That study is shown here with the Parke-Davis protocol number to which it was later assigned is contained in the NDA under consideration today.

[Slide.]

A December 1991 Federal Register Notice announced NCI's interest in forming a partnership with the commercial sponsor to further develop suramin in the treatment of hormone-refractory prostate cancer. Parke-Davis began discussions and worked with the NCI, and in 1994, a cooperate R&D agreement was signed.

[Slide.]

Parke-Davis met with the Division of Oncology Drug Products in August of 1993. Discussion of the Phase III protocol occurred at this end of Phase II meeting. At this time, no acceptable comparative agent was approved for this indication.

Later that year, the protocol was finalized. It was agreed that the primary efficacy endpoints in this double-blind, placebo-controlled study should be of meaningful clinical benefit to the patient, for example, relief of pain. Dr. Eisenberger will expand on the rationale for this decision following this introduction. The study was initiated shortly after protocol agreement was reached.

In May 1997, we were notified that suramin qualified for orphan drug status. A pre-NDA meeting was also held in 1997, and the NDA was submitted later that year.

[Slide.]

This morning's presentation by Parke-Davis will consist of the following: After this brief introduction, Dr. Mario Eisenberger from Johns Hopkins will provide an overview of prostate cancer and the use of suramin in hormone-refractory prostate cancer. Dr. Eisenberger was the lead investigator in our Phase III clinical trial.

Dr. Bill Slichenmyer from Parke-Davis will then present the results of the pivotal study of suramin. Following Dr. Slichenmyer's comments, Dr. Eisenberger will discuss the benefit/risk of suramin. Dr. Slichenmyer will then return to facilitate the Parke-Davis response to your questions on these presentations or any of the other information contain in your background documents.

[Slide.]

Also available today from Parke-Davis to answer your questions are Ms. Copley-Merriman from our Outcomes Research Department, Dr. Klohs from our Cancer Pharmacology Department, Dr. Olson from Drug Metabolism Department, and Dr. Wuu from Statistics Group.

[Slide.]

Additionally, the following outside experts are available today to answer your questions: Dr. Piantadosi is Professor and Director of Oncology Biostatistics at the Johns Hopkins Oncology Center; Dr. Portenoy is Chairman, Department of Pain Medicine and Palliative Care at the Beth Israel Medical Center in New York; Dr. Reyno is Assistant Professor in the Department of Medicine at McMaster University and Cancer Care Ontario in Hamilton, and Dr. Vogelzang is Professor in the Department of Medicine at the University of Chicago.

It is now my pleasure to introduce Dr.

Eisenberger.

Background

DR. EISENBERGER: Thank you. Good morning. Dr. Dutcher, Members of the Committee, ladies and gentlemen, it is a pleasure for me to introduce to you a new treatment for prostate cancer.

[Slide.]

First, a few words about the disease are important. In 1998, prostate cancer remains the most prevalent cancer in men. Every day 505 new cases will be diagnosed daily, and 107 men will die of prostate cancer every day.

The disease is curable only if organ-confined and the survival outcomes or the survival figures of patients with metastatic disease has remained relatively unchanged over the past half century.

[Slide.]

Prostate cancer involves the bone and bone marrow in at least 95 percent of the cases. Local extension of the disease into the bladder and lymph nodes is seen in 20 percent, and metastatic disease to the liver and lung and other visceral sites are uncommon in about 5 percent of cases. The less common sites are skin and central nervous system.

The disease is associated with a variety of

clinical manifestations - formidable bone pain, pathological fractures, epidural compressions, anemia, pancytopenia, urinary obstruction, renal failure, and pleural effusions.

[Slide.]

Androgen deprivation treatment or hormonal therapy is the most effective treatment for this disease and represents the mainstay of treatment. Most patients will respond to this modality of treatment, however, androgen deprivation remains palliative.

The figures in cohorts of patients over the past several years indicates a median time to progressions have ranged between 12 to 18 months, and the median survival figures have ranged between 2 to 3 years. The outcome on these patients has also remained relatively stable over the past five decades.

[Slide.]

Upon progression to androgen deprivation there is a progressive development of hormone resistance which is virtually universal. It is associated with major morbidity including severe pain and decrease in quality of life. In these patients, in cohorts of patients, survival has not been shown to be affected by treatment.

[Slide.]

For clinicians facing the challenge of managing patients with pain, we recognize that this is a formidable

challenge. Pain in prostate cancer is thought to be multifactorial. It is typically persistent and progressive where patients require increasing doses of narcotic analgesics, despite this control with such modalities are usually inadequate.

A number of cytokines including interleukin-6, endothelia, prostaglandins, perhaps tumor necrosis factor, may be important disease-related morbidity including pain mediating factors. This stresses that effective systemic treatment for hormone-refractory prostate cancer is critical for optimal palliation instead of analgesics or other palliative modalities of treatment.

[Slide.]

Now, what is available in terms of therapeutic alternatives in 1998 for the treatment of patients with hormone-refractory prostate cancer?

[Slide.]

First, estramustine phosphate is an oral compound, a complex of an estradiol derivative and a nitrogen mustard which was approved for the treatment of prostate cancer in 1974.

The drug since then has shown relatively negligible single agent activity in the disease. It has a questionable impact on disease progression, no demonstrative impact on survival, and palliation with this drug has never

been appropriately evaluated.

[Slide.]

Mitoxantrone was approved in 1996 for the treatment of hormone-refractory prostate cancer. The drug has modest single agent activity. In a prospective randomized trial reported in 1996, mitoxantrone and prednisone was seen to be superior to prednisone alone in improving symptoms of pain. This prospective randomized trial was an unblinded trial where non-narcotics and narcotics analgesics were allowed.

[Slide.]

What else is available for the palliative approach of patients with prostate cancer? First, external beam radiation therapy is aimed primarily as local control of treatment.

Radiopharmaceuticals affect bone pain only, and the most compelling data relates to an adjuvant effect of these modalities following local radiation therapy, and the benefit was to delay the need for subsequent local radiation therapy.

The chronic use of narcotic analgesics has been shown to be inadequate. It is associated with significant chronic toxicity and typically, these patients will require increasing dose for pain control.

The use of bisphosphonate, which has been shown to

be effective in the management of metastatic bone disease, has not been adequately studied in hormone-refractory prostate cancer, and more data are needed at this time.

[Slide.]

Suramin is a new compound. It is a novel compound that has been developed for hormone-refractory prostate cancer. The drug is a polysulfonated naphthylurea. It is a unique polyanionic compound which has complex pharmacology.

[Slide.]

It has a multiplicity of important, pertinent for cancer, biological functions including inhibition of growth factors, including decrease in receptor binding, receptors EGF, PDGF, fibroblast growth factor, vascular endothelial growth factor. It also decreases plasma level of insulin-like growth factor 1 and 2, and the preliminary data on the Parke-Davis trial will be presented to you on IGF-1, which is very interesting.

The drug also inhibits tumor antigen as it induces differentiation, inhibits DNA synthesis, inhibits cell motility and urokinase activity.

[Slide.]

The early experience with suramin during the late 1980's utilized a continuous IV infusion schedule. This schedule was associated with severe toxicities including neurotoxicity, coagulopathy, renal, hematological, vortex

keratopathy, malaise and fatigue also known at that time as "suramin blues," and toxicity in a retrospective analysis was perhaps associated with suramin plasma concentrations sustained above 350 mcg/mL.

[Slide.]

In addition to these initial observations, the preliminary data suggested activity against hormone-refractory prostate cancer, characterized by objective tumor responses, some of long duration, effective PSA reductions, and palliative benefits primarily manifested by improvement in pain. However, the pharmacodynamics remained unclear and it was obvious that further Phase I testing was warranted.

[Slide.]

In 1990, the National Cancer Institute sponsored two, Phase I trials for suramin. The first trial was a pharmacokinetically guided Phase I trial using a methodology known as adaptive control with feedback, and this was conducted by the University of Maryland, but we will focus our presentation essentially on the results of this trial, since this represents the background for the current schedule.

The second study, equally important however, was a conventional Phase I trial using pre-defined dose escalation, and this was conducted or is being conducted at the University of Chicago.

[Slide.]

The University of Maryland studies involved two stages of Phase I development. On the first stage, 73 patients were treated on three cohorts utilizing the methodology of adaptive control with feedback, which is a labor-intensive, very impractical methodology, which was essentially used to determine dosings and duration of treatment necessary to maintain plasma concentrations within a predetermined target. This methodology was based on a population model of suramin pharmacokinetics.

The second, or fourth cohort was then subsequently treated with a fixed dose schedule without adaptive control with feedback, and this included 42 patients, 40 of which had hormone-refractory prostate cancer.

[Slide.]

The conclusions on the adaptive control with feedback, the first cohort shown here, demonstrated a broad range of non-dose-limiting toxicities.

I should point out that on the adaptive control with feedback, all patients were treated in two dose-limiting toxicity or disease progression, which are standard endpoints for Phase I clinical trials.

A broad range of non-dose-limiting toxicities were documented. Malaise and fatigue, however, was the most common dose-limiting toxicities seen in 41 percent of cases.

The Grade 4 toxicities were uncommon especially the relatively low incidence of neurotoxicity, seen in only 4 percent of the cases. Dose-limiting toxicities were more frequently seen after three months of treatment, and responses were usually apparent within three months of treatment. Activity was observed in all three cohorts.

[Slide.]

I wanted to show two examples. These are patients with histologically confirmed adenocarcinoma of the prostate to the liver, and this is one patient who underwent treatment with suramin, had a complete response which lasted in excess of one year, and this gentleman survived for two and a half years.

[Slide.]

A second patient, a patient also with visceral involvement, which is traditionally resistant to conventional treatment, this patient had histologically confirmed lung metastasis which received treatment, and also had a very significant response of several months duration.

[Slide.]

In addition, the observations on the adaptive control part of the study demonstrated that it was insignificant inter/intrapatient pharmacokinetic variability, and the labor-intensive modality of treatment, modality of support was also seen to be very impractical and

because of these observations, it was questioned whether the adaptive control was actually indeed necessary.

[Slide.]

With this in mind, we initiated a fourth cohort using a fixed dose schedule, and this represented a prospective validation or pharmacokinetically based schedule with 17 predetermined outpatient dosings aimed at maintaining plasma concentrations at 150 to 250 mcg/mL for three months' duration to decrease or shorten treatment exposure.

[Slide.]

The first observation in this trial was that the observed plasma concentrations, of peak and trough plasma concentrations, were well within the range of the simulated plasma concentration. The observed concentrations are described to you in an open circle and the simulated concentrations are shown in the open squares. As you can see, the distribution of the observed concentrations is well within the range of the simulated concentrations.

[Slide.]

This schedule was relatively safe with a fairly low incidence of Grade 3 and 4 adverse events. There was a 14.3 incidence of asthenia, 9.5 percent incidence of edema, and 2 percent each incidence of paresthesia, leukopenia, and rash.

[Slide.]

As in the previous experience, we observed encouraging evidence to suggest antitumor effects. In 40 patients with hormone-refractory prostate cancer, 10 of 22 had pain improvement including 7 patients out of 15 with severe pain.

In addition, significant decline in PSA levels of 4 weeks or longer was seen in 23 of 39 evaluable patients, or 59 percent, and 18 of 39 patients had 70 percent decline in PSA also for 4 weeks or longer, representing a 75 percent decline in PSA.

The median time to progression in this cohort was 91 days, and the median survival was 18.9 months.

[Slide.]

So, the overall accomplishments from the University of Maryland studies included the following: all pharmacokinetics were defined prospectively, all toxicity was characterized, the drug administration was simplified, a fixed-dosing schedule was prospectively validated, and this treatment resulted in toxicity which was manageable and mostly reversible. In addition to that, anti-tumor activity was noted throughout the study.

[Slide.]

The next issue is how would one continue to develop this compound in prostate cancer. First, we needed

to recognize the difficulties which are inherent to prostate cancer in terms of new drug development assessment of efficacy.

First, the evaluation of bone metastases in prostate cancer is notoriously unreliable. Second, measurable metastases are uncommon and perhaps not necessarily representative of the entire patient population of hormone-refractory prostate cancer. The PSA is not an established marker, and no other reliable markers are available.

[Slide.]

In addition, in 1993, a number of confounding issues arose. First, the antiandrogen withdrawal syndrome was described by Scher and Kelly, and preliminary information suggested the possibility of significant contribution of hydrocortisone as a single agent and the efficacy observed with a combination of suramin and hydrocortisone.

[Slide.]

Based on this, obviously, special attention had to be taken in the design of a Phase III trial of suramin in hormone-refractory prostate cancer, which shows palliative endpoints as the major endpoints for this clinical trial for a number of reasons.

First, patients on narcotics pain represent a

homogeneous population with a short survival. With the advent of evolving new treatments for this disease which could possibly confound the evaluation of survival as an endpoint, in this patient population, it became apparent that post-study treatments were less likely to confound this issue.

In addition, the presence of pain with narcotics provided the possibility for an individual baseline comparison, all of which facilitated appropriate endpoint for study.

A variety of validated pain instruments were available for clinical use, and the one that was chosen for this study will be described later. Furthermore, the use of corticosteroids alone are suitable control, is an appropriate suitable, feasible control for a prospective clinical trial.

[Slide.]

So, the trial that will be presented to you next by Dr. Slichenmyer addresses all these issues. First, it effectively controls for anti-androgen withdrawal and hydrocortisone effects.

Second, it represents a multi-institutional test of the safety and drug administration schema developed by a single institution trial at the University of Maryland.

Finally, it adequately evaluates palliative

endpoints in the form of a double-blind, placebo-controlled trial.

I will now pass the podium to Dr. Slichenmyer. Thank you.

Efficacy and Safety

DR. SLICHENMYER: Ladies and gentlemen, thank you for the opportunity to share with you the results of a Phase III trial.

[Slide.]

In the next 30 minutes, you will hear that the results from that trial indicate that in hormone-refractory prostate cancer, suramin is effective for palliation, suramin delays disease progression, and suramin has an acceptable safety profile.

[Slide.]

This slide shows you the organization of the presentation. You will hear first about the design and conduct of the trial, followed by a description of the baseline characteristics of the study population.

You will hear about the endpoints that demonstrate the palliation effects of the drug, and then about the endpoints on disease progression. At the end, you will hear about some other related endpoints, and then a wrap-up of the safety profile.

[Slide.]

The rationale for this study was described by Dr. Eisenberger. Several previous studies had suggested that suramin is active in patients with hormone-refractory prostate cancer. The Maryland study confirmed this finding and indicated that the fixed dose outpatient regimen is feasible and the safety profile is acceptable.

These observations led to the design of a Phase III study of suramin and hydrocortisone compared to placebo and hydrocortisone.

[Slide.]

The heart of the study design is a randomized placebo-controlled, double-blind comparison of the two regimens. Patients and their health care providers remained blinded from the time of randomization until disease progression. After progression, patients assigned to the placebo group were offered the option to cross over to treatment with suramin plus hydrocortisone.

Because pain and narcotic use were a component of the primary endpoint, a run-in period of up to the two weeks was provided for optimization and stabilization of narcotic dosing. Treatment allocation was stratified by study site, baseline PSA level, and the presence or absence of measurable disease. Because patients are initially optimized on narcotics, this then becomes a test of the study drugs to exceed the optimum benefit that could be

achieved with narcotics alone.

[Slide.]

The planned sample size was 466 patients. Midway through the study, an interim analysis was performed to ensure the continuation of the trial was ethically justified. Because of the so-called alpha spending for the interim analysis, a p-value of less than 0.0475 was required for this to be considered a positive study.

The primary outcome variables were pain and narcotic use and performance status as measured by the Revised Rand Functional Limitation Scale. These will be discussed in more detail later.

[Slide.]

The study population was restricted to patients who required regular narcotic analgesics for the management of bone pain. They were required to have serum testosterone in the castrate range and a rising PSA documented at least 28 days after the withdrawal of any antiandrogen. Adequate performance status and organ function were required.

[Slide.]

Subjects were excluded if they had ever received chemotherapy or if radiation therapy had been delivered within the 28 days prior to enrollment. They were not eligible if they had any serious comorbid condition or a history of other recent internal malignancy.

[Slide.]

Suramin or placebo in a volume of 500 milliliters was infused at the doses and times shown. All infusions were given over one hour except the first one, which was given over two hours.

Treatment with suramin or placebo stopped after dose number 18, which was scheduled for week 12. Hydrocortisone was administered orally in a divided dose of 40 mg/day. Treatment with hydrocortisone continued until at least four weeks after completion of suramin or placebo and then could be tapered off at the discretion of the investigator. Patients who had not undergone orchiectomy remained on an LHRH agonist throughout the study.

[Slide.]

The schedule of data collection is shown here. Entries were made into the pain diary every night starting one week prior to treatment with the study drug. Performance status was assessed by the Revised Rand Functional Limitation Scale and by Karnofsky score. The FACT-G instrument was used for assessment of quality of life.

At the time that the study began, the prostate-specific module, now known as the FACT-P, had not yet been developed. Disease assessments by bone scan, chest x-ray, and CT of abdomen and pelvis were performed every three

months or more often if clinically indicated.

PSA was obtained weekly and assayed at a central reference lab. The week 13 time point is an important one in some of the analyses especially Kaplan-Meier analyses that you will see later. After week 13, PSA was obtained monthly and clinical labs, scans, diaries, and questionnaires were obtained every three months.

[Slide.]

The pain diary used in this study is part of the instrument known as the Brief Pain Inventory, or BPI. Among several questions in the BPI, the one prospectively selected for analysis in this trial is worst pain of the day. It, and narcotic use, were recorded every night, and the weekly average values served as the basis for analysis.

[Slide.]

Seventy-six study sites in the U.S. and Canada participated. These included both academic and community-based practice settings. We would like to take this opportunity to thank the investigators, their study staffs, and the patients who participated in the study. Without their perseverance and dedication, we would not be here today.

[Slide.]

We will now turn to the baseline characteristics. Enrollment began in February 1994 and was completed in

December 1996. 460 patients were enrolled. One subject in each arm never received any study drug, giving a sample size of 458 subjects analyzed.

[Slide.]

As shown here, the two groups were similar in terms of age, race, and baseline performance status. The median baseline PSA level was slightly higher in the patients assigned to the placebo arm, but this difference was not statistically significant. The multivariate analyses to be described later adjust for this covariate.

The two groups were similar in terms of baseline hemoglobin and sites of disease. As expected, bony disease predominated and the two groups were similar in terms of the proportions with measurable disease and extent of prior therapy.

As you will see in a moment, this was a population with advanced disease and who had persistent chronic pain in spite of optimized opioid analgesics.

[Slide.]

Of the 18 doses planned, the ranges in medians of delivered doses for both treatment groups are shown here. Fewer doses were delivered in the placebo group than in the suramin group primarily due to the impact of the higher rate of early disease progression in the placebo group.

[Slide.]

More subjects completed treatment on the suramin arm than the placebo arm. The biggest factor accounting for the difference is the lower rate of disease progression in the suramin group.

This foreshadows the findings from the analysis of time to progression that will be shown later and which favors the suramin plus hydrocortisone arm. As expected, this difference was offset in part by a lower rate of withdrawals for adverse events in the placebo group.

[Slide.]

We will now move to a discussion of the palliation endpoints.

[Slide.]

The primary endpoints of the study are changes from baseline in pain scores, narcotic use, and the RRFL score. The predetermined time points for analysis were week 6 and end of treatment. The statistical test to be applied to pain and narcotics was the rank-sum test. Analysis of covariates, or ANCOVA, was used as a statistical test for RRFLS and to estimate the magnitude of treatment effect for pain and narcotics.

After the primary endpoints, you will see the pain response rate and duration of response. This will be followed by a time to event Kaplan-Meier analysis. In this case, the event is time to pain progression.

Finally, you will see that some patients are able to be weaned off of their narcotics during the course of the study.

[Slide.]

The primary outcome variables for the study are shown here. The analysis plan called for comparisons of the two treatment groups for change from baseline values for each of these. Baseline means and standard deviations are shown. Pain is shown as points on the scale that runs from zero to 10. Narcotic use is expressed in equivalents of milligrams of oral morphine per day. Note the very large variability in this measure.

Performance status was assessed by the RRFL score which has a minimum value of 8 for best performance and a maximum of 40 for worst performance. As you saw with the other baseline characteristics, the two treatment groups were well balanced.

[Slide.]

This table shows you the p-values derived for the primary endpoints. For pain alone, narcotics alone, or the composite of the two, the p-values indicate a very high level of statistical significance in favor of suramin over placebo. These analyses used the rank-sum test. The RRFL scores changed very little and did not reach statistical significance. It was analyzed by analysis of covariates.

[Slide.]

Shown here are the mean and standard errors of change in pain from baseline to week 6 and end of treatment. In this analysis of covariance models, the means have been adjusted for the covariates of treatment center, baseline PSA, and presence or absence of measurable disease.

This analysis was performed to estimate the magnitude of the treatment effect and not for hypothesis testing. The rank-sum p-value from the previous slide was used for the hypothesis test.

The magnitude of treatment effect here is reflected in the roughly 2- to 4-fold higher change from baseline for the suramin group than the control group. This finding is consistent with the results of the pain responder analysis which you will see shortly.

[Slide.]

This is a similar analysis of covariance showing the mean and standard error for change in narcotic use at week 6 and end of treatment. You can see that both groups had an increase in narcotic requirement during this time period. Again, the hypothesis test was based on the rank-sum test, not the ANCOVA results shown here.

The ANCOVA was performed to estimate the magnitude of treatment effect. You can see from the graph that the increase in narcotic use was approximately half as much in

the suramin group as in the control group.

[Slide.]

This graph shows you the last of the primary outcome variables, the RRFL score of performance status. This is change from baseline analyzed by ANCOVA. Remember that the mean baseline scores were approximately 23 plus or minus 8 on a scale from 8 to 40.

The finding of stable RRFL scores during the treatment phase indicates that suramin did not compromise functional status and is consistent with other data that you will see that indicate that the drug is well tolerated.

[Slide.]

As was already mentioned, the mean pain score changes across the population demonstrated a highly significant advantage for suramin over the control group. It was appreciated after the study started that the determination of a pain response rate would also be useful in understanding the efficacy of suramin.

In 1996, an excellent example of how to apply such an analysis was provided by a multicenter trial of mitoxantrone in patients with prostate cancer. That led to the eventual approval of mitoxantrone in the indication and demonstrated that the endpoint was useful both clinically and from a regulatory perspective.

We think of this as a prospective secondary

endpoint because it was defined in the analysis plan which was completed prior to breaking the randomization code at the completion of the study.

On the next slide you will see how a pain responder was defined.

[Slide.]

Subjects could qualify as a responder based on either pain reduction or decreased narcotic use. The threshold for being classified a responder on the basis of pain was a drop of at least three points that was maintained for at least three weeks.

Subjects with a baseline pain score of 2 to 3 could qualify as responders if they achieved a score of zero. A reduction of narcotic use by 33 percent for at least three weeks was required to be considered a responder on this criterion.

[Slide.]

The results of the pain responder analysis are shown here. Forty-three percent of patients in the suramin arm achieved a pain response versus 28 percent in the placebo arm. The p-value of 0.001 and the confidence interval around the relative risk of 1.52 indicate that this result is highly significant in favor of suramin plus hydrocortisone.

[Slide.]

A question posed by the FDA for the consideration of the committee relates to data shown on this slide. It shows pain response rates for the two treatment groups stratified by baseline pain score.

Two points are important to consider here. First, remember that these baseline pain scores were recorded at a time when the patients were optimized on opioid analgesics. They still had pain in spite of this.

Second, it may be true that in one of these subgroups the data suggest that suramin and placebo are comparable in terms of the incidence of pain response, but perhaps even more important than the incidence is the duration of pain response.

[Slide.]

This Kaplan-Meier analysis shows the duration of pain response. The median for the suramin group is 240 days versus the median for the control group of 69 days. The treatment effect is also estimated by the hazard or risk ratio of 2.0. The confidence interval around that risk ratio and the log rank p-value of 0.0027 indicate that the difference is highly significant.

Many clinicians find the estimate of response duration to be a useful endpoint, but it is acknowledged that some do not like it because it applies only to the subset of patients who achieve a pain response. For this

reason, we retrospectively chose to perform an analysis of time to pain progression on an intent-to-treat basis.

[Slide.]

In this intent-to-treat analysis of the entire study population, a patient was considered a pain progresser when he had an increase in pain score of two points or an increase of narcotic use by 15 percent. Two consecutive measures above this threshold were required for a patient to be considered a progresser.

As you can see, suramin is once again associated with a highly significant advantage relative to placebo plus hydrocortisone. The median time to pain progression for the suramin group is 353 days, and the risk ratio is 1.7. This suggests that the durability of palliation associated with suramin is not an artifact of selection of a subset.

[Slide.]

The members of the committee have been presented with two versions of analyses of time to pain progression. With this slide, you will see why this happened.

In the NDA, an analysis of time to pain progression was submitted with results as they appear in the FDA's briefing document. The FDA commented on the methods of analysis which led the sponsor to tighten some of the definitions. This, in turn, led to the modified results presented in the sponsor's briefing book and which were

subsequently submitted to the NDA.

Regardless of the methods, the conclusion is the same. Suramin produces a powerful reduction in the risk of pian progression.

[Slide.]

An additional retrospective analysis of the narcotics use data was performed at the suggestion of an expert in the field as another indicator of the treatment benefit associated with suramin. It was observed the patients in the suramin arm were three times as likely as those in the placebo arm to have at least one week free from narcotics. Again, the results are highly significant.

[Slide.]

In many different analytical approaches to these data, suramin plus hydrocortisone is superior to placebo plus hydrocortisone. That includes each of the seven different endpoints listed here. Remember that the top three were prospectively defined primary endpoints of the study. It seems that no matter how we analyze these data in comparison to placebo, suramin is effective in palliation.

The palliative benefit was obtained in a population that was symptomatic with pain despite pre-study optimization of narcotic use. The additional benefit conferred by suramin was substantial enough that this alone would make oncologists and patients want to have access to

the drug. As you are about to see, the benefits of suramin are not restricted to palliation. Suramin also has a favorable impact in terms of delaying disease progression.

[Slide.]

We will now move to the disease progression endpoints.

[Slide.]

Here, you see named three different analyses related to disease progression. The first one is a Kaplan-Meier analysis which is defined in the protocol. The other two are retrospective, ad-hoc analyses.

The second of the three is a very simple look at the number of patients who have objective disease progression at the week 6 and end of treatment time points.

The third is a Kaplan-Meier analysis of only objective progressions or death, and which is referred to here as objective progression free survival.

[Slide.]

This slide outlines for you the definitions in the time to disease progression endpoint which were described in the protocol. In this analysis, progression could be based on either objective or subjective criteria. The objective criteria are conventional - new or enlarging lesions, new malignant effusion, cord compression, or urinary outlet obstruction.

Subjective progression was based on worsening performance status and either worsening pain or increasing narcotic use. The dates and reasons for progression were assigned by the investigators on a specific page in the case report form.

[Slide.]

This is the Kaplan-Meier estimate of time to disease progression for the two treatment groups. The risk ratio of 1.5, with its confidence interval and log rank p-value indicate a significant advantage for suramin plus hydrocortisone relative to the control group.

An interesting feature of this analysis is what visually appears to be a convergence of the curves around day 85. This time period corresponds to the protocol-mandated restaging at study week 13. In fact, the vertical separation between the curves is maintained at all time points as both curves shift downward sharply at the time that bone scans and radiographs identify a large number of progressions.

Because of this artifact, the difference in medians for the two curves does not reflect the magnitude of treatment effect which is more reliably estimated in the hazard ratio.

[Slide.]

After seeing the results of the Kaplan-Meier

analysis, we questioned how much of the delay in disease progression was attributable to subjective and objective progressions. Overall, approximately 80 percent of progressions were based on objective criteria.

The table on this slide shows you the proportions of patients who had an objective progression at week 6 and again at the end of treatment. The highly significant p-values shown here indicate that at these time points suramin therapy is associated with fewer objective progressions than placebo plus hydrocortisone. This is further evidence that suramin delays disease progression.

[Slide.]

We have also analyzed the data for objective progression free survival. For this analysis, only objective progression or death were counted as events. Again, the log-rank p-value and confidence interval around the risk ratio of 1.4 indicate a significant treatment effect. Suramin prolongs objective progression free survival.

Like the time to disease progression analysis, the restaging effect causes an abrupt downward shift in the curves that makes any difference in medians an unreliable indicator of treatment effect.

Because medians are a traditional and practical parameter for the estimation of treatment effect, we have

used statistical modeling to overcome the artifacts in the Kaplan-Meier curves.

The Weibull curve fitting technique has been applied to the curves for both treatment groups. This technique facilitates the estimation of medians that are consistent with the hazard ratios derived from the proportional hazard model. These medians are shown in the upper righthand corner - 124 days for suramin, 100 days for the control group.

[Slide.]

You have now seen evidence that suramin is effective in palliation and in delaying disease progression. Next, you will see the effects of suramin on PSA, insulin-like growth factor 1, quality of life, and also a brief discussion of the experience of the crossover group.

[Slide.]

The PSA response rate was a prospectively defined endpoint of the study. To qualify as a responder, the patient was required to attain at least a 50 percent decrease from baseline and have that decrease maintained for at least four weeks.

This definition was elaborated in the analysis plan and is more conservative than the original protocol-specified definition. Thirty-two percent of suramin patients achieved a 50 percent PSA response and 14 percent

achieved a 75 percent PSA response. These rates were twice as high as were observed in the control group, and the difference was highly significant.

[Slide.]

A growing body of literature suggests that insulin-like growth factor 1 is a survival factor for prostate cancer cells. Previous reports have indicated that suramin can depress plasma levels of IGF-1. We have now confirmed and extended those findings.

As shown in the light bars, patients treated with placebo plus hydrocortisone have an increase in their IGF-1 levels over time. In contrast, patients treated with suramin plus hydrocortisone have their levels suppressed through the end of treatment followed by a rise in the level after the conclusion of therapy.

These are new data for us. We have only had them for a couple of weeks and only recently submitted them to the NDA. We cannot yet say whether or not these effects on IGF-1 correlate with any clinically important outcomes, but we can say that one might expect a drug that acts through inhibition of a growth factor to behave like a cytostatic agent, that is, delaying tumor progression even if regressions are uncommon. This is exactly what has been observed in this trial.

Four percent of patients with measurable lesions

who were treated with suramin achieved a partial response. No such responses were seen in patients in the placebo plus hydrocortisone arm.

[Slide.]

The FACT-G is a general quality of life questionnaire with 28 items. The overall FACT-G scores changed little during the treatment phase, and there was no significant difference between the treatment groups. If anything, there was a trend toward slight improvement in both groups. This observation is consistent with the safety data for suramin which you will see in a moment and which indicate that the drug is well tolerated.

The FACT-G has a single question on pain, and these scores significantly favor suramin, but as only 1 of 28 items, it was not sufficient to make the overall score positive for suramin.

We did observe significantly better FACT-G scores for pain responders than for nonresponders. This effect was independent of assigned treatment, but remember there were significantly more responders on the suramin arm than the control arm.

[Slide.]

The study design included a one-way crossover from placebo plus hydrocortisone to suramin plus hydrocortisone. Seventy-one percent of patients assigned to the placebo arm

did eventually cross over to receive treatment with suramin. The number of patients who crossed over is shown here as 164. This matches the rest of the data we have chosen to present today and which does not differ significantly from the safety update database shown by the FDA.

The pain response rate of 21 percent in patients who had failed hydrocortisone was clinically gratifying. While this may be seen by some as evidence of activity of suramin, it must be interpreted with caution in this open-label, non-comparative setting.

PSA responses were observed in 14 percent of the crossover group.

The crossover group has provided some useful information, but has seriously confounded any attempt to analyze overall survival. In fact, over 85 percent of all patients on the study received suramin, so it is not possible to perform a legitimate analysis of the effect of suramin on overall survival.

The intention-to-treat analysis showed no difference between the treatment groups.

[Slide.]

We will now turn to the safety data.

[Slide.]

This table shows a comparison of the proportions of subjects affected by the listed adverse events at any

grade of severity. Overall, 97 percent of study subjects reported at least one adverse event. The crossover experience is not included in this or the following tables.

Some of the numbers shown here differ from what is shown in your briefing document because similar terms have been collapsed, for example, edema with peripheral edema. These are the same collapsed terms that appear in the draft product label.

The listed adverse events occurred in at least 20 percent of study subjects. Each of these was less often observed in the placebo group than the suramin group. The most common adverse event was rash. The rash associated with suramin is most often a morbilliform eruption, but can also be manifest as a UV recall rash, urticaria, hyperkeratotic lesions, and in other manifestations.

Asthenia and edema were reported in over half of suramin-treated patients, but were also seen in a large proportion of patients in the control group. In general, these adverse events were brief in duration.

[Slide.]

All Grade 3 or 4 adverse events that were observed in more than 2 percent of patients are listed here. Note the relatively high rates of Grade 3 toxicity in the placebo group, 36 percent. This may indicate that some toxicity is contributed by hydrocortisone, as well as the fact that

complications of prostate cancer are often captured as adverse events.

If we look for categories that show a difference between treatment groups, the two most pronounced are peripheral edema, here, and anemia, here.

Grade 4 toxicities are shown on the righthand side of the table. The overall incidence of individual Grade 4 toxicities is low, 11 percent of suramin patients and 4 percent of placebo patients experienced a Grade 4 toxicity.

[Slide.]

During the double-blind phase of the study, 11 percent of the patients in the suramin group had treatment discontinued due to adverse events. This compares with 3 percent in the placebo group. Events that led to discontinuation and occurred in more than one patient during the double-blind phase of the trial, included three cases each of thrombocytopenia and increased creatinine, two cases each of anemia, leukopenia, congestive heart failure, dyspnea, and abnormal kidney function.

Not shown here are serious adverse events which occurred in 32 percent of suramin patients and 14 percent of control patients. The most common cause of serious adverse events in the suramin group was pneumonia.

[Slide.]

This table shows all deaths recorded during the

span of the study. Their preponderance were related to tumor progression. A small percentage of deaths from both treatment groups was attributed to adverse events, but the interpretation of these findings is complicated by the crossover design. Six of the 9 deaths specified in the placebo group occurred after crossover.

Most of the deaths were observed in the setting of a heavy tumor burden and progressive disease with multiple organ system compromise, making the contribution of suramin difficult to gauge.

[Slide.]

To conclude the description of the safety findings for suramin, one can say that the drug can be administered on an outpatient basis with an acceptable side effect profile. Rash, edema, and asthenia are commonly reported, but generally mild to moderate in intensity.

This study has confirmed the observation from the Maryland trial that severe toxicities reported in earlier studies with other schedules of administration appear to be less common using the fixed dose regimen.

Treatment discontinuations and deaths due to adverse events are uncommon and are overshadowed by deaths due to disease progression in this population with a very poor prognosis and few treatment alternatives.

[Slide.]

This and the next slide are intended to sound a cautionary note about extrapolation of the findings of this trial to other studies. This applies in particular to the pivotal trial that served as the basis for approval of mitoxantrone, because the studies look similar, at least at a superficial level.

The Canadian multicenter trial was conducted under the leadership of Dr. Ian Tannock. It was an extremely important trial because it demonstrated that mitoxantrone could be of benefit to patients with prostate cancer.

It also illustrated that palliation in the absence of a survival benefit is sufficient for regulatory approval in this setting.

[Slide.]

The reason that one must be cautious about extrapolating or comparing results across trials is chiefly related to differences in study design, patient populations, and assessment instruments.

For example, the mitoxantrone trial was not blinded, and the suramin 001 trial uses a double-blind design. At the time that the mitoxantrone trial was started, the phenomenon of antiandrogen withdrawal response was not widely recognized. In the suramin 001 study, patients were required to have a rising PSA level at least 28 days after withdrawal of any antiandrogen.

Finally, the mitoxantrone study was a medium size trial. In contrast, the suramin 001 trial is the largest ever conducted in this indication as far as we know.

The impact of these and other differences is illustrated by the disparity in reported Grade 3 and 4 toxicities in patients in the control arms of these two studies. It is 40 percent for placebo plus hydrocortisone, and less than 3 percent for prednisone.

Why the big difference if the two regimens were at comparable doses of glucocorticoid? Was it different study populations, placebo effect, differing levels of vigilance in identifying adverse events? We don't know. The point is that it is problematic to compare this or any other endpoints across trials.

[Slide.]

I would like to now diverge from these slides that you already have and take just a moment to address the first question posed by the FDA and spell out for you the sequence of events and the thought processes that went into the selection of endpoints for the study.

As I go through the chronology of the endpoints, you may want to refer to Table 8 on page 31 in your briefing document.

Back in 1993, when the protocol was initially developed, three primary endpoints were proposed - pain,

narcotics, and performance status. At that time, the field of patient-derived endpoints was new, complex, and in evolution. The protocol was agreed with FDA and we acknowledged the importance of the need to combine pain and narcotics in a single endpoint, but neither we nor the FDA had a clear idea at that time of the best way to do that.

[Slide.]

In 1994, enrollment began. By late 1995, enrollment had slowed and questions were raised that perhaps the study was a futile effort. For that reason, an interim analysis was discussed with the FDA and agreement on the procedures was reached in January 1996. This was formalized in a protocol amendment in the following month, and then the interim analysis was performed in March 1996.

[Slide.]

The interim analysis examined only the protocol-specified endpoints, both primary and secondary. No additional ad-hoc analyses were done. Two Parke-Davis statisticians, one programmer, and the Vice President of Clinical Pharmacology performed the analysis. The results were not seen by any of the clinical investigators or company staff involved in the conduct of the study.

The results showed a nonsignificant trend towards superiority for suramin in regard to pain and narcotic use. The PSA endpoint was positive and RRFLS was neutral. The

decision was made to continue enrollment and the results were shared with the FDA.

[Slide.]

After the interim analysis was complete, attention was focused on the methodology of how to combine pain and narcotic use into a single endpoint. The company sought input on this from various sources.

One was the successful use of the clinical benefit endpoint in the development of gemcitabine and the reported responder analysis for mitoxantrone. Another source of input was the FDA, which helped us to understand how some of these endpoints had been applied.

The third source of guidance was an expert biostatistician, Dr. Gary Koch, of the University of North Carolina, who recommended the rank sum test for combined pain and narcotic use. He was not given access to any interim data from the trial.

After the input was received, it was integrated and formalized into the analysis plan which was finalized in April 1997. This plan was signed off and submitted to FDA before the study's randomization code was revealed.

[Slide.]

After the code was broken and the specified analyses was performed, we looked at the findings and were satisfied that the trial outcome was positive, but we did

generate additional questions about how to interpret some of the findings which led to the ad-hoc analyses listed here.

We have taken the time to review all of this in order to help you, the committee members, to respond to the first question posed by the FDA. We have conducted this trial with the best intention to protect the integrity of the data.

We recognize in retrospect that the analysis plan was not handled in the most ideal way, but we hope that by elaborating on these details, you will see that the changes were not made in an attempt to manipulate the findings of the study. On the contrary, this was an effort to provide the medical and scientific community and the FDA with the most meaningful analyses possible.

[Slide.]

To wrap up, the data from this Phase III trial indicate that in men with hormone-refractory prostate cancer, and using the schedule and doses specified here, suramin is effective for palliation, suramin delays disease progression, and suramin has an acceptable safety profile.

I thank you for your attention and I will now ask Dr. Eisenberger to return to the podium to put these findings into perspective.

Risk and Benefit

DR. EISENBERGER: Thank you, Dr. Slichenmyer.

[Slide.]

I would like to now in the next few minutes discuss the significance of the findings of the Parke-Davis trial and briefly mention some important points that I believe are critical for understanding these results and making your decision and recommendations regarding the drug.

[Slide.]

First, I wanted to comment on the Parke-Davis study and discussion of the results. During this, I wanted to focus on four issues, first, study design, treatment compliance issues, the safety, and the efficacy observed.

[Slide.]

The Parke-Davis pivotal clinical trial represents a landmark study. It is unique, it has never been conducted in hormone-refractory prostate cancer. It is the largest patient population entered in the clinical trial in hormone-refractory prostate cancer.

It will provide important information to be used for future clinical, regulatory issues in this disease.

Second, it is a prospectively randomized, double-blinded, placebo-controlled trial, which represent optimal conditions for evaluating the palliative endpoints chosen. The endpoints were well defined, the study was appropriately powered, and was completed in a timely fashion, and all objectives were accomplished.

[Slide.]

Treatment compliance was excellent. The median number of infusions administered in the suramin arm represented 100 percent of the infusion plans. The median total dose administered represented 99 percent of the planned dosing, which reflect in a similar fashion that was previously observed in the University of Maryland trial.

Finally, withdrawals due to adverse events were relatively low and seen in 24 patients, which represents 11 percent of patients treated with suramin.

[Slide.]

The treatment was safe. Fixed-dose schedule is well tolerated. It resulted in mild, moderate, and reversible adverse events. The most common adverse events, Grade 3 adverse events, were edema at 9 percent of the patients, asthenia in 8 percent of the patients, and anemia in 7 percent of the patients.

The severe toxicities observed with earlier schedules, which were reported or were discussed in my introduction, were rare. This study indeed confirms the observations of the single institutional trial previously done at the University of Maryland.

[Slide.]

A number of important patient benefits were observed. First, significant improvements include pain

response, and I should point out that the improvements in pain response are even more significant if one considers that patients with hormone-refractory prostate cancer and pain usually don't stabilize their pain. They have a typically increasing pattern of pain which requires an increasing amount of narcotic analgesics daily.

Once again, this has been shown to be inadequate treatment and associated with significant toxicity related to the use of narcotics. The study showed that besides an improvement in pain response, there is also a decrease in narcotics in a proportion of these patients.

Finally, the duration of response was significantly longer on patients who responded on the suramin arm, on patients who responded in the suramin compared to the placebo arm.

Finally, evaluation of time to pain progression and intent-to-treat analysis also was superior for the suramin arm.

[Slide.]

To further support the observations of pain benefits, even though we recognize that this would not necessarily support a treatment benefit, we observed the pain response correlated well with the improvement in performance standards in a RRFL scale and improvement in the quality of life on a FACT-G scale.

Furthermore, toxicity was modest and quality of life was not diminished.

[Slide.]

Suramin also prolonged various measures of progression and different criteria for measurement. It prolonged significantly time to disease progression, subjective plus objective, designed by protocol. It prolonged objective progression free survival, and prolonged the failure free survival as discussed and presented to you by Dr. Slichenmyer.

[Slide.]

So, the overall results of the Parke-Davis trial are significant. First, the drug has shown and accepted treatment has shown an acceptable safety profile. It was administered through convenient outpatient treatment schedule.

It produced significant relief of symptoms. It significantly prolonged duration of pain response, it delays progression of hormone-refractory prostate cancer. It also decreases PSA most frequently, and this was all determined in an outstanding prospective randomized clinical trial.

[Slide.]

So, why would I think that suramin should be approved? First, this is a compound that has been meticulously studied, perhaps more than many of the other

compounds available for treating cancer today.

Patient safety has been amply demonstrated. It has shown proven efficacy in hormone-refractory prostate cancer in more than one clinical trial. It produced clinically meaningful patient benefit in a randomized clinical trial. It represents a new treatment alternative for hormone-refractory prostate cancer, a disease which is in desperate need for new treatment alternatives.

Finally, it represents an exciting and innovative cancer treatment.

Thank you. I hope you agree with me today.

DR. DUTCHER: Thank you.

We now have some time for questions to the sponsor. We will start with Dr. Margolin.

Questions from the Committee

DR. MARGOLIN: Just a brief clarification question. Your treatment was sort of fixed -- I can't remember how many treatments it was on that graph you showed -- but you have objective progressions and subjective progressions in your charts that talk about patients being withdrawn from therapy because of progressive disease.

Is that based on objective or subjective progression?

DR. SLICHENMYER: That would include all progressions in that table.

DR. DUTCHER: Just to clarify, how did you assess the six-week time point? What did you use?

DR. SLICHENMYER: For?

DR. DUTCHER: For progressive disease.

DR. SLICHENMYER: This was based either on the subjective criteria or if it was based on objective criteria, it was based on scans or radiographs that were performed, not at the protocol-specified time, but because it was clinically indicated.

DR. DUTCHER: Dr. Raghavan.

DR. RAGHAVAN: I have a number of questions and comments. I think my first comment is that I actually agree with Dr. Eisenberger that this was just a very well conducted trial, and he should be proud of it. The dose intensity, the adherence to protocol I think is excellent.

The difficult question I think is one that we always face in dealing with prostate cancer. I think that the public speakers that came from the gallery, and the letters, identify the difficulty of coping with this disease. It is a painful, debilitating disease, and so the issue of symptoms really has to be dealt with very carefully by a committee like this.

So, then the question becomes does the information that we have heard today, which is clearly statistically significant in many of the parameters, is it also clinically

relevant, and so this is essentially what I am going to be asking Dr. Slichenmyer and Dr. Eisenberger.

One of the issues that we always deal with in cancer is the whole question of survival, and you have talked about the fact that the crossover design has vitiated survival as an endpoint. In looking at the data produced, I am not sure that I actually believe that, and I wonder, Dr. Slichenmyer or Dr. Eisenberger, if you could talk a little bit about the impact of the crossover design on the survival analysis.

From my reading of your data, it doesn't look like the crossover had a particularly big impact, and I just wondered if before we get to the pain endpoint, let's talk about an endpoint that relates to many other types of cancers.

Do you believe that crossover vitiated that as an endpoint, and if so, why?

DR. SLICHENMYER: Regarding overall survival, can we show Slide No. 182, please, maybe first just to remind the committee of what you already know, and that is that no drug or combination has ever been shown to increase overall survival in the setting of hormone-refractory prostate cancer, and that 85 percent of the patients in this trial did receive treatment with suramin.

[Slide.]

Shown here is the intention-to-treat analysis for the two different groups. You can see that it looks at the start as if the curves start to diverge. They then cross and there was no statistically significant difference between the two.

Can we see Slide No. 183, please.

[Slide.]

The previous slide was the intention-to-treat analysis. This is the as-treated analysis. The yellow line represents the patients who received treatment with suramin, and the white line those that were randomized to placebo and did not cross over.

We understand that we would never look at these data and try to make a claim of superiority based on this. We recognize that it probably represents bias in the selection of which patients are able to withstand crossover as opposed to those that do not. But these are the data that we have relevant to your question.

DR. RAGHAVAN: Dr. Eisenberger cited in one of the Hopkins' trials a median survival of 18.9 months, and looking at your survival curves, the median survival fits much more with the pattern of hormone-refractory disease, of around somewhere between 9 and 10 months.

Could you explain the difference between those two survival patterns?

DR. EISENBERGER: Those are important questions. First, I would like to address your first question, which will address your second, as well.

When we chose palliative endpoints on this clinical trial, we recognized that these represented patients who have a short survival, homogeneously short survival, for which one treatment would probably be unlikely to result in a major improvement.

The University of Maryland trial, in all the four cohorts, we only had about 30 percent of patients who actually had severe pain, any pain, so the patient population that we studied were completely distinct, and the University of Maryland patient population, it is my belief that this is a patient population that is in a more favorable condition, overall condition, where one treatment may perhaps make an impact enough to sustain a survival advantage later on.

So, I am not sure that the Parke-Davis trial actually provides us with a patient population where realistically we can expect a major survival impact. Having said that, I may be as skeptical as you are, but I do recognize that the crossover indeed represents a problem for analysis of survival.

DR. RAGHAVAN: Coming back to the palliative endpoints, you have made much -- I think appropriately --

much of the issue of pain control and perhaps a little less of the RRFL scores. One of the things that disturbs me a little is your selection of cutoff of really a relatively short time for decreased narcotic use. You know, in a disease like prostate cancer, to set a minimum criterion of greater than three weeks is perhaps not an ideal endpoint.

So, I wonder, firstly, if Dr. Portenoy is here, if he could maybe respond to the question of alternatives for pain management, is it his belief that this really represents a breakthrough, is it possible to control pain effectively without an agent like this, is he satisfied that the level of pain control in the trial was appropriate.

DR. PORTENOY: Thank you. I will respond really to two questions. As you know, the development of this endpoint of pain responder has now come into the regulatory community several times in an effort to try to answer this question of how much pain reduction is actually clinically meaningful.

Pain investigators are working on this, and there seems to be some now early empirical support for the idea that a 30 percent reduction in pain or a 30 percent reduction in analgesic consumption probably represents some degree of clinical significance when you talk about performance and quality of life in comparison to that degree of reduction.

The decision to use four or greater weeks at the point at which one defines pain responders is arbitrary, and I think people are experimenting with how long a response is necessary before you call it clinically significant.

My own view is that these are conservative indicators in this study. The pain responder data are important because they do indicate clinical significance, the criteria used to develop the pain responder measure more conservative, and the study came out clearly in favor of suramin, so I think that suramin does have a clinically meaningful effect on pain in terms of making this sort of randomized comparison against placebo.

In answer to your second question, how well do we do in hormone-refractory prostate cancer, you are absolutely right that there has been a great deal of advances in the last 10 years, in addition now to opioid analgesics and the tried and true nonsteroidal antiinflammatory drugs, disphosphonates, radiopharmaceuticals, calcitonin, gallium nitrates are all now used.

Having said that, however, I think the observation is true that there continues to be a subpopulation of patients who don't do well on any of those therapies or for whom those therapies are contraindicated, and I also think that having a drug that is also a drug for the neoplasm, that has palliative endpoints, may provide additional

benefit to some patients by delaying additional complications like cord compression, for example.

So, I think that there is clearly a role for this drug which can be complementary to currently available techniques and provide pain relief that wouldn't otherwise happen for some patients.

DR. DUTCHER: Dr. Portenoy, before you sit down, could you just tell us what was the definition of stabilized pain control prior to entry and how well that was assessed, your assessment of it?

DR. PORTENOY: When this was being designed as a multicenter trial, one of the concerns, of course, was to develop some criteria for this optimized pain control, and so a clinical protocol was written and vetted against some experts in the field, and then attached as an appendix to the protocol, so that all of the investigators who participated in the study were able to look at a set of very simple guidelines based on the World Health Organization guidelines for the so-called three-step analgesic ladder approach to cancer pain management.

So, the effort was made to provide all the investigators with some simple rules to follow about how to optimize therapy. The obvious question, of course, is whether or not every patient was optimized according to the standards that I might apply, I can't tell you, but at least

everybody was on a level playing field in terms of guidelines to follow.

DR. DUTCHER: Dr. Ozols.

DR. OZOLS: Maybe, Dr. Portenoy, the same type of questioning, but the real question is about the quality of life that we are struggling with here, and what is the correlation between quality of life and decrease in pain, and conversely, when the patients did according to the criteria have progression of pain, how did that adversely affect their quality of life.

I mean what we are looking at sort of globally is that it really didn't make much difference on their quality of life whether their pain decreased a little bit or whether it got worse.

DR. PORTENOY: Right. I will reply to that. Also, one of the Parke-Davis people has looked into this in some depth, as well.

I think it is just important to note how little is yet known about how quality of life scores are going to play out in the clinical trial context and how they might change in relationship to something like pain. It is also important to note that the quality of life measures all vary one from another and what they are assessing is a multidimensional construct and with multiple domains.

We don't really know how quality of life as

measured by the FACT, those specific questions will change in response to a pain score. We don't really know that.

We know that in other clinical trials, patients who are given chemotherapy will have a decrease, a temporary decrease in their FACT scores, most likely showing that the toxicities associated with the chemotherapy are capable of bumping down the scores at least for a time period in other trials, for example, adjuvant breast trials.

In this study, it is true that the overall multidimensional measure of the FACT didn't show improvement as the pain scores showed improvement, and that is probably a function of the questions that were asked or the likelihood that so many other things were happening in these elderly men with advanced disease that simply improving pain wasn't enough to change that global measure.

On the flip side, however, the fact that the scores didn't worsen in the suramin group in relation to the placebo group might be viewed in a positive sense that during that 12-week treatment period, there was not enough toxicity associated with the study agent to produce that negative bump that has been seen in other trials.

But given the current state of knowledge about quality of life assessment, I don't think you can say more than that.

DR. SLICHENMYER: Dr. Ozols, if I may, we have

Catherine Copley-Merriman from Parke-Davis, from our Outcomes Research Department, who may be able to comment further on your question, if that is all right.

MS. COPLEY-MERRIMAN: May I have Slide 189, please.

[Slide.]

When looking at the data by domain, it was apparent that the physical domain was changing the most in the study.

Could I have Slide 195, please.

[Slide.]

These are the questions in the physical domain, and this is the domain in the FACT-G where you would be most likely to pick up the counterbalance between the safety and the efficacy.

As you can see, there is one question directly related to pain, in fact, this is the only item in the whole survey that is directly related to pain, and there are three or four questions related to side effects, so it is fairly remarkable actually that the physical scores improved as much as they did given the circumstance of having much more weighting for the safety in this particular subscale.

We also looked at the comparison to mitoxantrone to see if we had a different result than they had. So, could I have Slide 190, please.

[Slide.]

They used a different instrument. They used the EORTC scale, and they also included the prostate-specific module, which has several questions on pain and also narcotic side effects.

Their results, however, were quite similar to ours. They have an actual domain on pain, and that was where their significant finding was, and we have a single pain item, but it was statistically significant in favor of suramin between the groups, and our other domains were non-discriminant, and they had basically the same result. Their pain domain was significant, and their other domains were non-discriminant.

If I could have Slide 192.

[Slide.]

This is their EORTC data. It is just a graphical view of what I just told you. As you can see, the median changes, the pain improved for mitoxantrone, but the other domains were fairly flat. When they looked at best changed scores, they had a little more improvement noted, but otherwise, the results are quite similar to ours.

However, when you look at pain responders versus nonresponders, that is where you pick up the effects of pain on quality of life, and that is demonstrated in Slide 193 for our data.

[Slide.]

You can see that again the physical domain is where the major changes are occurring, but for the responders versus nonresponders, there is a fairly large improvement in quality of life.

During the follow-up period it is hard to interpret because of the large dropout rate and also there is a bias confounding factor of who completed surveys during that time period, but it appears that pain does affect quality of life, but when you include the nonresponders in with the responders in the intent-to-treat analysis, and you have disease effects and treatment effects and disease benefits all together, it comes out to be more of a neutral story.

DR. DUTCHER: Dr. Simon.

DR. SIMON: I have a basic question about the interpretability of the pain data. You obviously recognized the importance of a placebo-controlled trial when pain was the primary endpoint, but I am wondering whether the placebo control actually worked in the sense that there are known toxicities of suramin, suramin had an effect on PSA, probably the patients had access to their PSA data, and from your questionnaire, it seemed like for both the physicians and the patients, certainly those on the suramin arm knew that they were taking suramin.

So, I wonder since basically, you are showing a pain effect, what looks like primarily for the patients who have relatively low levels of baseline pain rather than the patients who had high levels of baseline pain, whether this is just bias.

DR. SLICHENMYER: Perhaps it would be useful just to review the data since we did not show that. Remember that in a trial with two arms, if patients are asked to guess their treatment assignments, just at random chance alone, they would guess correctly approximately 50 percent of the time.

In the placebo arm of this trial, correct guesses were obtained from the patients in 43 percent of the cases. That contrasts with the finding in the suramin arm of the trial where correct guesses were obtained in 93 percent of the patients who provided guesses. So, that at least speaks to what you mentioned.

We do know, as well, that the reason cited for a correct guess among those in the suramin arm was improvement in condition in 71 percent of the subjects who guessed correctly, and 51 percent -- I am sorry -- 51 percent cited the reason being some evidence of drug toxicity.

I just want to put the data out there for everyone's consideration. Now, we will ask Dr. Portenoy to put that into perspective for us.

DR. PORTENOY: I would only respond that that obviously is a concern. I think having a study where so many patients recognize that they are taking active therapy can potentially compromise the blind, and anytime you compromise the blind in a study of subjective endpoints, you get concerned.

One reassuring piece of data in this study, though, is the time to pain progression. In studies of primary analgesic drugs that include repetitive dosing over time, it looks like the placebo effect tends to wane over a period of weeks, say, about six weeks, although it is true that there are other surveys that suggest that in some settings, the placebo effect can go on much longer than that. The median time to pain progression in this study -- correct me if I am wrong, Bill -- I think it was 240 days, right?

DR. SLICHENMYER: That was the duration of pain response.

DR. PORTENOY: The duration of pain response is 240 days, which would far exceed the usual duration of placebo effect if that was the primary generating force for the pain response. I found that to be very reassuring myself, that even though there was concern about the blinding, it probably didn't have an impact on the overall favoring of suramin in the trial.

DR. ALBAIN: On that same subject, is it possible for you to have your slide put back up, pain responder rates by baseline pain that we are discussing right now? If you could clarify in that slide where there was statistical significance versus not, and comment on the types of pain meds these patients were on, were these like Tylenol 3, et cetera, at these lower levels, or were they all on morphine or fentanyl, oral morphine or fentanyl patch.

DR. SLICHENMYER: We have not analyzed these data for statistical differences between the treatment groups at each of the different strata. I believe that you may see such an analysis in the FDA presentation in a few minutes, however.

We have analyzed the suramin response rate data to see if there are differences in rates across strata, and found no significant differences looking at the data in that respect.

I am sorry, the second part of your question?

DR. ALBAIN: The types of narcotics at these lower levels.

DR. SLICHENMYER: I do not know the answer to that. I wonder, does anyone else here in the group know the answer to what specific narcotics were administered in the different strata? I think we might be able to get that information for you after the break.

Dr. Reyno, would you like to comment?

DR. REYNO: Just a comment related to pain control run-in phase. The answer to your question is it was not predefined which opioid analgesic would be used for any given pain. Rather, what was predefined or advised was that investigators work with patients to try to achieve at the very least moderate pain control.

Moderate pain control for the purposes of this study was defined as pain that the patient describes as moderate, requiring up to four rescue doses of an appropriate drug daily.

So, you can that during the run-in phase of the protocol, we were in fact pushing such that more patients would end up in the first two levels of pain. With respect to your specific question, however, we felt it was inappropriate to advise clinicians as to which precise opiate they would use and rather converted them all to opioid equivalents in morphine.

That is entire appropriate in view of the fact that patients may have various tolerance to different drugs and to prescribe that one should one be on a codeine drug versus hydromorphone would not fit with good clinical practice.

DR. PORTENOY: Just to help clarify that a little bit, the median oral morphine equivalent milligrams taken by

the patients at the start of the trial was between 85 and 90 milligrams. If you buy into the three-step analgesic ladder concept, you would expect about 60 milligrams oral morphine equivalent milligrams to represent the jump from step 2 to step 3. So, it would mean that more than 50 percent were on the drugs that you were talking about.

DR. OZOLS: In that same regard, again, the question of optimal management for that group of patients as far as pain control goes before, I mean presumably we weren't pushing higher on the morphine drugs because of drowsiness, constipation, things like that, so then you have to face that side effect with potential adverse side effects that you had with the suramin, if that decreased some of the pain.

That is the question were they optimally managed to begin with, and how much more pain medications were required and how that impacted on their toxicity and quality of life if they had to be a pain progresser and if they had to go back on an increased dose of morphine, if you increase it by 20 milligrams again, is that really an adverse effect on their quality of life.

DR. DUTCHER: Dr. Johnson.

DR. D. JOHNSON: I actually had a question relating to the same slide that Dr. Albain was asking about, the pain responder rates by baseline pain. I may have just

misunderstood the purpose of that slide. If you would reproject it, it may help.

[Slide.]

DR. D. JOHNSON: That is the slide. A couple of points to be made from my perspective. Maybe I just didn't understand it in the briefing book, but during the course of your oral presentation, the point was made that one needed a two-point improvement in pain score in order to be characterized as a pain responder unless one had a pain score of 1 --

DR. SLICHENMYER: Three-point decrease.

DR. D. JOHNSON: Excuse me, three-point, unless one had a score of 1 or 2, in which case you had to go to zero.

DR. SLICHENMYER: In the 2 to 3 range, they had to go to zero.

DR. D. JOHNSON: As I look at the improvement in percentage of pain, it looks like the worse your pain, the placebo gets better, the percent of patients respond, so that makes me wonder how many of the patients in that zero to 4 range in the suramin arm had a baseline score of maybe 1 or 2 and went to zero as opposed to the 122 patients on the placebo side.

In other words, how many of your responders in that lowest group had a baseline score that was 1 or 2, and

therefore, went to zero.

[Slide.]

DR. SLICHENMYER: I believe these are the data that you are inquiring about. You can see that the numbers get to be relatively small in each of the groups, but these are what was observed.

DR. D. JOHNSON: Actually, this is not correct because I am asking in your group there, you have 114 patients reportedly in the suramin group and 122, and here you are showing me 18 and 25.

DR. SLICHENMYER: This is zero to 2. I believe the other slide included zero to 4.

DR. D. JOHNSON: So, all the rest of the patients had a pain score of 3 or 4 is what you are saying.

DR. SLICHENMYER: Yes, that is my understanding, right.

DR. D. JOHNSON: The only other question I had, had to do with the IGF levels. That was a very impressive slide, but you didn't show us the IGF values at baseline. Do you have those data?

DR. SLICHENMYER: Those were percent changes from baseline.

DR. D. JOHNSON: Oh, I see.

DR. SLICHENMYER: Normalized for each patient.

DR. D. JOHNSON: Okay. Thank you.

DR. DUTCHER: Dr. Schilsky.

DR. SCHILSKY: You didn't tell us too much, Bill, about what happened to the patients who crossed over, and I realize, of course, that they are at a different point in their illness than they would be at the beginning of the trial, and then, of course, the trial was then unblinded, but I am curious to know if you have any data to suggest that after they crossed over from placebo to suramin, that the progression of their illness changed in any way.

Is there any data to suggest that the rate of worsening of their pain diminished or that the rate of disease progression slowed after crossover to suramin?

DR. SLICHENMYER: I think the best data that we have relative to that is what we showed on the slide earlier. We did see some PSA responses, did see some pain responses, but I don't think that we had time to pain progression or any of the other Kaplan-Meier analyses performed in the crossover group, because it was not in the double-blind context.

DR. SCHILSKY: Just one other question just to clarify. Did the patients and the treating physicians know the PSA results sort of in real time? The PSAs were checked weekly, so were those results reported back?

DR. SLICHENMYER: Often they were, but it was not uniform.

DR. DUTCHER: Dr. Raghavan.

DR. RAGHAVAN: I have just two last questions. Your median time to progression was 87 days versus 79 days, and your percentage of progression at three months was 42 percent versus 57 percent, which is not worse than other drugs, but certainly is not all that encouraging.

The flip side, of course, is that we have heard from individual patients, and Dr. Eisenberger has spoken about sustained improvement beyond that sort of time frame, can you give us some figures that might help us deal with real benefit?

I noticed on one of your slides that you had a median of 240 versus 69 days, that I think related, if I recall, to time of pain progression, and that is a pretty impressive real difference.

Can you take a snap frame and tell me how many patients had control of pain for three months or longer in the placebo arm versus in the treatment arm, in other words a quantum of pain control that to me, as a clinician, or maybe to the patients who have spoken, would be more meaningful?

I get the sense you have got those patients who are long-term remitters and who have had good pain control. Can you give me figures that would suggest, take a bigger quantum of, say, three months or four months or two months,

do you have any figures that would show that?

DR. SLICHENMYER: Probably the most relevant is the time to pain progression analysis. Can we show that one again, please.

What you will see in a second is a Kaplan-Meier analysis on an intention-to-treat basis following patients from baseline until they had a pain progression, and pain progression was defined as the time when they had an increase in their pain score of two points or an increase in narcotic use of 15 percent from baseline. That rise above that threshold had to be repeated on two consecutive measures.

[Slide.]

Here, you can see that the time to pain progression, the median in the suramin group was 353 days, and in placebo group, 78 days.

DR. RAGHAVAN: My last question. Prostate cancer obviously is a disease that affects African-Americans substantially, and I recognize there are a whole range of issues that relate to trying to make available participation to African-Americans and then getting African-Americans to participate.

You had about 20 or thereabouts patients in each arm. Any data that would suggest whether this agent works differently, doesn't work, does work in that group? I

recognize all the flaws of subgroup analysis, so it is within the constraints of understanding that this is a small snap frame, but do you have any data that relate to those groups?

DR. SLICHENMYER: We did see a trend, a nonsignificant trend towards higher rates of pain response with suramin in African-Americans. That was not true for PSA response.

DR. DUTCHER: Dr. Margolin.

DR. MARGOLIN: Along similar lines, do you have any data even though one has to take into account that it would be retrospective, on the predictiveness of prior hormone responses and duration of hormone responses however that might have been used to label these patients versus suramin benefit?

DR. SLICHENMYER: We do have baseline information about that, but I don't believe -- that is time from hormonal therapy -- I don't believe that we have looked at it formally as a covariate in any of the multivariate models, though.

DR. DUTCHER: Last question, Dr. Simon.

DR. SIMON: When did the adverse events to suramin occur, what percentage of the patients were still on study at six weeks?

You have given two kinds of analyses, a six-week

analysis and a last treatment analysis, but last treatment analysis is either 12 weeks or last treatment, and roughly 50 percent of the patients didn't make it to 12 weeks, and so you have sort of taken their data at their last treatment and sort of pooled it in with the patients who were still on study at 12 weeks.

The problem I have with that is that for the patients who went off study because of adverse event, may have different sort of pain distributions than patients who went off study because of disease progression or because objectively or subjectively, and so I have some difficulty with your 12-week analysis.

So, I am wondering on the six-week analysis, what percentage of the patients, say, in the suramin group, went off study before six weeks because of an adverse event?

DR. SLICHENMYER: That total number for subjects treated with suramin who went off study due to adverse events was 11 percent. The majority of those were early on in the treatment course. I can't give you the exact figure right off the top of my head.

DR. DUTCHER: Dr. Ozols.

DR. OZOLS: I just want to return just briefly to survival in the crossover. If you look at it as an objective thing, your PSA responders in the initial randomization, I guess the PSA response was close to 50

percent to suramin, and then when they crossed over from placebo, that dropped down I think 14 percent.

Why would you predict that or why would you expect that, particularly since many of the crossovers were relatively early and why would the response rate drop so low, and if it is such a low response rate to PSA, then, one would not really think they would influence survival since you are not seeing much objective evidence of anti-tumor effect?

DR. SLICHENMYER: Dr. Eisenberger, would you like to address that?

DR. EISENBERGER: You are correct. We are not going to be able to resolve that, of course. I mean your concern is that the response or the evaluation of crossover was not completely done, is that correct, in terms of frank survival? What was your question, Bob? I am sorry.

DR. OZOLS: I think you had a response rate, a PSA response rate of 50 percent almost to suramin, and the initial 14, I think, percent were 75 percent greater, and 32 percent were 50 percent greater, and then if you randomized to placebo and you crossed over, your response rate dropped to 14 percent. Why would that be?

DR. EISENBERGER: Well, I think that these patients obviously -- first of all, there are data prior to this trial that show that patients that progress on the

corticosteroids will have a much lower response rate compared to those that were treated with suramin and hydrocortisone upfront, so this is not inconsistent data.

Remember these are end-stage patients, these are patients who have a very limited survival, and by the end, by the time that they cross over, some with a median of somewhere around maybe 12 weeks or so, they are really very end stage, unfortunately. At that stage, I think it is unreasonable to expect a major therapeutic effect from one therapeutic modality.

I think you are correct, however. I mean we cannot assess the survival, but there is room for skepticism, but we have not chosen survival as an endpoint in this patient population. We think that if we would choose survival as an endpoint, it would be a different patient population than the one that was chosen here.

DR. RAGHAVAN: It is a relatively short time, and the other hypothesis that is equally reasonable is that that group has already seen the steroids, and they are not getting that benefit the second time around.

DR. DUTCHER: We are going to take a break. We will come back at 11:15 for the FDA presentation. If there is anyone in the audience that plans to speak at the open public hearing this afternoon, could you please let us know beforehand.

[Recess.]

DR. DUTCHER: We would like to proceed with the FDA presentation.

Dr. Chiao.

FDA Presentation

DR. CHIAO: Good morning, ladies and gentlemen, members of the ODAC Committee, it is my pleasure to present the FDA review of New Drug Application of Metaret, also known as suramin.

[Slide.]

The applicant, Parke-Davis, is seeking marketing approval of suramin to be used with hydrocortisone for the treatment of hormone-refractory prostate cancer.

[Slide.]

Review of the NDA is a team effort. This slide lists the members of the FDA team who participated in this NDA review.

[Slide.]

This slide shows the outline of my presentation.

[Slide.]

The combination of suramin plus hydrocortisone is proposed as chemotherapy for the treatment of patients with hormone-refractory prostate cancer. The Agency met with Parke-Davis in August 1993 to discuss the development plan for suramin. The proposed basis for marketing approval of

suramin for the treatment of hormone-refractory prostate cancer is shown on this slide.

FDA stated that suramin treatment should result in a clinically meaningful improvement in cancer-related pain, performance status, and some measure of objective tumor response.

In addition, federal regulations require that marketing approval be based on the results of two or more well-controlled clinical trials except in instances where results are dramatic and convincing.

[Slide.]

Clinical studies submitted in this NDA include one pivotal trial, one Phase II supportive trial, and two pharmacokinetic studies in patients with renal dysfunction or patients taking warfarin.

[Slide.]

Pivotal trial 1003-001 is a randomized, double-blind, placebo-controlled study. Patients were randomized to receive suramin plus hydrocortisone or placebo plus hydrocortisone. The primary efficacy endpoints are reduction in pain, narcotic analgesic use, and improvement in performance status.

The study is powered to show treatment differences using a two-sided T test at a 5 percent level of significance. Treatment differences, defined in the

original protocol, are as follows - a two-point difference between treatment arms in the mean changes from baseline in nightly worst pain scores, 20 percent improvement of pain symptoms over anticipated 38 percent improvement with hydrocortisone alone, although the definition of pain improvement is not specified in the original protocol.

Also, the study is powered to show a difference between treatment groups of 15 percent in the rates of patients who had decrease in their PSA level by 50 percent or more, and the difference between treatment groups of 20 percent in the measurable disease response rate from 16 percent on placebo to 36 percent on suramin given there was about a 45 percent incidence of measurable disease.

An interim analysis was performed after 50 percent of patients completed double-blind treatment. The purpose of the interim analysis was to rule out the possibility of such negative or positive results that the study should be stopped.

Many changes were made in the inferential analysis plan after the study was closed. I will go over these changes in the next six slides.

[Slide.]

The first patient received study treatment on February 14, 1994, and the last patient received the last study treatment on March 14, 1997. The protocol was last

amended on February 12, 1996. The pain responder analysis was not in the final amended protocol, and was added one year later after the interim analysis and after the study was closed.

Amendment one to the inferential analysis plan, dated April 1, 1997, which was submitted NDA, stated that pain responder analysis will be repositioned as secondary, consequently, a positive pain responder analysis will not be a sufficient condition for when on pain.

[Slide.]

On July 18, 1997, the Agency met with Parke-Davis for pre-NDA meeting. In the meeting package from Parke-Davis, the pain response rate on suramin arm was 30.7 percent and that on the placebo arm was 24.4 percent with p equals 0.125, which is not statistically significant.

The Agency was later informed that an error was found in entering doses of narcotic analgesics in the data set. After data set was corrected, pain response on the suramin arm is 43 percent compared to 28 percent on the placebo arm, with p equals 0.001, which is highly significant.

Pain responder analysis was changed to be one of the two primary analysis in NDA submitted on December 29, 1997, however, in the ODAC briefing document, the pain responder analysis is once again considered a secondary

analysis.

[Slide.]

I will now briefly mention other changes to the inferential analysis plan. Pain response criteria was retrospectively established after the study was closed. Initially, either a 25 percent or 33 percent decrease in narcotic analgesic use was considered clinically significant. A week later, the pain response criteria was changed.

[Slide.]

Time to pain progression underwent the most recent change four weeks ago. Initially, only one single assessment meeting pain progression criteria, shown here, was sufficient to declare a patient progressed. In two assessment meetings, slightly different progression criteria are required. This change resulted in an increase of 260 days in time to pain progression on the suramin arm, and an increase of 34 days on the placebo arm.

[Slide.]

PSA response criteria was also changed after the study was closed as indicated on this slide.

[Slide.]

This slide summarizes the changes made in the inferential analysis plan after the study was closed. Two new efficacy endpoints and four new analyses were added, two

criteria and one analysis were changed.

[Slide.]

I will now discuss the efficacy results of the pivotal trial 1003-001. Because of the specific toxicities of suramin, a question now is constructed to assess the integrity of the study blind. Patients and physicians were asked to guess the treatment a patient received.

The results showed that the majority of patients on the suramin arm guessed their treatment correctly. Physicians administering either suramin or placebo could guess the treatment correctly most of the time.

[Slide.]

There were 132 patients who did not meet the eligibility criteria. Most of these patients did not meet the laboratory criteria. Ten patients stopped flutamide, casodex, or cytadren less than 28 days prior to the start of the study medication. Four of these patients were on the suramin arm, and five were on placebo arm. One of these four patients on suramin arm and two out of these five patients on placebo arm achieved pain response.

Six patients did not undergo orchiectomy or receive hormonal therapy according to the database submitted. Five of these patients were on the suramin arm and one on placebo arm. Two out of these five patients on suramin arm achieved pain response.

Other ineligible patients had missing baseline KPS, PSA, or violated other eligibility criteria.

[Slide.]

Baseline characteristics are comparable between the two treatment arms except that there were more patients who did not receive medical hormonal therapy on the suramin arm compared to those on the placebo arm. About 50 percent of the patients on both arms had only mild pain at study entrance or required less than 50 mg/day morphine equivalent narcotic analgesics.

[Slide.]

Eligible patients must have disease progression defined as worsening pain, new lesions, increasing measurable disease, or new tumor-related symptoms in order to enter the study. This slide shows the distribution of the type of disease progression at study entrance for the double-blind phase and at crossover.

About 70 percent of the patients had tumor progression, about 30 percent of patients had nuance of pain or worsening pain requiring increasing amount of narcotic analgesics.

[Slide.]

Primary efficacy endpoint prospectively defined in the protocol are changes relative to baseline in pain score, narcotic analgesic use, and performance status. Rank sum

and analysis of covariance, also known as ANCOVA, were the statistic analysis tests performed to analyze the data at week 6 and at the end of the treatment.

The last observation carry-forward techniques were used to capture data from patients who dropped out from the study prior to week 6 or the end of treatment. Whether the last observation of the dropout patient is a true representation of the patient's pain status and narcotic use at two future time points is questionable.

Also, results from rank sum and ANCOVA are difficult to interpret clinically. Differences in two treatment arms at week 6 and end of treatment may be statistically significant, but is not clinically meaningful.

[Slide.]

For example, ANCOVA of changes from baseline in nightly worst pain showed a one point decrease in pain in the suramin group compared to 0.6 or 0.2 eight-point drop in pain in the placebo group with a highly significant p-value less than 0.05.

What is the clinical significance of one-point drop in pain score out of an 11-point pain scale?

[Slide.]

Pain responder analysis was retrospectively defined after the study was completed. To meet the pain response criteria, patients generally need to have a drop of

three points in pain score with stable or decreased narcotic use or a 33 percent drop in narcotic use with stable or decreased pain.

A patient must meet the response criteria for two weeks. The third week does not have to meet the criteria if the average of three weeks meets the response criteria.

The overall pain response rate for the suramin arm is 42 percent and that for the placebo arm is 28 percent with p equals 0.003. Twenty percent of patients on suramin arm compared to 13 on the placebo arm achieved pain response based on reduction in pain with p equals 0.03.

Some of these patients also met the 33 percent drop in narcotic analgesics criteria; 22 percent of patients on suramin arm compared to 16 percent on the placebo arm did not have a three-point drop in the pain, but had 33 percent drop in narcotic use. P-value for response based on reduction in narcotic use only is not statistically significant, at 0.12.

173 patients from the placebo group crossed over to receive open-label suramin according to the most recent updated database submitted by the applicant; 18 percent of these patients achieved pain response, 5 percent with a three point or more reduction in pain, and 13 percent with 33 percent or more decrease in narcotic analgesic use.

[Slide.]

Duration of pain response is greater than 240 days in the suramin group, compared to 84 days in placebo group, with p equals 0.02. About 70 percent of responders on suramin arm and 70 percent of the responders on placebo arm were censored at the last available pain and narcotic scores. Response duration in crossover group is greater than 62 percent. A significant number of pain responders on the crossover group were also censored.

Pain progression is defined as a two-point increase in pain or 15 percent increase in narcotic use over baseline. In the NDA, one single assessment meeting pain progression criteria is sufficient. Now, two assessments at one week apart are required. This change resulted in an increase of 169 days in time to pain progression on the suramin arm and an increase of 20 days on the placebo arm according to our analyses.

[Slide.]

Improvement in patient performance status measured by the Revised Rand Functional Limitation Scale, also known as RRFLS, was prospectively defined as one of the primary efficacy endpoints. ANCOVA analysis of RRFLS showed no improvement in patient who received suramin compared to patient who received placebo.

I should also mention that our FDA statistician, Dr. Takeuchi and his colleagues have performed time trend

analysis of RRFL scores. According to their analysis, the RRFL scores are worse in the group of patients treated with suramin compared to those treated with placebo.

Quality of life was a secondary endpoint and was measured by the Functional Assessment of Cancer Therapy-General. There was no improvement in quality of life in patients treated with suramin and also the time trend analysis, known as longitudinal analysis, showed that those scores are worse in patients treated with suramin.

[Slide.]

This slide shows some of the secondary efficacy endpoints - 33.8 percent of patients on the suramin arm achieved greater than 50 percent decrease in their PSA values compared to 17.4 percent on the placebo arm with p less than 0.001.

Seventy-six patients on the suramin arm had measurable disease and 3 out of 76 patients achieved a partial response with the response rate of 3.9 percent. No response was observed on the placebo arm.

Comparison of survival on the two arms may be confounded by the crossover design. As listed here, the survival on the suramin arm was 279 days, and the survival on the placebo arm, including the crossover patients, is 302 days, and a separate analysis on the patients who crossed over to receive open-label suramin showed a survival of 173

days.

FDA has performed time to objective tumor progression using imaging studies and findings from physical examinations. We used the tumor progression criteria in the disease progression definition in a protocol. Specifically objective tumor progression refers to new lesions, spinal cord compression, urinary tract obstruction, or increase of more than 25 percent in a measurable disease.

Patients who had no baseline and follow-up studies were excluded from the analysis. Thirty-five patients on the suramin arm and 25 patients on the placebo arm were thus excluded from the analysis. There is no difference in time to objective tumor progression between the two treatment arms.

[Slide.]

In the ODAC briefing document from Parke-Davis, objective tumor progression free survival was added as a new analysis. Depending on how the crossover patients were handled, objective tumor progression free survival can be either statistically significant or statistically insignificant between the two treatment groups.

First, if patients without baseline or follow-up imaging studies in the placebo group are treated as progressed at the time of crossover, progression free survival is slightly longer on the suramin arm compared to

placebo arm with p equals 0.014.

Second, if the same group of patients were censored at the time of crossover, there is no statistic difference in the progression free survival between the two treatment arms.

Third, if the same group of patients we used death as progression and as an event, there is no statistic difference in the progression free survival between the two treatment arms.

[Slide.]

This is the Kaplan-Meier curves of progression free survival when the crossover is treated as an event, and the p-value is 0.014.

[Slide.]

This is the Kaplan-Meier curve when crossover is censored and with a p-value greater than 0.05, which is statistically insignificant.

[Slide.]

This is the progression free survival when death was counted as progression with a p-value greater than 0.05, again is statistically insignificant.

[Slide.]

We have performed a Fisher's exact test on a subgroup analysis that was submitted in the NDA, and you have seen this slide from the applicant, the presentations,

earlier this morning. This is pain responder rates by baseline pain and narcotic scores.

On the 11-point pain scale, pain of less than 4 points is considered mild pain. Pain of 5 to 6 points is considered moderate pain. Pain of 7 or more points is considered severe pain.

A statistically significant difference in pain response rate is found only in the subgroup of patients with mild pain or who take less than 50 mg morphine equivalent narcotics per day. This finding is confirmed by time trend analysis, also known as longitudinal analysis.

[Slide.]

I will now discuss the safety results from the pivotal trial. There are more patients who withdrew from the treatment or refused treatment on the suramin arm compared to those on the placebo arm. Similar observations are found in patients who crossed over to receive open-label suramin.

[Slide.]

There are 16 deaths attributed to adverse events, 13 of these 16 deaths occurred in patients who received suramin either during double-blind phase or after crossover. Cardiovascular events, such as MI, cardiac arrest, congestive heart failure, and respiratory insufficiency are the most common causes of death. Two patients on the

suramin arm died of encephalopathy and coma.

[Slide.]

More patients on the suramin arm suffered Grade 3 or 4 adverse events compared to those on the placebo arm according to the database submitted by the applicant. Similar incidence of Grade 3 or 4 adverse events is observed on the crossover patients.

[Slide.]

Specific types of Grade 3 and 4 adverse events are listed on this slide. Except constipation, patients on the suramin arm had a higher incidence of Grade 3 or 4 adverse events than patients on the placebo arm.

[Slide.]

This concludes the discussion on the pivotal trial 1003-001. I will now briefly mention the supportive studies.

Phase II trial 1003-901 included 40 hormone-refractory prostate cancer patients treated with suramin using the fixed dose schedule. The objective of this study is to characterize the safety and efficacy associated with different targeted plasma concentrations of suramin using two different dosing schedules.

Efficacy evaluations were based on measurable disease response, PSA response, progression and survival. Pain response was evaluated retrospectively by extracting

data from medical records. Because of the different study objectives and efficacy endpoints, this study cannot support the pivotal trials in the endpoints of pain, narcotic use, and performance status.

The regimen also contains two active drugs, suramin and hydrocortisone, and the contribution of suramin cannot be assured. Incidence of Grade 3 and 4 adverse events is 83 and 47.6 respectively according to the database submitted.

Study 1003-002 and Study 1003-003 are pharmacokinetic studies in patients with renal dysfunction who are taking warfarin. I will not go into details at this moment.

[Slide.]

In November 1996, the Agency approved the combination of mitoxantrone plus prednisone for the treatment of patients with pain related to advanced hormone-refractory prostate cancer. Approval is based on significantly higher pain response rate, pain response duration, and time to progression among patients who received mitoxantrone plus prednisone compared to those who received prednisone alone in a randomized trial.

This slide shows the efficacy results of the mitoxantrone pivotal trial. The primary criterion for pain response is a two-point drop in pain on a six-point scale

maintained for six weeks with stable or decreased dose of analgesics. Twenty-nine percent of patients on the mitoxantrone arm met this criteria compared to 12 percent on the prednisone-alone arm with p equals 0.01.

The second criteria for pain response is a 50 percent or more decrease in analgesic score. Nine percent of patients on both arms met the second criteria for pain response. Pain response duration is 168 days on mitoxantrone arm compared to 57 days on the prednisone-alone arm with p equals 0.0004.

Time to progression, which included pain or tumor progression, is significantly longer for patients on mitoxantrone arm compared to those on prednisone-alone arm.

[Slide.]

This slide listed the pain responder analysis of suramin pivotal trial. Time to disease progression in the suramin trial included progression due to tumor, pain, and deterioration in performance status measured by the RRFLS.

[Slide.]

This slide shows the safety profiles of mitoxantrone and suramin. The toxicity criteria used in mitoxantrone trial is the WHO criteria, and the one used in the suramin trial is the COGB expanded toxicity criteria.

[Slide.]

The next few slides listed the differences in

study design and definition of endpoints from the mitoxantrone and suramin pivotal trials. The mitoxantrone trial is an open-label study, while suramin trial is a double-blind, placebo-controlled study.

Only patients with pain were eligible for the mitoxantrone trial. Patients without pain were eligible for the suramin trial if they are taking scheduled doses of narcotics. Eligible patients are not required to take narcotics on the mitoxantrone trial.

[Slide.]

Pain response criteria is prospectively defined in the mitoxantrone trial, but is retrospectively defined in the suramin trial. Different pain scale were used. Mitoxantrone trial required a pain response last at least six weeks, where the suramin trial required a pain response last three weeks.

[Slide.]

Pain progression criteria is prospectively defined in the mitoxantrone trial, but is retrospectively defined in the suramin trial. Increasing pain or analgesic use were assessed over the lowest score in the mitoxantrone trial, and those were assessed over the baseline score in the suramin trial.

[Slide.]

This concludes my presentation on the FDA review

of the New Drug Application of Metaret, also known as suramin.

In summary, suramin plus hydrocortisone treatment resulted in a modest decrease in pain and narcotic analgesic use in one large randomized controlled trial. Subgroup analysis showed benefit in patients with mild pain or daily narcotic requirement less than 50 mg.

No improvement of performance status or quality of life was observed. There is a non-negligible risk for severe side effects and death in patients who received suramin plus hydrocortisone compared to those who received placebo plus hydrocortisone.

Thank you for your attention. I will be happy to answer any questions.

Questions from the Committee

DR. DUTCHER: Questions for the FDA review? Dr. Ozols.

DR. OZOLS: You said that not only there are no improvement in quality of life, I think earlier you said that there actually was a decrease in quality of life for patients on suramin.

DR. CHIAO: That is correct. Actually, the statistician in our division did the time trend analysis of RRFL scores and FACT-G-general scores, and both these scores showed for the patients who stayed to the end of treatment,

there is a decrease in their performance status and a worsening in their FACT-G scores.

DR. OZOLS: One of the main points that came out of the sponsor's presentation was the sort of dramatic time to pain progression for the suramin, of 353 days, and the placebo, of 78 days. You are saying at least part of that 160 days was due to a retrospective change in how they defined time to pain progression?

DR. CHIAO: Well, I think that by requiring two assessments instead of one and also by requiring greater but not equal to two-point increase, and greater but not equal to 15 percent increase in analgesic use has significantly changed the time to pain progression.

DR. DUTCHER: Other questions? Dr. Raghavan.

DR. RAGHAVAN: I wonder if you could address one of the questions that I posed to the sponsor from having had intimate exposure to their data.

Can you give us a handle on the sustained palliation that is afforded by suramin, what sort of proportion of patients do you think actually get sustained benefit that would translate into something that would make them want to buy the product, as it were?

DR. CHIAO: I can give you some information on the duration of pain response divided into who has less than 21 days of response duration and who has less than 28 days, and

who has less than 42 days, and I think about -- I will try to remember -- about two or three patients on suramin that has less than 21 days in response duration compared to about two patients on placebo arm, and I think about 15 of those on suramin compared to 13 had less than 28 days' response duration, 27 compared to like 20 or something on placebo had less than 42 days in pain response.

DR. DUTCHER: Dr. Simon.

DR. SIMON: Could you clarify -- you went over it pretty quickly, this is follow-up on Dr. Ozols' question -- could you clarify the changes in the definition of duration of pain response and when these changes were made and whether they were made after the data were unblinded or before?

DR. CHIAO: You are talking about the pain response criteria?

DR. SIMON: Yes, the duration of pain response.

DR. CHIAO: I don't think duration of pain response was changed. I think the time to pain progression is changed, and that was changed about four weeks prior to the ODAC meeting. I think the first time we saw that was in ODAC briefing document.

DR. SIMON: Well, if you analyze it the way it was defined presumably beforehand in the protocol, what do you get?

DR. CHIAO: Time to pain progression analyzed to the criteria that was submitted in the NDA is 99 days on the suramin arm compared to 44 days on the placebo arm with p equals 0.003.

DR. SIMON: So, if you analyze it as it was defined in the protocol --

DR. CHIAO: It is not defined in the protocol, it is defined in the NDA, because that time to pain progression was not defined in the protocol, it was retrospectively added.

DR. SIMON: So, you are saying the change came after the NDA was submitted?

DR. CHIAO: That is correct.

DR. SIMON: But if you analyze it as -- well, was there ever any definition of time to pain progression defined before the data was collected?

DR. CHIAO: There is a definition of time to disease progression in the protocol.

DR. SIMON: No, but pain progression.

DR. CHIAO: I don't think so. Maybe the applicant wants to comment on that.

DR. SLICHENMYER: Time to pain progression was strictly a retrospective endpoint, and as was mentioned in our presentation, it was conducted in an effort to try to validate the duration of response seen in the pain

responders, concerned about the possibility that that duration of pain response might only apply to a subset, so the time to pain progression was performed on an intent-to-treat basis to test the robustness of that durability effect.

DR. DUTCHER: And you said in your presentation that those points were defined before you unblinded the study, is that correct?

DR. SLICHENMYER: Not this particular one. Time to pain progression was a strictly retrospective analysis, an ad-hoc analysis, and it was changed as Dr. Chiao points out, but it might be useful for you to understand the reason why it was changed.

After the first time to pain progression analysis was conducted and the results were sent to the Agency, it was pointed out to us that 29 patients who had been found to be pain progressers based on the original definition, later went on to have a pain response, suggesting that the initial criterion for pain progression was not sufficiently strict.

So, the definition was then changed. The criterion level remained the same, but what changed was we went from requiring a single measurement above the threshold to then requiring, in the modified criteria, two consecutive measures above the threshold.

That then is the modified analysis which you have

heard about, a change that we felt was one that made the criteria more conservative and more rigorous, and as you have seen, it also turned out that the results suggested a greater difference between the treatment groups.

DR. SIMON: The other part of my question for clarification. In one of your slides, you have 7-18-97, pre-NDA meeting. This is on pain responder analysis. Suramin arm 30.7 percent, placebo arm 24.4 percent, p equals 0.125.

Could you clarify how that pain responder analysis compares to what was presented?

DR. CHIAO: As I mentioned, this is the information that we received from the meeting package, and we received a letter, as a matter of fact afterwards, stating there was a mistake made in the data set in terms of entering the narcotic dose, and I think that the numbers that we saw in the NDA submission reflected the correction of the database.

DR. SLICHENMYER: Maybe just to clarify the nature of the error that was discovered, in the case report forms, the data that were entered for patients whose narcotic use went to zero, in some cases it was entered as the word "none." The data entry people, seeing the word "none," interpreted that to mean that the data were missing, and so entered into the database that these were missing data.

Later, that misinterpretation was recognized and corrected, and what had been considered missing data were changed to zeros, and of course, zero narcotic use is a very important finding in this trial. So, it was not that we changed the data, it was correction of a misunderstanding and a miscommunication.

DR. DUTCHER: Before you sit down, when you said you did the second endpoint in the second assessment of pain evaluation, were you able to determine that that late improvement, even if the first point had shown progression of pain and then there was a later improvement, is that what you said occurred in some cases, was not due to analgesic changes?

DR. SLICHENMYER: Patients had their narcotics modified on an ad-lib basis. The change in the time to pain progression criteria simply came about because of the observation that it appeared inconsistent that some subjects would first be pain progressers and then later pain responders.

What it indicated was that there was some random variation in their net pain and narcotic measurements, and by requiring two consecutive measurements, that limited the impact of that variability.

DR. DUTCHER: Dr. Schilsky.

DR. SCHILSKY: Can I just follow up on that a

little bit further because I must say that during the sponsor's presentation, the thing that impressed me the most was the time to pain progression, and my sort of confidence has been shaken by the FDA analysis.

The requirement for two consecutive demonstrations of progression in order to qualify as a progresser, then, is also going to be influenced, I would assume, by the completeness of the data.

So, what I am concerned about is the impact of potentially missing data points on that analysis. Maybe you can just clarify, either one of you, how this was actually done.

Let's just say for the sake of discussion that at week 6, someone meets the criteria for pain progression, and at week 7, they again meet the criteria, so that person would be considered a progresser by virtue of having two consecutive qualifications.

However, if they meet the criteria at week 6, and at week 7 the data is missing, then, they presumably would not qualify as a progresser. Would you then have to wait until another point in time, maybe four months later, when they have two consecutive points at which there is clear pain progression before qualifying them as a progresser? How is missing data handled in these analyses?

DR. CHIAO: The way that we did it is that

according to the submitted information, if you have a single progression at the end of therapy, that is sufficient, say, like at day 78, after the double-blind phase, only one assessment meeting the pain progression criteria, and the patient is progressed.

If you have one assessment during a follow-up phase, because patients were assessed infrequently, every three months, one assessment is sufficient, you don't need two assessments. So, I think those two consecutive assessments only apply probably during the double-blind phase.

DR. SLICHENMYER: If I may just add, in our handling of the data, if a measurement was missing and would have been required to make the second consecutive measurement above the threshold, a subject could be considered a progresser based on one abnormal and one missing.

DR. DUTCHER: Dr. Margolin.

DR. MARGOLIN: I have two questions about how you interpreted some of the data and reported them to us. It was quite a whirlwind tour.

First of all, there were quite a number of ineligibles based on mostly missing baseline data. Presumably, they fell equally into the two groups, and it didn't seem to bother your analysis too much.

DR. CHIAO: Yes, correct.

DR. MARGOLIN: So, that is reassuring that most of those were really what we might call minor violations. Were the rest of the data for the follow-up equally good or bad depending on how you interpret that? In other words, were the biggest infractions really minor violations in terms of missing laboratory data in your mind?

DR. CHIAO: We did not specifically look into the missing laboratory data issue except that the study entry time point. We only looked at the data at the study entry time point. We didn't look over all the laboratory data set to see who are missing during a follow-up phase.

DR. MARGOLIN: I would think that would influence your adverse event and toxicity reporting, if anything, and that might be important.

DR. CHIAO: It could be.

DR. MARGOLIN: The second question I have is regarding in your handout about some of the questions to the committee. Some of the p-values in the charts don't seem to go with the actual numbers.

Can we assume that that is based on what the sponsor said earlier, that these numbers refer to medians and that the p-values refer to hazard ratios, the difference between hazard ratios?

For example, at the bottom of your first table,

time to tumor progression, median 86 and 85 days with a p-value of 0.06 doesn't seem to make sense unless you are using that p-value to look at something that really differed.

DR. CHIAO: The curve looks kind of funny because it is bulging on both parts and does meet at the middle, and we struggled with that, and we don't really have a good explanation for this phenomena, but it is sort of meets in the middle.

DR. MARGOLIN: So, that does explain those funny numbers.

DR. CHIAO: I think so. I think that is probably the most likely explanation.

DR. DUTCHER: Dr. Simon.

DR. SIMON: Two questions. We are talking about missing data, baseline data. These were pain assessments?

DR. CHIAO: Right. There is some patients who did not have baseline pain score narcotics, and we can't evaluate them for pain response.

DR. SIMON: What percentage were those?

DR. CHIAO: I think it was in my draft review I listed them under the study execution section. Let me see if I can find it here.

DR. SLICHENMYER: Dr. Simon, our data indicate that missing baseline data were present for less than about

2 percent of the patients, and some of the data that we showed early on -- I guess we didn't show the slides in the presentation -- we have some back-up slides that show you that. It is roughly 216 out of the 228 that had data at baseline.

DR. SIMON: The other part of my question is did the FDA do any kind of a longitudinal analysis of time to pain progression? I mean that seems to be kind of a key thing here. One the one hand, we are saying if you require two instances before you call it progression, then, there may be a missing data problem, if you use only one, that it may not be meaningful because what you see in one may reverse in the next, and I am just wondering, was there any kind of an analysis done that tried to get at the durability of pain control in a longitudinal type of analysis by the FDA?

DR. CHIAO: I don't think we performed longitudinal analysis on time to pain progression.

DR. JUSTICE: Before Dr. Takeuchi answers, Karen, do we have that overhead projector?

DR. SIMON: The reason I ask it is when you talk about time to pain progression, the thing that bothers me about it is that you are censoring huge numbers of patients whose tumors are progressing, and so you have a very biased sort of set of patients, it looks to me like, because if you

look at the curves of time to tumor progression, these curves stay up very high, but if we look at the overall time to tumor progression, the curves are dropping down, so the tails of these curves are being dominated by very small numbers of patients, and most of the patients are going off study because of tumor progression or adverse events.

DR. CHIAO: That is actually correct because, as I understand, once they progress, the tumor progress, the pain scores and narcotic scores are not collected.

DR. SIMON: So those patients are censored in these Kaplan-Meier curves, and that raises an issue of is that analysis valid.

DR. CHIAO: As I mentioned, I think it is about 70 percent of patients were censored on both arms.

DR. TAKEUCHI: My name is Masa Takeuchi from Biometrics.

I would like to explain a little bit about this may not be equivalent to Dr. Simon's question, but I wanted to make sure what kind of data we are talking about for the pain score.

[Slide.]

This all the data points I have for that. That is suramin.

[Slide.]

This is placebo.

[Slide.]

So, the question comes is, there any difference within this data, if there is, find it. As you know, pain score is measured over time, a couple of times, and as Dr. Simon mentioned, by the end of the double-blind, more than 75 patients are dropout, and also the question comes, is there any difference between dropouts and completers, the time trend is different, especially in the pain scores.

We are very interested in the baseline scores on the pain score, and if we analyze for the patient who had minor pain, this is almost 50 percent of patients, categorized in this direction, and people who drop out before six weeks. This line is suramin groups, and that line is placebo groups.

Both patients, pain score is increasing until dropout, but for the patients who could stay longer in the study, those pain scores is decreasing in the suramin groups but just stay the same in the placebo groups. But this is statistically significant. That means that is good.

[Slide.]

How about the patient who has a high pain score at the baselines? In this case, placebo groups, pain score just stayed until they drop out, but the patient in the suramin groups, pain score is decreasing, so this is good, but still, placebo patients who could stay longer beyond six

weeks, pain score also decreasing, so the question comes how about narcotic scores along with this.

[Slide.]

This is narcotic analgesic consumptions, so people who could drop out before six weeks, baseline pain scores, for example, those narcotic score is increasing with pain increasing, but for the suramin groups, for this group, pain was decreasing in addition to the decreasing of narcotic scores. That is good, but placebo groups, pain stay the same, and narcotic use stay the same.

[Slide.]

How about the patient with high pain scores at the baselines? This suramin group, pain scores decreasing, but narcotic scores increasing, so pain decreasing may be due to this narcotic use, we don't know, but other narcotic uses does not change over the time.

[Slide.]

The question comes how about RRFLS. For this patient with low pain score at the baselines, pain is increasing, analgesic consumption is increasing, also RRFLS is increasing. That means no good. But for the suramin groups, pain is decreasing over the time, and analgesic consumption is decreasing over the time, and RRFLS is decreasing over the time, so these patients can get a benefit from this.

[Slide.]

For this group with high pain score at the baselines, RRFLS just stays the same, but slightly placebo groups, RRFLS score is decreasing compared to the suramin groups. That means placebo patient has a benefit for this RRFLS scores.

[Slide.]

So, in the bottom lines, I confirm Judy's result. For the pain score, if patient can stay longer in the study, let's say after six weeks, with a very low pain score, this patient has pain decreasing, analgesic consumption is decreasing, also RRFL score is decreasing. That means everything goes together, but for the other groups, some has yes, some has no, so I am not sure what kind of a benefit suramin has.

So, this group truly has a benefit.

DR. DUTCHER: Thank you. Any further questions for FDA? Thank you both.

Committee Discussion and Vote

DR. DUTCHER: Discussion? Comment? Dr. Albain.

DR. ALBAIN: Can we ask other questions to the sponsor at this stage, Dr. Dutcher?

DR. DUTCHER: If they are brief.

DR. ALBAIN: One brief question.

I was wondering if you had any data on what was

given to these patients after the 13 weeks? For example, mitoxantrone, what happened after this fixed treatment schedule ended, and might that perhaps explain some of these differences?

DR. SLICHENMYER: Other anti-tumor agents were not supposed to be administered to the patients while they were on the study. Some of our Kaplan-Meier analyses have had patients censored at the time of other intervening therapies, such as radiopharmaceuticals, new hormonal agents, or some other agents that might be thought to modify the natural history of the disease, but other anti-tumor agents were not permitted.

DR. ALBAIN: How many patients were such censored?

DR. SLICHENMYER: It was relatively small, less than a dozen in each treatment group.

DR. DUTCHER: Any comments or do you want to go directly to questions? Okay.

The first question. Study 1003-001 is a randomized, controlled trial comparing the combination of Metaret (suramin) plus hydrocortisone with placebo plus hydrocortisone in patients with hormone-refractory prostate cancer. Primary endpoints are reduction in pain, narcotic analgesic use, and improvement in performance status. Efficacy results are shown in the following tables.

I will give you a moment to review the tables.

As we have discussed, the shaded areas in the above tables indicate that many of the reported efficacy endpoints were not in the protocol and/or the criteria for the endpoints were changed after the study was completed, and I think we have gone through which ones were prospective or retrospective.

In view of this, does the committee have confidence in the credibility of the study results?

Dr. Simon, do you want to make a couple of comments about prospective/retrospective from what you have heard?

DR. SIMON: Well, in terms of the credibility, I guess my only concerns, I think it was a very good clinical trial, at least compared to other trials that have been done at this stage of disease, but my concerns here are, one, I think there are lots of ways of defining endpoints and lots of potential variance on endpoints, and it is really important to have the definitions of the important endpoints before you collect the data, and when you sort of define your endpoints, even with the best of intentions, after collecting and decoding the data, I think it loses credibility.

The only other aspect of it is an aspect of it, what effect the fact that patients were aware of their PSA values and because of the toxicities of suramin, most of

them on suramin at least knew that they were on suramin, whether that had enough of an effect on potential self-assessment of pain that the relatively small differences we are seeing, at least a substantial part of that, may be due to them.

I don't know how to answer that kind of question yes or no.

DR. DUTCHER: I think perhaps a discussion is more appropriate than a yes or no vote.

Any other comments about concerns? Dr. Raghavan.

DR. RAGHAVAN: Well, I think my perspective, I think was somewhat similar to the one that Dr. Schilsky expressed. I thought that the duration of pain response was an important issue, and started out, having read the data, thinking there wasn't a big difference, listened to the presentation and thought that I had misunderstood the data, and then heard the FDA presentation and came back to my original position, which comes back to the issue of statistical significance and clinical relevance.

I keep getting trapped at the point where this is a disease that runs for many months and it doesn't seem, as I judge it from hearing the various presentations, the lack of counterpoint from the sponsor, it doesn't seem that there has been a substantial disagreement with the FDA analysis.

So, I think the way the question is framed is

difficult because it is a good study and it is demeaning to a good study to say that you don't find the results credible, and I guess what it comes down to is the interpretation of the data as presented. That is difficult to deal with.

DR. SIMON: To me, I guess the analysis that I have the most confidence in is the -- I think it is called the failure free survival analysis where essentially any bad thing that happens like death, progression of disease, adverse event, at least those bad things that happen are all considered endpoints, and I guess one could also do that analysis with a significant increase in analgesic requirements or pain score causing an event and then say, okay, given all of the bad things that can happen, and does suramin delay that time to event.

I think that was -- I don't remember offhand the figure number -- I guess it's figure 12 on page 56 of the sponsor's presentation, and there is a very small difference between the suramin group and the other group in that failure free survival analysis. I guess I view that as sort of the most reliable sort of analysis.

I guess some of that effect, this includes subjective progression which I guess could potentially include pain increases, so part of this may be biased, but it may be that there is a small effect that may be real.

DR. DUTCHER: I think our assessment is that we have confidence in the study and the data as presented. It seems that there is some interpretations that can be different depending on who is looking at the information and how we are looking at it. Is that fair to say? Is that sufficient feedback? Okay.

No. 2. Do the pain response criteria in the randomized, controlled trial assure that a patient with a pain response has a clinically meaningful benefit?

Does anybody want to tackle that? Mr. Anderson.

MR. ANDERSON: As perhaps the only layman in this group of very learned people, did I understand correctly that after all is said and done, the only people that get any pain relief are the ones in the low pain category? That is what I heard you say?

Well, that is disappointing, I will put it that way. It would seem to me that if this drug has a significant impact on pain reduction, that people at a high pain level would certainly have a dramatic reaction to this drug. That concerns me that the only reaction we got was to the people with a low pain which you can talk yourself out of, if that is possible.

DR. REYNO: May I make a comment?

DR. DUTCHER: You may make one comment, sure.

DR. REYNO: Just a comment that I would be the

first to admit that the data to both lay people and physicians alike are difficult to interpret, but in interpreting it, I would ask that we all think about what this pain is.

This is chronic and persistent pain occurring in a patient population with relentlessly progressive disease. It is not known to undergo spontaneous remissions, at least certainly not curable ones, and so while I would admit that it looks that way, I think that it is much more difficult data to interpret.

The other issue is that the median survival of these patients even without therapy may certainly be measured in many months, and certainly the pain literature and the effects of chronic uncontrolled pain is substantial on the patient and the health care system.

So, I think we have to be careful that we apply with rigor our analysis to the data, but at the same time recognize that it is difficult data to interpret.

DR. DUTCHER: Carolyn.

MS. BEAMAN: At the same time, the side effects that I heard mentioned and that are listed, certainly do not far outweigh a day or two of benefit. The reduced pain response for any notable period of time is certainly beneficial, however, the pain response criteria is simply not clear and the tumor growth appears to me to be

progressive. Would someone clarify that if that is not the case?

So, you have a small number of people with the type of pain that probably can be, as you say, talk yourself out of, plus tumor progression, and the horrendous side effects for a relatively short period of time. I am just very concerned about quality of life when it comes to that.

DR. CHIAO: Well, I can help the time to tumor progression if that is helpful, because our analysis for time to tumor progression shows not much of difference between the two treatment arms, strictly talking about tumor. We did not include the analysis of pain or performance or quality of life.

DR. DUTCHER: Dr. Albain.

DR. ALBAIN: Going back to the question Dr. Raghavan asked two different times, I think, I still don't have a good sense of how many patients were like the moving testimonials we heard earlier. That is well beyond treatment. How many patients were still doing as well as the man on the video or the patients who spoke at the microphone? Can we get a handle on that issue?

DR. DUTCHER: What we are looking for are long-term disease responses.

DR. SIMON: If you look at figure 12, figure 12 gives failure free survival, so you drop off of this if you

die, if you stop treatment, withdraw because of an adverse event, or if you have progressive disease.

So, the tail of the curve has something that looks like, you know, at one year I guess it is, what, less than 10 percent, and I think pain is not fully represented here, but you could draw this kind of a curve in which you include pain progression as one of the events, in which case it would be even lower, so it has got to be somewhere less than 10 percent, and it looks like it is the same for the placebo group.

DR. ALBAIN: Does the sponsor have any information on this type of a curve for pain alone, at least in the intermediate follow-up, not way out there on the tails beyond the year, but perhaps in that 6- to 12-month period?

DR. SLICHENMYER: That is all contained within the time to pain progression analysis. That is the analysis that captures that.

DR. ALBAIN: The retrospective analysis.

DR. SLICHENMYER: It was defined and undertaken retrospectively, it is true. It might just serve to help you, just to remind the group that as Dr. Simon pointed out, protocol-defined endpoints are often the most useful, and of all the various analyses that have been under discussion here for the last 30 minutes or so, there is only one that was defined in the protocol and analyzed and displayed for

you today, and that is the time to disease progression endpoint that we showed initially. That was defined in the protocol, analyzed as defined. All the others, including the FDA's definition of time to disease progression, differs. This one was done prospectively in a blinded manner. All of the others have been in an unblinded, retrospective manner, and I think the criticisms that Dr. Simon raised are valid for all of those except time to disease progression.

DR. DUTCHER: Dr. Schilsky.

DR. SCHILSKY: Coming back to the pain issue again for a moment, I guess the things that concern me are that, first, it seems as though the patients who have the greatest potential to benefit with a reduction in pain from suramin are the patients who have the most mild pain to begin with.

Second of all, if you look at the criteria for pain response, the percent of patients who meet those criteria based on a reduction in pain is relatively small in both arms, in the FDA analysis, it is 20 percent in the suramin arm, 13 percent in the placebo arm, and all of the other patients who meet the criteria for pain response, meet those criteria based on change in narcotic dosage.

I really think it is questionable whether a change in your morphine dose from 90 mg a day to 60 mg a day really means that you are benefiting from any sort of therapy. I

would suspect that most patients probably don't really notice the difference between taking 90 mg or 60 mg a day, they are still having to take morphine every day.

Of course, we have the quality of life analyses that don't suggest any difference between the two treatments albeit it seems to me that the particular instruments chosen probably were not optimal to address the specific endpoints of interest in the study, but nevertheless, there doesn't seem to be any substantial improvement in quality of life.

So, it seems pretty clear to me that with respect to the second question that we have been asked to address, that any improvement in pain does not necessarily relate to a clinically meaningful benefit for the patient, because I just don't think that we have seen enough improvement in patients with severe pain to suggest that a clinically meaningfully benefit is occurring.

DR. RAGHAVAN: I would like to come back to one issue that was raised by the FDA, which I am sort of stuck on, and that is the issue of consistency. Mitoxantrone is currently approved for this indication based on quality of life endpoints, and I have heard the summaries of the differences in study design, and I do understand those differences.

I wonder if I could ask the reviewer, qualitatively, do you view the two sets of data that have

been presented to the FDA as being different, are we talking about apples and oranges, are we talking about blunted endpoints. I didn't participate in the discussion on mitoxantrone many months ago, so I didn't have the benefit of hearing the presentation.

So, my question is, are there significant qualitative differences or quantitative statistical differences that would lead us to view the quality of pain assessment in this trial as giving us outcomes that are different from the data that were presented for mitoxantrone?

DR. CHIAO: Well, this is a difficult question to answer, but all I can do is I can try to see if this makes any sense by making some comparison and to point out what are the most important differences.

Let's separate the pain responder rate into two categories, decreasing pain with stable or decreased narcotics or decreasing narcotics only, because that is very similar to the primary response criterion of mitoxantrone trial, which is only decreasing pain, and the second criteria in mitoxantrone trial, which is decreasing narcotics.

Let's put 50 percent versus 33 percent, a different pain scale, in the site, so reduction in pain only in the suramin trial is 20 percent versus placebo, 13

percent reduction in pain in mitoxantrone trial, is 29 percent on mitoxantrone arm versus 12 percent on the prednisone arm. Reduction in analgesic only in the suramin trial is 22 percent versus 16 percent on the placebo arm, and on the mitoxantrone study it is 9 percent on both arms.

I think the other thing important in assessing response duration is that the mitoxantrone trial requires six weeks duration of pain in order to have the patient declared as a responder, and for the suramin studies, that is not the requirement. As a matter of fact, you only need two weeks for failing the pain response criteria. Your third week doesn't have to meet the pain response criteria, but the average of three weeks meets the response criteria, that is still fine.

So, I think you can make an argument if you look at the response duration of the suramin trial and say, well, how many patients had less than six weeks of response duration, I think the number was about 27 on the suramin arm, so if you subtract that, you will probably further decrease the responder rate a little bit.

DR. SLICHENMYER: The pain instrument used in the mitoxantrone trial was administered once every 21 days, and it is true that two consecutive readings were required to be considered a responder, but that instrument only assayed for pain in the previous 24 hours, so during that first three

weeks, up until the first assessment on therapy, there is no gauge of what was happening to the pain during that time.

In contrast, we assayed pain on a daily basis, so fluctuations in pain over that week to week period were captured in a very sensitive manner by our pain instruments. So, in comparing the durations required for being considered a responder, the two trials were quite comparable.

DR. JUSTICE: I will try to address that further in terms of the differences. Just off the top of my head, I think besides what was mentioned about the six-week duration of pain required for a response of mitoxantrone versus the three, which I think is a major difference, another difference was that even though the mitoxantrone trial was unblinded, it was supported by a Phase II trial in which the pain response criteria were prospectively defined, not retrospectively defined, and I think there was a big difference in the toxicity profiles, where with mitoxantrone you saw a lot of hematologic toxicity, which was usually not symptomatic, whereas, with the suramin you see non-hematologic toxicity, and you had a difference in death rates.

There is a hazard in comparing doing cross-studies comparisons, such as the company pointed out, and I would agree with that, but those are some of the differences.

DR. DUTCHER: So, we are still addressing Question

2, which is whether the pain response as utilized in this study, using their scales and the way the data was collected, do the pain response criteria assure that a patient with a pain response has a clinically meaningful benefit.

We have heard that Dr. Schilsky is not sure that is the case.

DR. SCHILSKY: I would answer that no.

DR. DUTCHER: Shall we vote? Okay. All those who would vote yes, please raise your hand.

[No response.]

DR. DUTCHER: And all those who would vote no?

[Show of hands.]

DR. DUTCHER: Ten vote no. Zero yes.

Question No. 3. In the randomized, controlled trial most of the effect of Metaret on pain and narcotic reduction is in the subgroup with mild pain and narcotic use at study entry. In view of the efficacy results, is the safety profile of Metaret acceptable?

Just a comment from me is that oftentimes better patients do better with anything we do, so I don't know, even though it is disappointing that the patients with worst pain didn't seem to show as much difference, I don't suppose it is surprising in view of other drugs that we use for things.

So, the question is whether this is the group of patients for which this drug would want to be used or we would want it used. We have heard from Mr. Anderson and Ms. Beaman who are concerned about that. Do any other people want to make a comment? Dr. Ozols.

DR. OZOLS: I guess I am concerned in this group of patients who have less than a 50 mg morphine equivalent, I mean are they really optimally managed, would that be a choice, and if they are having mild pain on this amount of narcotics, would you add a drug with considerable toxicity, such as suramin, to it, or would you try to alter their pain management.

DR. DUTCHER: I guess the other question that we are sort of dancing around is are we looking at this as a pain management drug, or are we looking at this as a drug that treats prostate cancer.

Dr. Margolin.

DR. MARGOLIN: I think that is really a key point. I mean I am sure the sponsors don't want us to really come out and say that patients with mild pain can easily be managed by, not so much talking themselves out of it, but by improving their pain regimen, and the patients with severe pain aren't helped by this drug anyway.

If you can't demonstrate that you have an anti-tumor, a measurable anti-tumor response, then, we really

need to think about the ratio of the toxicity to the really questionable benefit and how we can get that benefit by using some other regimen, whether it be mitoxantrone or whether it be pain medications or steroids alone.

DR. DUTCHER: Dr. Raghavan.

DR. RAGHAVAN: I think that one of the things that we are sort of struggling with -- and I must say as someone who treats an awful lot of prostate cancer, I am kind of puzzled because I know some of the clinicians who have worked with the sponsor -- and I think this is a drug that has always been portrayed in clinical environments as a drug that actually kills prostate cancer in some people.

I am sort of surprised at the line that has been taken, because I don't think the data that we have heard today are tremendously compelling that this a great quality of life drug, and the most compelling piece of information is probably the least in a way reproducible, which was the non-professional, from the heart, pleas from people who have had suramin and done very well, and we have been struggling. We have gone around and around on the point of how many such patients are there.

If we could convince ourselves that there were a lot of patients who got long-term benefit, this would be an approvable drug, and that is kind of what I would have expected to hear today, but, in fact, we have seen a pivotal

trial, which after all the analyses and all the statistics, leave us with real uncertainty about how useful it is for a patient who walks in the door, and I think that is the problem that we continue to deal with, and it makes it difficult that somehow, today, we have heard that the people who have the least bad prostate cancer get some benefit from it, and as Mr. Anderson said, the patients who are really in need to help seem to miss out.

That isn't what I have heard on the grapevine, and yet I want it to be clear that when we are making our decisions today, we have to make decisions on the basis of data presented, not based on the grapevine, and it is kind of a frustration in way, because this may be a drug that has some activity, but the way it has been portrayed today, it certainly hasn't made it easy to cull that from the information.

DR. SIMON: To some extent we have the benefit of a good clinical trial here to see what the drug really does rather than what the grapevine says it does.

DR. RAGHAVAN: Sure, I understand that.

DR. MARGOLIN: I think one way to answer the question, although it is no based on any comparative information, is this is the group of patients that would otherwise have gone with mitoxantrone trial either off-study or on some study, and we can ask ourselves, in order to help

us answer No. 3, what we would be putting out patients on if we had the choice between suramin plus steroid or mitoxantrone plus steroid.

If we had data this good or better in patients who had already failed the trial with mitoxantrone, or an equivalency study which would have to be enormous and very carefully done, then, it might convince us more of the usefulness of this drug.

DR. DUTCHER: Or if we had a defined population that could, other than by pain response, could benefit.

So, shall we answer Question 3? Okay.

In the randomized, controlled trial most of the effect is in the subgroup with mild pain and narcotic use. In view of the efficacy results, is the safety profile of Metaret acceptable?

All those who would vote yes, please raised your hand.

[No response.]

DR. DUTCHER: Zero.

All those who vote no, please raised your hand.

[Show of hands.]

DR. DUTCHER: Ten no, and zero yes.

Question No. 4, do you want us to answer? Is this New Drug Application approvable? I guess the corollary is in the population for whom it seemed to benefit.

Do you want to vote?

All those who would vote yes?

[No response.]

DR. DUTCHER: Zero. All those who would vote no?

[Show of hands.]

DR. DUTCHER: Ten. So, that was 10 no.

So, I think we have completed this morning's session. We will reconvene at 1:45.

[Whereupon, at 12:45 p.m., the proceedings were recessed, to be resumed at 1:45 p.m.]

AFTERNOON SESSION

[1:45 p.m.]

Call to Order and Introductions

DR. DUTCHER: Good afternoon. We are going to proceed with the afternoon discussion. We have a few new people at the table, so we will reintroduce those of us that aren't new and introduce those who are.

I am Dr. Janice Dutcher from Albert Einstein Cancer Center in New York.

We will start on this end with Dr. Schilsky.

DR. SCHILSKY: Richard Schilsky, University of Chicago.

MS. BEAMAN: Carolyn Beaman, consumer representative, and Sisters Breast Cancer Network.

DR. SIMON: Richard Simon, National Cancer Institute.

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

DR. D. JOHNSON: David Johnson, Vanderbilt University.

DR. SLEDGE: George Sledge, Indiana University.

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

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

DR. SCHER: Howard Scher, Memorial Sloan-Kettering in New York.

COL SCHULTZ: Jim Schultz, Patient Rep.

DR. OZOLS: Bob Ozols, Fox Chase Cancer Center, Philadelphia.

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

DR. WILLIAMS: Grant Williams, Medical Team Leader.

DR. ODUJINRIN: Wole Odujinrin, Medical Officer.

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

DR. BEHRMAN: Rachel Behrman, Deputy Director, Office of Drug Evaluation I, FDA.

DR. DUTCHER: We are expecting Dr. Schoenberg any minute. We will first do the conflict of interest statement.

Conflict of Interest Statement

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

Based on the submitted agenda for the meeting and all financial interests reported by the participants, it has been determined that all interest in firms regulated by the

Center for Drug Evaluation and Research which have been reported by the participants present no potential for a conflict of interest at this meeting with the following exception.

Dr. Ozols has been granted a waiver which permits him to participate in all matters concerning Valstar.

A copy of this waiver statement may be obtained by submitting a written request to the FDA's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

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

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

Thank you.

DR. DUTCHER: Now we will begin with the open public hearing, and we have two people who have requested to speak. First is Abbey Meyers. If you could please identify yourself, your organization, and any sponsorship.

Open Public Hearing

MS. MEYERS: I am Abbey Meyers, President of the National Organization for Rare Disorders. Some of you may know us as NORD. We deal with approximately 5,000 rare diseases, each disease affecting fewer than 200,000 Americans, and the disease we are talking about today is an orphan disease.

I have no financial interest, no stocks. This company has not even contributed to us. They will, however, reimburse me for this travel down here to speak to you today, because I want to speak to you about this drug as an orphan drug and what that means because the difference between an orphan drug and normal drug development is very important.

Under federal law, an orphan disease is a condition that affects fewer than 200,000 Americans. The drug valrubicin, which we are reviewing today, is intended to treat a very small subset of an already small population of people with bladder cancer.

Approximately 50,000 Americans get bladder cancer every year, and this drug is targeted to patients who are refractory to standard therapy. So, the number of people in the United States who might be candidates for this drug is about 5,000 people or fewer. This is truly an orphan condition.

The reason for the Orphan Drug Act was to create incentives to entice drug companies into developing drugs for these small numbers of people. Today, patients with refractory bladder cancer face an incomprehensively difficult situation. Not only do they have a terrible disease, but they have a very troublesome decision, whether to have their bladder removed, which will dramatically affect the quality of their lives, or they could try other off-label cancer drugs with no proof of safety or efficacy, but success will be very unlikely, or they can go without therapy and die from their disease, but for a small number of patients, even the surgical option is not available because cystectomy is contraindicated.

Do the drug application that you are considering now offers these patients another option. For people with orphan diseases, an option is a miracle. Unlike patients with breast or prostate cancer, these patients and the doctor can't choose between dozens of possible therapies that have been carefully studies in controlled clinical trials. There simply are no comparable studies on bladder cancer.

It is important to note the evaluation of an orphan drug requires your thinking in a different way. With orphan diseases, the numbers plainly aren't there. Traditional means of drug development simply won't work.

There just aren't enough patients to participate in traditional randomized clinical trials.

It is impossible to set up large clinical studies at academic medical centers and enroll a sufficient number of patients for a typical study. There are only a few patients with the disease, and some of them may not want to go into a clinical trial. The rare disease patients are scattered all across the country. They don't live near medical centers and because of the nature of their disease, they may be unable to travel, so a single clinical investigator would be very fortunate to enroll 10 people in one study. A study of 90 or 100 patients would be stupendous. Many clinical research centers would have to be involved.

It is my understanding that it took four and a half years to enroll 90 patients into this clinical study at 50 sites across the country. That averages less than two patients per site.

Orphan disease patients want drugs that are safe and effective, and you must understand the special nature of the small size of the affected population, which precludes common ways of gathering data and the tragic situation of patients with awful choices.

Thanks to FDA's efforts and to the incentives of the Orphan Drug Act, we do have orphan drugs on the market

today that were studied on very small populations, and it is therefore an excellent precedent for evaluation of valrubicin. There are approved drugs for severe combined immune deficiency which affects less than 40 patients in the United States, and the drug was approved on a study of less than 20 patients. For urea cycle disorders, which affects 275 American children, and there are two approved orphan drugs for Wilson's disease which affects only 2,000 Americans, but both of these drugs offer treatments of a tiny subset of those 2,000 patients who couldn't tolerate the standard therapy, and, of course, Ceredase, an orphan drug for Gaucher's disease, was approved on a trial I believe of 15 patients, so it is possible to get the data from a small clinical trial, and understand the difficulties that any investigator goes through in trying to attract people with a very rare form of cancer.

I would just like to mention one more thing, and that is that Hubert Humphrey died of bladder cancer. You may not remember that Hubert Humphrey was a registered pharmacist, and he certainly knew all of the medical options, and he tried everything he could, but he succumbed to the disease.

So, in your consideration of this drug today, I would like you to be fair and open and understand that the data is limited and it will always be limited on an orphan

disease.

Thank you.

DR. DUTCHER: The next person who has requested to speak is Mr. Thomas Bruckman.

MR. BRUCKMAN: Thank you very much and good afternoon. My name is Tom Bruckman. I am the Executive Director of the American Foundation for Urologic Disease. I would like to thank the FDA and the ODAC Committee for a chance to speak here about bladder cancer in situ.

I would like to disclose that the AFUD has a relationship with many medical providers including Anthra which sponsored a $2,000 summer scholarship in 1997. I have not received any reimbursement for being here today.

By way of background, the AFUD is a national leader in urologic research, public awareness programs, such as Bladder Health Week and Prostate Cancer Awareness Week. There is a gigantic difference in Prostate Cancer Awareness Week and Bladder Health Week.

As a result of these and other efforts, we have one of the most extensive databases of patients affected by urologic conditions, such as prostate disease, bladder disease, incontinence, impotence, et cetera.

We use this data as a source of surveys and research on patients' knowledge of disease, treatment options, and screening guidelines. Specific to our bladder

cancer efforts, we have written extensively in Family Urology and have a series of brochures and booklets for bladder cancer and bladder disease that we send to the public through one of our toll-free 800 numbers.

In 1997, we implemented Bladder Health Week with a national campaign to educate the public about bladder cancer, and we had free screening sites at clinics and doctors' office for hematuria. We did have Mr. Skip Humphrey, who is Hubert Humphrey's son, as our national spokesperson, and as Abbey Meyers mentioned, Hubert Humphrey died of bladder cancer in February of 1978. Skip Humphrey was a very motivate spokesperson.

As part of the screening effort for Bladder Health Week in 1997, we coordinated over 60 sites and had over 1,400 patients come in for hematuria screening. We are still analyzing the results of that particular effort.

Some of the things we learned about bladder cancer from our programs follow.

1. Bladder cancer still remains in the closet as a disease and cancer killer, with 54,500 new cases and 11,500 deaths according to the American Cancer Society. We must continue our efforts to educate the public about risks and symptoms. Clearly, bladder cancer does not get the attention of other cancer killers like lung cancer, breast cancer, colon cancer and prostate cancer.

2. Patients with bladder cancer are in need of education including the most effective management strategies for their particular stage of the disease. Patients with bladder cancer place a great demand on the foundation's ability to serve their educational needs.

3. Patients with bladder cancer are looking for alternatives and new treatment options with great anticipation. They question specifically what effect new treatments will have versus the old treatments for their quality of life.

4. From the patient's standpoint, there is a dramatic need for additional new therapies to be used in the diagnosis, staging, and treatment of bladder cancer.

On behalf of the annual 54,000 new cases and the 5 to 10 percent of those new cases who progress to cancer in situ, and the 11,000 deaths attributable to bladder cancer, we urge the FDA to continue to give bladder cancer therapies prompt and professional review.

Thank you very much.

DR. DUTCHER: Thank you, and thank you for bringing your informational brochure.

Are there any other people who would like to speak at the open public hearing?

Then, I guess we will proceed with the sponsor's presentation. Our urologist for the committee has not

arrived as yet, but his schedule says he is here, so we are looking for him.

NDA 20-892 Valstar (valrubicin) Sterile Solution for Intravesical Installation

Anthra Pharmaceuticals, Inc.

Sponsor Presentation

Background and Preclinical Data

DR. GULFO: Good afternoon. I am Joseph Gulfo. On behalf of the entire Valstar development team, I am privileged to be here this afternoon to present data for your review and consideration.

[Slide.]

Three months ago, at the June 1st ODAC meeting, eight members of this panel reviewed some of the data that were accumulated and analyzed with respect to valrubicin for the treatment of patients with BCG refractory carcinoma in situ.

Dr. Grossman, one of the experts from whom you will be hearing a little bit later on, summarized the basic proposition as follows. Carcinoma in situ, in contra-distinction to all other forms of cancer, carcinoma in situ with respect to bladder cancer is a high risk, aggressive disease that is actually more dangerous than the superficial transitional cell carcinoma itself.

Once diagnosed, in patients who can tolerate the

procedure, cystectomy was considered the treatment of choice, however, in landmark studies conducted by the South West Oncology Group, BCG, Bacillus Calmette-Guerin therapy was shown to be highly effective in inducing complete responses, thereby delaying the need for cystectomy.

Unfortunately, not all patients respond to BCG, and a growing number of patients become refractory to BCG immunotherapy. For those patients in whom surgery can be tolerated, cystectomy is considered the treatment of choice as no other agents are approved for BCG refractory carcinoma in situ, and no agents used in off-label fashion have shown to be of clinical utility.

Valrubicin was developed as salvage treatment in patients having failed BCG immunotherapy who are facing cystectomy.

[Slide.]

Thus, at the June 1st ODAC meeting, valrubicin was evaluated for this orphan indication, intravesical use in the treatment of patients with biopsy-proven carcinoma in situ of the bladder who are refractory to BCG immunotherapy.

In the risk-benefit discussion that ensued during that meeting, the ODAC panel expressed reservations with respect to the analyses that were used to support benefit, and as such, they recommended against approval at that time. The panel did request additional analyses, as did the FDA in

a private closed meeting that we had following the ODAC session.

The main goal of our presentation this afternoon is to address the unanswered questions and to present the new analyses requested by the ODAC panel in June, which focused primarily on patient benefit.

It was apparent to us that we really didn't present the data from the pivotal studies in the most effective and appropriate manner during our last session. We thank the panel for their insights, questions, and comments, and most of all, the opportunity today to discuss the data and present the additional analyses that were requested.

[Slide.]

Considering that carcinoma in situ of the bladder is a specialist disease, we have asked the most distinguished group of bladder cancer experts to present the data that were obtained from our pivotal clinical trials in a difficult disease that they truly know best - Dr. Barton Grossman from the M.D. Anderson Cancer Center, Dr. Paul Lange from the University of Washington at Seattle, and Dr. Michael Droller from the Mt. Sinai Medical Center.

[Slide.]

I will provide background, preclinical and overview clinical information. Dr. Grossman will present

efficacy information, focusing on the patient benefit analyses requested by the panel. Dr. Lange will review the safety of salvage intravesical therapy and discuss issues regarding cystectomy in patients with BCG refractory carcinoma in situ. Dr. Droller will provide an overview and synthesis, focusing on the results obtained in the pivotal trials relative to the issues that confront both patients and physicians in the management of this disease.

[Slide.]

Valrubicin is the product of an anthracycline research program sponsored by the NCI and undertaken at the Dana Farber Cancer Center by Drs. Mervin Israel and Emil Frye. It is a semi-synthetic analog of doxorubicin differentiated from [doxin 2] of the molecule.

On the 14 carbon of doxorubicin there is a valerate group and on the glycocytic amine there is a trifluoroacetyl. These substitutions render the molecule highly lipophilic, allowing for enhanced cellular uptake and result in important pharmacologic differences.

In work performed at the University of Wisconsin, both valrubicin and doxorubicin were shown to be active against a variety of bladder cancer cell lines including those derived from patients with high-grade, invasive tumors exhibiting mutations in P53, RB, and P16 methylation, known genetic aberrations in patients with aggressive disease.

[Slide.]

Doxorubicin is a vesicant and as such is associated with significant contact toxicity. A dramatic illustration of this are the sequelae seen upon inadvertent paravenous extravasation with severe skin reactions including ulceration.

What immediately impressed the early researchers with valrubicin was this type phenomenon was not observed upon inadvertent paravenous extravasation. This led them to begin to contemplate the use of this agent local regionally. When Anthra took over the development of this product, we performed several special studies of contact toxicity. In the rabbit, abraded skin dermal toxicity model, it was shown to be a nonirritant, and in the ocular model of toxicity, the drug was shown to be a mild irritant, but if the eyes were flushed, a nonirritant.

[Slide.]

Intravesical pharmacology and toxicology studies were performed in rats and dogs. The results indicate minimal systemic exposure as documented by recovery of near all drug in the bladder, and detection of low anthracycline levels in blood, and no significant histopathology in the bladder or in distant organs.

[Slide.]

By virtue of its lipophilicity, cellular

penetration, cytotoxicity against aggressive bladder cancer cell lines, reduced contact toxicity, and animal studies validating negligible systemic exposure and local tolerability, valrubicin was considered an ideal agent for intravesical use in patients, and clinical studies were initiated in 1992.

[Slide.]

The NDA consisted of six clinical trials in which 230 patients received at least one intravesical dose of valrubicin. The primary studies, the pivotal studies A9301 and 02 will be discussed in some detail.

A9101 was the first study conducted. It established the 800 mg dose as the dose for further intravesical treatment in further studies, and it documented activity in patients with BCG refractory disease.

Studies A9501 and A9303 were supportive safety studies, and study A9305 evaluated the depth of penetration of valrubicin following intravesical administration to patients into the bladder wall.

Pharmacokinetic data were derived from 50 patients enrolled across all six clinical trials.

[Slide.]

This slide demonstrates the area under the curve calculations for systemic exposure following intravesical and intravenous administration. Note there is minimal

systemic exposure following intravesical administration especially when compared to intravenous.

Myelosuppression is routinely associated with intravenous administration, however, no myelosuppression has been observed following therapeutic or prophylactic intravesical doses of valrubicin.

[Slide.]

Regarding the depth of penetration of valrubicin into the human bladder, this slide demonstrates the anthracycline concentrations as a function of distance from the luminal surface in three areas of the bladder, dome, left and right wall, IC50 concentrations of bladder cancer cell lines in cultures are shown, as well.

Absorption through the bladder wall does not vary by site, and at the level of a submucosal T1 tumor we see 3 times IC50 concentrations of bladder cancer cell lines in culture, and we note a very impressive multiple of those concentrations at the cells mucosal surface.

[Slide.]

The remainder of the presentation this afternoon will focus on the data obtained in the pivotal studies A9301 and 02. These were identical studies conducted at different centers, and it was agreed with the Agency that the two studies would be pooled and presented in one study report so as to provide more robust estimates of the various safety

and efficacy parameters.

[Slide.]

In order to be eligible for this study, patients must have had pathologically proven carcinoma in situ at baseline. In addition, they must have received at least two prior intravesical regimens for their treatment of carcinoma in situ, and one of those treatments must have been BCG. Thus, the patients must have had at least three documented presentations of carcinoma in situ to be eligible, two for which they were treated previously, and one at baseline entry.

[Slide.]

At baseline, patients were evaluated with cystoscopy and biopsy and cytology. Drug was administered for six weeks intravesically through a catheter, six-week respite, and at 12 weeks a repeat evaluation, cystoscopy with biopsy, and cytology. Evaluations in similar fashion took place every three months thereafter or until failure.

[Slide.]

In patients in whom failure was demonstrated, disease status updates were obtained at six-month intervals or until death.

[Slide.]

Complete response was the primary endpoint of the study as prospectively stated in the protocol and discussed

with FDA at various time points in the development of the product and though the NDA review.

A most conservative definition of complete response was used in contrast to many other studies in this disease. In order to be a complete responder, patients must have had no evidence of disease at both the three- and six-month time point.

Because cystectomy is the principal therapy for patients with BCG refractory carcinoma in situ, our investigators wanted to be extremely cautious before designating a patient a complete responder.

[Slide.]

The median age of the 90 patients was 69.5 years. Males outnumbered females 7 to 1. There were 2 non-caucasian patients. The median duration of transitional cell carcinoma from earliest diagnosis to entry in the study was 3 1/2 years. The median duration of carcinoma in situ from earliest diagnosis to study entry was 25 months, and the patients again had to have three presentations of carcinoma in situ to be eligible.

[Slide.]

This slide summarizes the prior treatments that the 90 patients received. All but one patient received the protocol specified, two prior intravesical regimens, 100 percent of the patients received the protocol specified at

least one dose of BCG, and 70 percent of patients received at least two prior intravesical regimens of BCG.

[Slide.]

This slide summarizes the complete responders, 19 patients who failed the criteria for complete response as stated in the protocol, shown here as the Anthra number and here the FDA number. The TTF is the time to failure column. Note there are 7 patients who were still disease free. They are denoted with the plus sign.

The median time to failure or median time to follow-up was 18-plus months in the 19 responders.

[Slide.]

In the benefit-risk discussion that took place during the ODAC session on June 1st, we understood the panel to have concluded that although the risk of salvage treatment with valrubicin as measured by direct toxicity and the likelihood of developing advanced disease was acceptable, benefit was not quantifiable given the analyses that we presented.

[Slide.]

ODAC recommended against approval at that time, but requested additional analyses aimed at determining the benefit of treatment with valrubicin.

[Slide.]

We can summarize the points made by ODAC in the

following session. The appropriateness of the complete response endpoint was questioned. The committee wanted data to support that complete response indeed correlated with patient benefit.

Demonstration of patient benefit was felt by the panel would be best shown by documenting a change in the course of disease prior to entry and on study in individual patients.

An appropriate endpoint advanced by the panel was time to a bad event, and we were asked to provide an analysis of time to cystectomy not as we had done in those one-to-one cystectomy, but in the entire population.

The panel was very concerned about disease heterogeneity as a basis of selection bias, and we were asked to provide an analysis of that.

[Slide.]

I would like now to ask Dr. Barton Grossman to come up and review in detail the efficacy data generated in the pivotal studies with special emphasis on the reanalyses of patient benefit requested by the committee.

Dr. Grossman is Deputy Chairman of the Department of Urology from the M.D. Anderson Cancer Center, and he is the South West Oncology Group Local Bladder Organ Site Chair.

Dr. Grossman.

Clinical Efficacy

DR. GROSSMAN: Thank you, Dr. Gulfo.

[Slide.]

Anthra Pharmaceuticals asked me to address the following question - based on my experience in treating patients and conducting and managing studies in superficial bladder cancer, carcinoma in situ specifically, was patient benefit observed in the primary efficacy studies of valrubicin?

In my presentation, I will share with you the new analyses that were requested by ODAC in June, and after careful review of this data, I can honestly answer this question in the affirmative.

[Slide.]

There are several ways of addressing patient benefit. The most obvious, of course, is complete response and time to treatment failure. However, as you will see, patient benefit can also be demonstrated by change in disease course, and, as requested, we will also present data on time to bad event, namely, cystectomy.

An interesting question is whether patient benefit can be seen in the non-responding population, and, of course, in any Phase II study, patient selection and heterogeneity is an important issue which will be addressed.

Finally, in patients who have carcinoma in situ

and fail BCG therapy, what are the alternatives aside from cystectomy.

[Slide.]

The first issue, of course, is complete response and time to failure. These patients are a highly refractory population. They had carcinoma in situ at baseline and at least twice in the past. Therefore, this is at least their third diagnosis of carcinoma in situ. They have had at least two prior intravesical treatments for carcinoma in situ, and at least one of these was BCG.

Meticulous follow-up was employed including cystoscopy, biopsy, and cytology every three months. A very conservative definition of complete response was employed using complete response both at three months and at six months. Furthermore, patients failing with only low grade TA disease were included in the failure category, and this has not always been employed as a criteria for failure in other drug applications recently before ODAC.

[Slide.]

This is the complete response data which was recently presented by Dr. Gulfo. It shows 19 complete responders, 7 ongoing, and the median time to treatment failure of 18-plus months.

[Slide.]

Now, ODAC asked us to present data on change in

disease course. This is the data, and it shows in the 19 patients who were complete responders from valrubicin, they had a median time to treatment failure of approximately 18 months. Considering their last three courses of therapy, all of those courses had a median duration of failure of approximately six months showing a two to three time prolongation in the time to treatment failure with valrubicin.

Seven patients are still ongoing. There are 3 patients at the 21-month mark that are censored, and 2 at 24 months. Most of the patients who failed their prior therapy failed BCG. In their last intravesical treatment, 70 percent had BCG. In their second to the last treatment, 75 percent received BCG, and in their third, last intravesical treatment, 60 percent received BCG.

This clearly shows that the patients responded much better to valrubicin than the last three prior treatments, most of which were BCG.

There were 9 patients who can be considered a very high risk population. These were 9 patients who failed very quickly after receiving BCG in the time frame of six months or less. You can see that all of these patients had a better response on valrubicin than with BCG, 5 of these achieving a response ranging from 12 to 25 months with 2 ongoing to 21-plus months.

Notably, only one of these patients received only a single course of intravesical BCG. The mean number of BCG courses in these 9 patients was 2.2, and the mode was three courses of intravesical BCG, again, a highly treated population.

[Slide.]

I will present two examples of patient benefit with valrubicin. These slides demonstrate several things. The first column are the cystoscopic findings, which may be either abnormal, in red, or normal, in green. These are visual findings which do not always correlate with the presence of disease.

This is bladder map findings. For example, in this patient, it is posterior wall, right wall, left wall, prostatic urethra, trigone, dome, nonspecified. Again, a red signifies presence of tumor with the type of tumor marked, green is a negative biopsy.

Cytology is the next to the last column. Green is negative, red is positive, and the type of intravesical therapy employed is listed in the last column.

This patient had carcinoma in situ at two different sites in March 1994, and was treated with BCG. In August 1994, carcinoma in situ was again noted. BCG was again administered.

At baseline, carcinoma in situ was present at two

biopsies at the right wall, positive cytology was present, and the patient received valrubicin. With meticulous follow-up, multiple biopsies, multiple cytologies, the patient remains disease free at 24 months. This patient has achieved benefit and a change in disease course with valrubicin.

[Slide.]

The second patient, FDA 11, presented with papillary disease in 1989, and was treated with mitomycin. In June 1991, carcinoma was seen near the left ureteral orifice. Patient received BCG.

March 1993, carcinoma in situ at the dome. BCG. September 1995, carcinoma in situ. BCG. In January 1996, carcinoma in situ, and the patient was switched to interferon therapy.

In June 1996, the patient had carcinoma in situ at yet another site, here at the bladder neck. Cytology was negative. The patient received valrubicin. The patient had multiple biopsies obtained at three months, but specifically, a biopsy was not obtained at the bladder neck.

Finally, at 18 months, a biopsy was obtained at the bladder neck, as well as at other sites, documenting no evidence of tumor recurrence. Cytologies remained negative. In the 21 months, this patient remains tumor free. This patient again has had a change in disease course and benefit

from intravesical valrubicin.

[Slide.]

The next issue, of course, is time to bad event, and cystectomy or bladder removal is frequently considered a bad event by patients having this procedure.

[Slide.]

The initial analysis presented at the June 1st ODAC meeting is shown in blue. At this point, there were 37 patients who had cystectomy, 33 patients of the non-responder group had cystectomy, and 4 patients in the complete responder group had cystectomy, and the period at that initial analysis there was a plateau at roughly the 50 percent level.

Concern was engendered that this may indicate that this was a non-cystectomy population. With additional follow-up, 7 more patients have gone on to cystectomy. At the present time, in the non-responder group, 40 patients have had cystectomy, and in the complete response group, the same 4 patients have had cystectomy.

What you can see at this point is that this curve steadily goes down in the proportion of patients remaining without cystectomy steadily is diminishing, demonstrating that this is a pre-cystectomy population.

In fact, if you look at the patients who had valrubicin and failed with carcinoma in situ or greater

disease, two-thirds of those patients have already gone on to cystectomy.

[Slide.]

At the June 1st ODAC meeting, time to cystectomy was presented for 4 patients in the complete response group and 33 patients in the non-response group. Anthra was asked to present data for the entire population, and this is the data updated including the additional 7 patients who had cystectomy.

This shows that the median time to cystectomy in the nonresponders was 24 months, the median time to cystectomy has not been achieved in the complete response rate, and this is a very dramatic difference in these two curves, again showing benefit in the complete response category.

[Slide.]

Now, as I mentioned, an interesting question is what about the nonresponders, and was any benefit seen, any clinical benefit seen in this population. As you recall, patients who failed with low-grade TA disease were included in the failure category.

These patients are not indicated for cystectomy. They are indicated to receive additional local therapy. There are 10 such patients which failed at 3 or 6 months. With additional follow-up, only one of these patients has

gone on to muscle invasive disease.

[Slide.]

If we do a similar clinical benefit analysis looking at time to cystectomy, and look at all patients who received clinical benefit, that includes the 19 complete responders and the 10 patients who failed with TA disease, so for a total of 29 patients versus the remaining population who did not achieve apparent clinical benefit, you see that the time to cystectomy now is less than 15 months. The median has not yet been achieved in the clinical benefit group. These curves are even wider apart and the p-value is highly significant.

[Slide.]

Now, in any Phase II trial, patient selection and heterogeneity is an important consideration, and I am pleased to say that the patient selection is not an issue and, in fact, this is a very homogeneous population.

[Slide.]

If you look at the complete responders versus the nonresponders, the incidence of patients that are male, white, median duration of bladder cancer, median duration of carcinoma in situ, is remarkably similar in both populations.

In the complete responders, the number of patients that are 60 to 79 years of age appears to be

overrepresented, as well as an increase in proportion of patients who have baseline local bladder symptoms, however, there is no reason to expect increasing age or baseline local bladder symptoms would affect response to valrubicin.

[Slide.]

More importantly is this slide showing characteristics involving prior therapy, presence of carcinoma in situ, and cytology. Again, here, the patients are quite homogeneous. The number of patients who had two or more prior BCG therapies is 68 and 70 percent. One patient in each category received BCG less than or equal to three months prior to going on study.

The proportion of patients who had last BCG 3 to 24 months, baseline-positive cytology, and a baseline two or more positive biopsy sites is very similar in both groups. We only have data in the complete response category for history of two or more positive biopsy sites, but that figure is 89 percent, and it is hard to imagine that the nonresponders could be much higher than that.

The number of patients who had two or more positive biopsies for carcinoma in situ and positive cytology is very similar, at 32 and 39 percent, and the proportion of patients who went on to receive intravesical therapy after failing valrubicin was identical, at 37 percent, in both the complete responders and the

nonresponders.

[Slide.]

If we analyze the data and look at the response to last prior BCG in the complete responders and nonresponders, these curves are virtually identical, again suggesting that these patients are homogeneous and do not differ in their response to prior therapy.

[Slide.]

Lastly, is the question of what are the options open to these patients aside from cystectomy.

[Slide.]

Well, one obvious alternative is giving more BCG. As I will mention in a minute, the problem with more BCG is that the risks start to outweigh the benefit, and as demonstrated in South West Oncology group data, there is increasing toxicity with additional BCG.

Radiation therapy has never been shown to be an option for carcinoma in situ, and I will discuss second line chemotherapy and immunotherapy in patients who have failed BCG and have carcinoma in situ.

[Slide.]

Bill Catalona at Wash U. in St. Louis had published data stating that patients who fail two courses of BCG should be considered for alternative therapy.

[Slide.]

This is his data. After two courses of BCG, additional BCG is associated with a decreased proportion of patients remaining tumor free, an increased proportion of patients developing invasive cancer, and an increased proportion of patients developing metastatic disease.

This should not really be a surprise. In patients who have metastatic bladder cancer and fail systemic chemotherapy with a given drug regimen, you don't usually continue that same regimen, you switch to something else. There is no reason to believe that BCG is any different.

[Slide.]

This is the data for other alternatives. Mitomycin has been published by Lundholm, et al., with a 7 percent complete response rate in 14 patients, obviously, not very effective. Interferon, there is a publication and abstract. Glashan has published in the Journal of Urology, 2 of 9 patients, 22 percent obtained a complete response at three months at interferon. The duration of response was short, ranging from 5.8 to 11 months.

Dick Williams has published in abstract in the Journal of Urology having a higher response rate 50 percent at four months, but again responses were not durable with this agent.

[Slide.]

So, what are the alternatives for these patients

who have high-risk disease, they have carcinoma in situ refractory to BCG? At the present, there is no approved therapy, and there are no treatments which have been shown to be safe and effective until now.

[Slide.]

Valrubicin has demonstrated activity after BCG failure. There is a significant increase in time to treatment failure when compared to prior treatment. There is an increase in time to treatment failure in the worst group, the patients with rapid BCG failures, and the time to treatment failure is durable at 18-plus months.

[Slide.]

Patient benefit has been seen. There is a change in the course of disease, cystectomy has been delayed and hopefully obviated. It is, therefore, a therapeutic option in BCG failures. It provides obvious benefit for the patients who have achieved a complete response, and in patients who haven't achieved a complete response and fail with carcinoma in situ, it is a strong indication that there is an alternative therapy indicated that these patients should then promptly be treated with cystectomy.

DR. GULFO: Thank you, Dr. Grossman.

[Slide.]

Before asking Dr. Lange to discuss several safety issues with respect to valrubicin treatment and cystectomy,

I would like to address some of the issues of direct toxicity with valrubicin.

[Slide.]

A total of 230 patients received at least one dose of drug, however, 170 received the agent most consistent with the proposed labeling, that is, in multiple weekly cycles of 800 mg.

[Slide.]

This slide summarizes the most common adverse events, both local and systemic. Most of the events were Grade 1 or Grade 2 in character using the South West Oncology Group criteria.

Local bladder symptoms by far and away was the most common adverse event. Let's take a closer look at these.

[Slide.]

We see that both the incidence, 45 percent, 88 percent during treatment, 51 percent after the treatment period, and severity, I will do the severe category, low, 26 percent and 9 percent. Both the frequency, incidence, and severity increases during the treatment period and returns to near baseline levels after treatment, thus, local bladder symptoms were shown to be both transient and reversible.

[Slide.]

The sites reported back to Anthra any adverse

events that were considered serious as defined in the Code of Federal Regulations. Three patients were considered to have serious adverse events that were associated with the use of valrubicin, one each of reflux nephropathy, transient azotemia, contact dermatitis, and myelosuppression.

The reflex nephropathy was observed in a patient who had a history of reflux nephropathy following both BCG and mitomycin in the past with transient azotemia. The patient developed the same constellation after valrubicin and it was transient.

Contact dermatitis was observed in a patient several hours after receiving the agent on his way home from the clinic. The patient had some erythema on his leg, it was mild, self-limited, not requiring treatment. It was reported by the investigator because it had not appeared in our investigator's brochure up to that time.

One patient who was enrolled in our [peri-TURB] study, that is, the patient received one dose of the drug within five minutes of a transurethral resection of the bladder. He had very high blood levels, those approximating systemic administration, and indeed transient myelosuppression. The patient had a iatrogenic bladder perforation at the time. Very interestingly, the patient developed no signs of peritonitis.

[Slide.]

I would like now to invite Dr. Paul Lange, Chairman, Department of Urology, University of Washington Medical School in Seattle, and President of the Society of Urologic Oncology, to discuss two things - safety issues with respect to salvage treatment with valrubicin and various cystectomy issues.

Safety Data

DR. LANGE: Thank you, Dr. Gulfo.

I am obviously here from a fairly long way because I believe in the benefit of this agent and particularly the benefit as it relates to risk.

[Slide.]

There are several issues when it comes to risk. One, of course, is if you delay cystectomy or don't want to do cystectomy, does the waiting period increase the patient for risk with regard to the tumor, and then what are the risks with regard to cystectomy itself.

So, what we are really asking when we are talking about the delay question, we are talking about 12 weeks, the 6 weeks of treatment, the 6 weeks of quiescence before another observation into the bladder is made.

[Slide.]

There are several ways of looking at it, ranging from the obvious to the more sublime, and that is, first of all, you look inside the bladder and see if it has gotten

any worse, the clinical stage.

Then, of course, the better one is pathologic stage in those patients who did come to cystectomy, what, in fact, was the pathologic stage, and then, of course, the last one being death.

[Slide.]

Let's look at the first one here, which is clinical stage. It is shown on this slightly busy slide, baseline, and then failure, and I think you can see that in the patients who were at the muscle invasive disease, in other words, that trigger point when we do perform cystectomies in most patients. There were basically two, both of them coming from the T1 category.

In those patients who were eventually in the T1 category, that is, into the submucosa, 7 of them came from TIS category and 1 came stayed in the T1 category. So, looking at this slide, you would say that, at first blush, by at least looking in the bladder, there was nothing to suggest that the patients had been adversely affected by this brief waiting period in terms of the severity of disease.

[Slide.]

But let's now look at the more important thing, which is pathologic, that is, the patients who did agree to or did come to cystectomy, what was the final disease that

was found in the bladder pathologically.

[Slide.]

Let me just remind you all that we usually, when we look in the bladder and look at the Path report, et cetera, we divide it into two areas, those that we feel fairly good about, that is, patients who don't have invasion into the muscle, or patients who have only invasion just in the muscle, which has about the same survival, and those in which the degree of penetration into the bladder is significantly greater to the outside of the bladder or even beyond the bladder, the T3 and 4 categories.

So, let's look at the eventual stages in these patients who waited and then compare them to maybe other series where there was no wait.

[Slide.]

Here is, in fact, the series in which cystectomies were done, and, in fact, 11 patients had stages that were in the serious category, that is, pT3. Now, this doesn't surprise the urologist because of upstaging, which we will talk about in a minute, but let's look, for example, at a series, and there are several.

[Slide.]

The best one is shown here on this slide by Amling with a much greater percentage of patients, and these patients received immediate cystectomy. It looked like they

needed a cystectomy, they had one. In fact, you see that the upstaging, that is, the patients who had serious disease when the bladder was taken out, was the same. In fact, this may even be slightly better because I need to remind you that the patients who did get the cystectomy didn't get it right away as they did in this group, but in many cases, got it substantially later than when it was indicated that they should have it.

[Slide.]

Of course, pathological upstaging is what we have implied, that is, you look in the bladder, you take a biopsy as best you can, but you have sampling error, you have observational error, and when you get the bladder out and have a whole specimen in your hand, this is something urologists always see, the so-called pathologic upstaging.

[Slide.]

So, let's look at specifically the 01 and 02 study, and here you see that the pathologic upstaging is about the same, in fact, a little less. So, let's talk a little about that and see a little bit about when their cystectomies were performed and then move on a little bit to the death rate, which was in fact about 5 percent in this group and 5 percent even in the total group including the 03 study.

[Slide.]

Here are the patients in that group who went on to cystectomy, and you can see that I would say that really only one got the cystectomy at the appropriate time, and the rest of them, for one reason or another, at the time they failed and when they finally got their cystectomy, were significantly later in cystectomy.

Maybe you could say this one was appropriate if you happened to be a busy surgeon who has a long waiting list, but even that is stretching it a little bit. I mean the rest of them are really out of bounds with what would be considered reasonable in terms of when the cystectomy was done.

[Slide.]

Here are the patients who died in these groups, and, in fact, none of these patients had a cystectomy, and as you saw from other slides, none of the patients who are responders to the agent in fact died from bladder cancer.

[Slide.]

Let's look at the other side of the coin, which is the risk of cystectomy, because urologists always have to struggle between these two opposing risks. But again in summary, the treatment did not I think represent a risk. It was 12 weeks, two only progressed to clinical progression, 18 progressed pathologically, which is about what you would expect from a series of experience, and the death rate from

bladder cancer I don't think was excessive, and was, in fact, in the group that did not get a cystectomy.

[Slide.]

So, again, let's talk about the cystectomy problems and what does a patient and a physician have to grapple with when they are faced with the possibility of a cystectomy.

[Slide.]

Now, anybody who comes up here would throw this slide up here and say, well, this is what they have in the literature, but this isn't me, I am much better than this, and, in fact, even if you looked at the cold, hard data, you might be able to prove that, but, in fact, this is what is seen in many different series as what the mortality is in cystectomy, and this is a lot better than when I first started urology. It was very common. At the M and M or Mortality and Morbidity Conference, it's almost inevitable that every month we would have at least one cystectomy death, and the mortality then was 10 percent. We have, for the obvious reasons, gotten it down to lower levels, but it is still substantial across the board, and as I will show you, much greater in the higher risk patient, and the morbidity is substantial.

Some of these may be not terribly substantial, others, like fistula or dehiscence, et cetera, obstruction

are significant, and the same thing with long term morbidity in terms of how much that impacts on the patient's quality of life and the surgeon's quality of life, for that matter, in handling these complications.

[Slide.]

Indeed, when you get to patients who are more elderly -- and again, when I first started, we would hardly ever think of doing a cystectomy with a 10 percent mortality to a patient who is 80, but now, of course, we do, and we do get away with it, but we do pay a price, and it is the operative mortality is certainly higher and the morbidity is greater, and in many cases, more severe and prolonged.

[Slide.]

So, from the surgeon's point of view, we don't take this lightly even if we have gotten better, and even among those of us who do this weekly, but also, from the patient's point of view, this is a tremendous thing to have to face. Impotence, yes, can be corrected, but it is usually inevitable in most patients getting cystectomy, and urinary diversion. Until recently, that required a bag, and a bag is extremely threatening and it does impact on quality of life even among the most adaptable. Now we have gotten better with neobladders and continent reservoirs, where they cannot wear, they don't need to wear a bag, but still the quality of life is not as good as your own bladder in most

cases, and in addition, to the patient facing this, it is a much more threatening thing even than it turns out to be.

[Slide.]

So, again, and during the surgery, which can be lengthy, in fact, there is a significant problem. There are certainly comorbidities in these aged patients which make it worse, and as you know, they are all over the map, from patients who are healthy and running triathlons to those who have extreme cardiovascular disease, et cetera, and, of course, age is by itself an increased morbidity. I always tell my residents that if a patient doesn't look 80 before surgery, he certainly will after, and that is a real important thing that has to be considered.

[Slide.]

To some extent this is an experience unique to urologists. They are the ones that have to grapple with these questions, not medical oncologists, not primary doctors, internists, but it is the urologist who has to sit there and try to decide when to hold and when to fold with these two terribly difficult risk-benefit ratio things with regard to surgical factors, with regard to the individual patient, and with regard to what else is there.

In many respects, this is not something that can be easily defined, because every patient is different, every patient has his lifestyle concerns, every patient is

different with regard to his disease, every patient is different with regard to his comorbidities, and that is very difficult to try to put into data, much less explain, particular to the nonverbal physicians, which are usually surgeons.

[Slide.]

So, in summary, there is value in many patients to try to delay and avoid cystectomy, and the attempt at salvage, I don't think at doing this does not incur increased risk as indicated in some of the earlier slides, and certainly to the urologist who has to face this issue in a somewhat private manner at the cystoscopy table, et cetera, having another alternative to try to help make these decisions would certainly be valuable.

Thank you.

DR. GULFO: Thank you, Dr. Lange.

I would like now to ask Dr. Droller to speak to us, providing a perspective on valrubicin. We have asked him to provide an overview and synthesis of the results that you have just heard with special emphasis on the issues that confront both patients and physicians in the management of this disease.

Dr. Droller is from the Mt. Sinai Medical Center in New York. He is the Co-Chair of the Bladder Health Council of the American Foundation for Urologic Diseases.

Dr. Droller.

Summary and Patient Management

DR. DROLLER: I appreciate the opportunity of speaking to the panel today about something that, as you have already heard from my colleagues, we share an enthusiasm for the opportunities provided by this agent because of the efficacy and because of the difficult questions that treatment of this very difficult problem poses.

[Slide.]

In summarizing much of what you have already heard, what I will be addressing are the issues as to these studies providing meaningful data. The study population that was used to obtain this data, the benefit that these patients derived, the sorts of risk these patients faced either through treatment or through consideration of alternative treatments, and finally, what can we consider the role of valrubicin to be in these patients.

[Slide.]

Firstly, the data provided by these studies about which you have heard this afternoon. Here we have a series of data that indicate that this agent provides in a well-documented way a treatment option for patients with carcinoma in situ that has been shown to be refractory to intravesical BCG, the standard treatment approach, the only

accepted treatment approach other than cystectomy for tis disease.

The data have indicated a very substantial response, nearly 20 percent of patients who were rapid failures to intravesical BCG showing a complete and durable response to this agent. As impressive was the complete response and the durability of response to a single course of treatment with this agent, and the response rate itself was significant in this group of very hard-core patients, patients who had already failed multiple attempts to control their disease with multiple agents and multiple treatment courses with intravesical BCG.

[Slide.]

What sort of study population was this? Well, traditionally, this is the population that has as its only other choice undergoing cystectomy. Their carcinoma in situ, having failed intravesical therapy with BCG, were facing the risk of progression. The only thing that would be unknown about progression was when it would occur, not if it would occur, when it would occur, and when it occurred, these people would not only have to face cystectomy, but would have to face cystectomy with a substantially poor outlook for having successful treatment even though they had undergone this very extensive surgical procedure, and at least 50 percent of them would demonstrate metastases within

two years and the majority might well succumb to their disease well within the five-year standard period of monitoring these patients.

They were a particularly difficult group to expect a complete response in, because they had been treated multiply, and they were particularly difficult, as well, because they had been treated multiply with other agents, suggesting that both they are their physician for whatever reason were searching for a means of avoiding undergoing cystectomy in an attempt to cure them of their disease, and this study population demonstrated a well-document and durable response to this agent, a study population that was well described, well defined, and a homogeneous population.

[Slide.]

The benefit, as you have heard from some of the statements and the review that Dr. Lange provided was the avoidance of cystectomy, not that cystectomy can't be done technically and achieve good success and attempt to maintain quality of life in a large number of patients who undergo that procedure, but even with the advances that have been made in alternatives to urinary diversion, the quality of life is not the same as it is for those who have been fortunate to be able to maintain their normal bladder and normal bladder function, and in addition, the ability to maintain normal sexual activity, and in addition, the

ability to maintain a normal quality of life without the need for a postoperative recovery and the ability to maintain a normal quality of life without the risk of complications as occurs in 30 percent of these patients, and in the elderly especially, the risk for requiring rehospitalization for significant complications in as many as two-thirds of patients who undergo cystectomy in the elderly age group, and this in centers who do cystectomy often and select their patients for this procedure.

Many of these patients have comorbid conditions. In those, the risk for additional morbidity and even mortality is increased, and in the centers that have done large numbers of cystectomies and have just been presented to you by Dr. Lange, the mortality is much higher in those patients, the morbidities are higher, and those patients have been selected as being more optimum to undergo the procedure, so in summary, this is not a procedure that we as urologists undertake lightly. It is a significant decision that we are forced to reach.

If nearly 20 percent of these patients can achieve a durable complete response with this agent, what a Godsend.

In addition, this group of patients already have had a lengthy time living with their disease, and we know that since carcinoma in situ is likely to progress in the majority, if not all, patients with this disease if they

live long enough, that these patients were at particular risk for the possibility of progression of disease.

Toxicity was very low with this agent, and it was reversible, so in effect, this does not seem to be an issue and is certainly a fair trade for the potential 20 percent response rate.

[Slide.]

Is there a risk? Well, certainly there is a 12-week delay until we see what the efficacy with the use of this agent is, but as has been shown, the risk for progression during this 12-week time was not documented, and in the overall course of the disease, no risk for the 12 weeks needed for this treatment has been documented.

As I have mentioned, cystectomy is not a benign treatment, and those patients who fail standard therapy with BCG, without any options, then have all of the risks implied by having to undergo cystectomy - the complications, the comorbidities that increase the risk of complications and mortality, and in the elderly where bladder cancer is often seen, the increased operative mortality even in the best of hands.

The clinical practicality is also that many patients will refuse to undergo cystectomy even knowing the risk, or their physicians may well be reluctant to perform cystectomy because of their recognition of comorbidities,

their intuition of the potential comorbidities, their intuition that that patient will just not do well with cystectomy. So, the options there, and the risks, as well, are exposure to other agents that are available, that have been shown to be ineffective, and then ultimately, the risk of progression and death due to disease.

[Slide.]

I would like to conclude in addressing the question of the role of valrubicin by addressing the questions that have been posed to this panel by the FDA in an open summary of the data that has been previously presented.

First, does valrubicin have efficacy? Clearly, it does, and the efficacy is not only in the development of a positive response in very high-risk patients, in patients who have been demonstrated to fail currently available therapies, but that complete response was a durable response, and a durable response lasting for a year and a half and still an ongoing durable response in many of these patients.

Is valrubicin generally applicable to patients with BCG refractory disease? Well, how can it not be? If there is the chance for a complete response in nearly 20 percent of patients who see this drug, why not offer that option to patients with this condition? It has been shown

that those patients will not have any demonstrable risks to trying the patient. Many of them will choose to try it anyway or other agents if this agent is not available.

Then, is valrubicin beneficial in patients who are not candidates for cystectomy or is valrubicin an option for patients who refuse cystectomy? The same argument holds. If there is a chance for some patients to achieve benefit, and there is no demonstrable risk for those who undergo the 12-week trial, and the 12 week is really 6 weeks with an assessment at the end of an additional 6 weeks, if there is no risk, and there is the possible benefit of a complete and durable response, how can we deny the patients, as well as their physicians, with this option for use of this drug.

We all thank you for your attention. All of us would be delighted to answer any questions that may arise in the discussion. Dr. Gulfo, do you have any final words?

DR. GULFO: No, just to thank Dr. Droller and to thank the panel for entertaining us again.

DR. DUTCHER: Thank you very much.

Questions from the Committee

DR. DUTCHER: Now we have time for questions from the committee for the sponsor.

Dr. Sledge.

DR. SLEDGE: When I looked at this last time, the risk side of the equation never particularly bothered me,

but the benefit side did then and still concerns me somewhat now. It is based primarily on the data from the study, and I guess I would like to ask the clinicians who so eloquently discussed this to explain something that may not be obvious to a non-urologist.

If I heard Dr. Lange and Dr. Grossman's comments correctly, basically, a patient who had progressive disease on valrubicin should have had an immediate cystectomy, and yet the majority of the patients who were entered on this trial did not have an immediate cystectomy, and, in fact, the median time to having a cystectomy for the progressers was two years.

Now, when I heard that sort of data, there is only three possible explanations I can come up for it. One is that the urologists involved in the trial weren't very good. Second, is that the patients involved in the trial were particularly stubborn about losing their bladders, or third, and I think this is the one that concerns me, and I think concerned many members of the committee, is that the natural history of this group of patients is just simply not quite as aggressive as comparisons with historical experience would suggest.

I would love to hear your comments.

DR. GROSSMAN: I would like to suggest a fourth possibility, and the fourth possibility which encompasses a

little bit of the one to two anyway, is that the data simply did not exist at that time, that the patients went on the study because they wanted something else, they didn't want to have their bladder out.

Now that the study is completed, we know that when patients fail this drug and are treated with conventional agents, two-thirds of them are going to have their bladder out anyhow. The ones that don't have their bladder out are at increased risk of dying of their disease, and there is now convincing evidence to suggest that yes, if you fail with carcinoma in situ, there is very good data that sooner or later you are going to need your bladder out and there is risk in delaying, so you had better not delay.

That data just didn't exist before, and so this is really new information and just wasn't present before.

DR. DROLLER: I think your question hits at one of the cruxes -- I don't know if that is a word -- of this issue, and we can't predict the history of this even with BCG, just to give you an example, where the original responses were so optimum, we are now seeing reports of late failures with progressive disease.

It is very difficult to eliminate carcinoma in situ completely from the bladder, and that is why personally I was so impressed with the data that was shown to me in those who responded. A complete response is very difficult

to achieve. Even with BCG, sometimes you get little blips.

Eventually, all of these people will progress. What was very impressive about this group of patients to me, as much as the complete responses with the course that was chosen, was the durability of that response.

We spoke a little bit about issues of maintenance, what if, et cetera, et cetera. It is entirely possible that not only does this produce a complete response for those who can't undergo cystectomy, whose comorbid condition may ultimately lead to patients not surviving for a particular period, but certainly within the time frame of the durability of the responses that were seen, it is entirely possible that maintenance therapy with this agent, which is really the only one that seems to show some response rate, will even create a longer maintenance of complete disease free survival, avoiding the need for a cystectomy, and it is even possible to get to that group of patients who may well be candidates for cystectomy and then just refused, that a failure with this agent that has shown efficacy in a certain proportion of patients can be used as an even more convincing argument for those patients not to diddle around any further, that they do need to have cystectomy, which has to remain the definite treatment for this unfortunate disease.

So, we can't predict when, but we can predict that

if patients will live long enough, they will fail with the disease that is no longer curable.

Now, I don't know if that exactly answered the question, but I am trying to put a perspective on what we all deal with when we see these people.

DR. SLEDGE: I guess the question, though, gets back to what you just said. If we cannot predict with any certainty the natural history of these patients, then, how in a nonrandomized setting are we certain of clinical benefit?

DR. DROLLER: Our diagnosis of disease is only as good as the sensitivity of our methods. Here, this group was treated, they had no evidence of disease. If we assume that for whatever reason that enough of these cells were eliminated, there still remained a couple of cells that may have been dormant and then gave rise to additional tumor to come within the sensitivity of our disease, at least we have moved the curve.

Now, are they still at risk for disease, for disease progression? That is virtually impossible to answer, but if we can't even diagnose disease, we can't detect disease anymore, that is a plus both in terms of will those people die of disease, we haven't shown that, and just the cancer anxiety that people will have is another quality of life issue that we can provide to those patients.

It is difficult to answer your question because that is really the $64,000 question of any of the cancers that we treat.

DR. GROSSMAN: The issue of individual patient benefit addressed that to some degree and that it is clear that at least in a proportion of patients, there was evidence for accelerating of disease, that is, the duration of response on successive courses of therapy appeared to be diminishing, and then with instituting valrubicin, you again experienced a long duration of response, suggesting a real change in disease course.

Does this absolutely prove that? Well, I mean if you want to be a realist, no, it doesn't absolutely prove that, but clinically, when you start to see an acceleration of carcinoma in situ and rapid failures despite conventional therapy, that is a real warning signal to the urologist if something isn't done promptly, these patients are going to present with very bad disease, and there is documentation that at least in some patients, that has occurred in the past and that pattern has been altered to the positive with valrubicin treatment.

DR. SCHER: I have two questions. One relates to essentially looking at time to cystectomy, and the second relates to a methodologic issue for refractory superficial bladder cancer trials, notably CIS.

If you look at the time to cystectomy using that as an endpoint, which would include patients either with documented invasive disease or to the point where the urologist deemed that local therapies were no longer suitable. That is a constant function and even with the updated analysis, recognizing there is no plateau, so in essence you are playing with fire from day one.

So, the question gets back to again what Dr. Sledge was asking, how can you convincingly show that delaying cystectomy is your appropriate endpoint if you are really not altering the risk of progression.

DR. GROSSMAN: Again, it is a very difficult issue with risk-benefit ratio, and Harry [Herr] from your institution has demonstrated with very long follow-up, over a 10-year follow-up in a very small but well studied cohort of patients who received a single six-week course of BCG, that with prolonged follow-up, many of these patients fail, and not only do they fail in the bladder, a significant proportion fail with upper tract disease, they fail with prostatic involvement even if their bladder remains clear.

So, the question is are you going to take everybody who has carcinoma in situ and say, well, the chances are you are going to fail 10 or 15 years from now, we will just take your bladder out right now? No, that is not being done. BCG is still being done even though we know

that in the long term, that may not be curative, but we don't know what is going to happen three years or five years or seven years, and whether another drug is going to come out and be the next drug which is going to build on the currently available drugs.

Before BCG, cystectomy was the only alternative, and cystectomy was done. BCG came, and it has had dramatic responses. The long-term responses are not ideal, and so these patients need to be followed carefully, and they may fail, and they may fail outside the bladder, so taking their bladders out may not cure them anyhow, and you need to follow up with yet additional agents.

I am a firm believer in chemo prevention, and we are doing chemo prevention trials, and I think that is an exciting thing for the future, but we are not near to bring chemo preventive drugs to ODAC, but, you know, trying additional strategies to change the urothelial instability is important, and it is an incremental step, and I believe this is a significant incremental step and the only one which I know of that is currently available, hopefully, will be available soon.

DR. SCHER: Well, given the difficulties of doing a randomized trial in this population, and the difficulties in interpreting some of the data related to methodology, if you look at one side of carcinoma in situ in the bladder, it

would be easy to envision that that side could be resected, and if there is no positive cytology to confirm residual disease, you are really not looking at a response endpoint, you are looking more at a progression endpoint.

I would like to see more discussion as to what is the appropriate endpoint for this type of study, because it will come up again. It will come up again in the prevention studies. Again, seeing the data on the antecedent history, knowing that the time intervals between previous failures was relatively constant prior to intervention downstream, when presumably the disease might be more aggressive, that would suggest to me that you have changed the natural history for that patient.

But that is really a progression endpoint, and not a response endpoint, and maybe that is part of the difficulty that many of us are having.

DR. GROSSMAN: I don't know a single urologist who thinks he can treat carcinoma in situ by transurethral resection.

DR. SCHER: That is not the point. The point is you know there is probably something there, but what are you actually measuring, what should you be looking at, is it response or is it progression.

DR. WILLIAMS: Dr. Scher, I just want to ask you about progression. You can't progress unless you have

responded almost. I mean unless you have a response at the first visit, you have a progressed, so I mean there is not really a distinction between complete response and progression I don't think.

DR. SCHER: I would argue that the progression is probably longer for some patients.

DR. WILLIAMS: If you do a full follow-up --

DR. SCHER: It would include those patients who are resected, as well as those with some residual disease.

DR. WILLIAMS: You would get a bigger population then.

DR. SCHER: You would get a bigger population. That is the point.

DR. DROLLER: Some years ago we reviewed, when the National Bladder Cancer Group was doing studies with thiotepa and mitomycin, we reviewed and wrote up an article about just this question, intravesical chemotherapy, is it safe, and we reported on those who had persistently positive cytologies or positive biopsy failure to respond, and seven of those eight people whom we ultimately explored for cystectomy where we didn't suspect any disease endoscopically, we found to have either deeply invasive disease or metastatic disease at the time of exploration.

The clue in those people was not the biopsy that had been done, but the positive cytology which was

persistent, and in no patient who eventually underwent surgery for failure, if they initially had a negative cytology and that was durable over a period of time, small numbers of patients, they did not have invasive disease.

So, the suggestion is that in those who have had a response, their degree of progression seems to be somewhat dampened in comparison to those who have a persistently positive urinary cytology.

Similar findings have been made with a course of intravesical BCG, and again, Harry Herr in your institution has shown that those patients who don't have a response to intravesical BCG and undergo a second course, and then are operated on within a six-month period, many of those will have the same findings as we originally had, that they have deeply invasive disease, some of them have metastatic disease.

The data that Bart showed, the group with the two courses of intravesical BCG, the comments that Dr. Catalona made were that 50 percent of those patients with carcinoma in situ who fail an initial course of intravesical BCG can be salvaged, and no emphasis was even given, although this was just as important, that 20 percent of those who fail the initial course went on to metastatic disease.

So, we are dealing with an issue that yes, we get a clue as to those who are the bad actors from those who

have persistently positive cytologies or possibly persistently positive biopsies, and those who seem to respond clinically as best as we can judge seem to have a more favorable course.

We don't have anything else, but we know that the urgency is placed on our doing surgery in those patients who don't seem to respond. The other issue then is all of the patients who may not be good candidates for cystectomy, what do you do with them.

DR. SCHER: I was referring more to the entry criteria of a positive cytology as a mark of persistent disease, which I think will come up.

DR. DUTCHER: Dr. Simon.

DR. SIMON: I am still having some trouble with the question that Dr. Sledge raised that I don't think really was answered. It seems to me that really to demonstrate efficacy and safety, you sort of have to demonstrate two things - one, that the natural course of the disease is such that if the patient is not effectively treated with, of example, the drug, and is left sort of for a long time with ineffective treatments, that that will translate into advanced disease, and therefore, if one can assume that that is the case, then, obtaining durable complete remissions of some patients is a demonstration of efficacy.

If that is not the case, then, demonstrating complete remissions is not a demonstration of efficacy because your patients who didn't have complete remissions, they went for long periods of time without being effectively treated, and you are saying that there was not any high incidence of advanced disease at surgery than you would expect.

So, you don't have a natural course of disease here that is appropriate for concluding that complete response is a demonstration of efficacy.

The other side of it, for demonstrating safety, we would have to demonstrate that over the period of time that you are talking about observing the patients, that that doesn't itself translate into a high rate of advanced disease at surgery for the patients who don't respond.

You have suggested that that is the case, but I really don't see how given the natural -- you know, what is striking about the clinical trial you presented is not that you presented new data showing the urgency of surgery, you have presented new data for a bunch of patients who didn't want surgery, and who went on for two years, and apparently did just as fine when they got surgery as they would have otherwise.

DR. GROSSMAN: But the data also shows that the patients who achieved complete response did not need

surgery.

DR. SIMON: The patients who didn't have complete response went for two years and didn't need surgery either.

DR. GROSSMAN: Two-thirds of those had cystectomy and a minority of the complete responders had cystectomy. That is a fairly significant difference especially if you are the one having your bladder out.

DR. SIMON: Well, but at the time, they had cystectomy at a very delayed time, and they did not have apparently an increased percentage of advanced disease at cystectomy, so them delaying their cystectomy for two years apparently didn't cost them anything even though they weren't effectively treated.

DR. GROSSMAN: Well, there were a number of patients that died of metastatic bladder cancer.

DR. GULFO: And with pathologically advanced disease.

DR. SIMON: You were suggesting that 18 percent of the patients at cystectomy had stage 3 or 4 disease, and that that is what you would have expected from some other series with cystectomy, and that there were four patients who died. So, if that is a higher rate than what you would have expected from immediate cystectomy, then, we sort of need to know what that rate is, because that side of the equation is the risk of administering this drug and delaying

cystectomy.

DR. DUTCHER: But I also think, remember from the last discussion, we talked about that maybe these patients, because they could get into this trial, were a different group of patients, and the patients that responded and then re-responded, and then re-responded to BCG, I mean some of the BCG responses were well over a year or a couple of years.

So, I mean part of what you are disturbed about may well be that this is a different group than the run-of-the-mill patient that would come in starting from day one and then you would have to make changes in therapy.

Can the urologists give us a feeling for that?

DR. GROSSMAN: Well, you are suggesting that there is a dramatic difference between the complete responders and the nonresponders, and there isn't anything in the analysis which suggests that the complete response group, either from their overall demographics or past history of disease or current history of disease, or the response to prior therapy is any different than the nonresponders.

If the complete responders are not any different than the nonresponders, why didn't they need their bladders out when the nonresponders needed their bladders out? You know, it is either magic or it's valrubicin.

DR. SIMON: You haven't really demonstrated that

the nonresponders needed their bladders out.

DR. GULFO: Well, the prior course to BCG -- let me ask Dr. Droller a question. When you give BCG, what do you expect, do you expect one year disease free? No, you expect --

DR. DROLLER: It is just a very complicated issue, and it is just not a black and white issue. We are delighted, I think, when we see a response, and the response, the only thing that we have by response is to get a negative biopsy and a negative urinary cytology.

The 70 percent response rate that is described for BCG is probably higher than what we actually see, and what we will not uncommonly see is an initial response after the first course with negative cytology, negative biopsies, and then as we follow these patients along every three months, their cytology will revert to positive.

We may or may not get a positive biopsy. That is a sampling issue. So, we will be tempted to give another course. Because of the inadequacy of treatment even with BCG, there have been a number of studies that have addressed the issue of maintenance.

Originally, maintenance was felt not to be necessary, and now there is much more consensus in urologic circles that maintenance is necessary because of the failures that have been seen.

There has also been emphasis on the development or the use of other agents that might be effective when BCG fails. There are some patients who will continue to respond to maintenance therapy, and then the issue is how long do you maintain patients on that therapy.

As you go on with some of these patients, failures are seen in sanctuary sites, the lower ureters, the prostatic urethra, and at the time that those failures are seen, as usually detected again by a positive cytology, oftentimes those patients are beyond the realm of cure.

Now, clearly, those sites were not involved initially, otherwise, the cytology would have been persistently positive despite a response in the bladder. So probably there is an issue of a pagetoid spread of the disease when it has lost its control to the BCG or even not controlled initially to those sanctuary sites.

Since the only way that we have of monitoring the disease and the response to therapy is with a urinary cytology and the conversion to negative indicates to us that a patient doesn't have their disease, nor do we generally see disease progression in the absence of a persistently positive cytology or conversion again to a positive cytology, the conclusion that we make is that we have been able to control the disease with presumably the BCG.

We generally don't see a disappearance of the

disease if you don't treat, and we don't have good treatments other than BCG. So, when I looked at the data that Dr. Gulfo showed me -- and I wasn't involved in these studies at all, and my response initially was show me -- my impression was that here we had an agent that was potentially useful in those patients who had failed several courses of BCG.

I asked him to provide for me those who had been more rapid failures to BCG, and the impression that I had from looking at those patients was that while some of them may have initially responded for a durable time, their period of time of response was growing less and less, and if I saw that patient clinically, that patient would have been a candidate for cystectomy, and oftentimes in the conversations we have with these patients, they will say isn't there something else I can do, isn't this a big operation, how can I avoid it.

So, you try to proceed to another treatment knowing that that patient may be at risk. Can you quantify that risk, can you predict when that risk will manifest itself? No. So, this particular group of patients was impressive because of their failure to multiple courses and their more rapid recent failure to the course of standard treatment.

So, would we consider them at risk clinically?

Yes. When would they fail? I don't know, but in the absence of being able to document the presence of disease, our feeling of comfort would be substantial that those patients either did not have disease or had disease that was not particularly active in providing a sufficient number of cells to detect clinically.

DR. DUTCHER: Go ahead, Dr. Grossman.

DR. GROSSMAN: It is a very confusing issue, and let me try and shed another way of looking at it.

Carcinoma in situ is by nature noninvasive superficial disease, and there is a natural reluctance both on the physician and the patient to take their bladder out for something that is not even invading the lamina propria.

These patients are meticulously followed, and being meticulous followed with superficial disease, a proportion of these patients are not going to fail immediately and all of a sudden develop muscle invasive disease because their disease hasn't even bridged the lamina propria yet, so it really is carcinoma in situ. Eventually, it will if it's ignored, but it hasn't just yet.

With meticulous follow-up and close observation, with good urologists, many of these patients can, in fact, have their bladders out at a time, "in the nick of time," before they develop real bad disease, and it is shown that these patients were followed very carefully and, in fact,

most of them had their bladders removed before they developed real bad disease, and that is a testimony to the care of the urologists treating them.

But the point was the patients failing treatment still had to have their bladders out, and the patients not failing treatment, most of those did not have their bladders out, and that is the fundamental difference.

It is not a matter of, you know, these people had their bladders out two years later, and these people didn't have their bladders out. Well, if you wait enough time, maybe eight or nine years later, these people might need their bladders out or maybe they may never need their bladders out, but there is really a traumatic difference in the proportion of patients having cystectomy, and with careful follow-up, you can skate a very thin line and say, okay, we won't take your bladder out today, but maybe next week you might have it out, and most of the time when you do that, you will be able to take their bladder out in time, in some people you won't even with meticulous follow-up, the disease can explode without you realizing it.

But I think the time to cystectomy analysis is very worthwhile, and you should really consider it carefully.

DR. DUTCHER: Dr. Schilsky.

DR. SCHILSKY: Actually, I guess I was going to

say something similar. It seems to me that if nothing else, valrubicin might be a strategy to assist clinicians in selecting those patients who might be more safely observed over time.

I mean I am persuaded that carcinoma in situ probably doesn't have too many spontaneous complete remissions, so I think that the drug probably has biological activity. We have seen that 20 percent or so of patients have complete resolution of disease.

I think that Dr. Sledge hit the nail right on the head in terms of what the issues are, but it seems as though the conundrum we are facing is that we are told, on the one hand, that patients who have BCG-refractory disease, that appropriate treatment is immediate cystectomy, and yet the data in this trial suggests that many patients who have BCG-refractory disease are not have immediate cystectomy.

Now, it is likely that there are many, many reasons to explain why they are not having immediate cystectomy. I guess the concern that I would have is that if I was just observing the patient even meticulously, it seems to me that there is perhaps a greater risk that by the time they have a cystectomy, they are going to have invasive disease if they have persistent carcinoma in situ. Then, is the risk that they will have invasive disease if they have a complete response to valrubicin.

I don't know that this is an issue that we are ever going to actually be able to sort out based upon the data that we have, because we don't have randomized clinical trials data, but my conclusion from this discussion so far is that, if nothing else, valrubicin might be an effective tool of selecting patients for whom observation may be a more comfortable approach.

DR. DUTCHER: Are there other questions for the sponsor? This is question part. We have discussion later.

DR. LANGE: I would just like to say something because I have to catch a plane.

First of all, I don't think there is any urologist who believes that you see CIS, that you can look in again in three months and six months, and it will be gone. That doesn't happen.

So, at least I am convinced about that. Secondly, I have always been somewhat of an opponent of BCG, thinking that it was shifting the curve to the right, but not ultimately doing any good, and that if we could snap our fingers without any morbidity and mortality, everybody should have their bladder out as soon as CIS is found, but, in fact, while it does look like if you live long enough, you are going to get it back, and maybe it does just shift the curve to the right, the advantages of delay are, from an individual patient point of view, and a patient position

point of view are considerable, and at endpoint is whether you still see it, and that is an endpoint.

As far as using this drug to select out the good actors, which has always been a problem in these kinds of studies, all we can say is that on the basis of comparisons as best we can do them, there doesn't seem to be that kind of factor. There is no difference between responders and nonresponders in terms of the adversity of things that you say.

So, I have become a true believer in the sense that I do think that seeing a response is useful clinically in dealing with these very difficult patients, and it doesn't bother me that after two courses of BCG, when the books say take your bladder out, but these are the patients that you can't take their bladders out right away, and so the delay is not unusual. That doesn't bother me.

DR. DUTCHER: A question for the urologists. Let's assume that response indicated clinical benefit. How persuaded are you by the patient as their own control, the curves that showed the shorter responses and the longer valrubicin response? Is that unexpected in your experience with other agents, if you were to follow two courses of BCG with thiotepa, mitomycin? I mean that is the data that we are expected to look at, and we need to get a sense of is this a real thing.

DR. GROSSMAN: The response rates with other agents are terrible. The response rates with mitomycin, there is one published report of 7 percent.

DR. DUTCHER: Not rate, duration, the durability issue.

DR. GROSSMAN: Well, there is no data on durability for mitomycin, and the durability for interferon is terrible, and most people would not use thiotepa in this setting, and the proportion of patients that received doxorubicin in this population was essentially zero. So, that tells you what is being done.

So, your only drug out there is mitomycin with a 7 percent complete response rate, no known durability.

DR. DROLLER: Just to quickly address, that was exactly what impressed me when I first looked at this group of patients, and yes, if I have an agent where the BCG didn't control the disease as best we can tell with positive cytologies or biopsies, but usually cytology, and we have an agent that now, in the same patient, has effectively decreased any indication of disease, and that is in a very compressed period of time, that to me was impressive.

DR. GULFO: Dr. Dutcher, may I follow up on something? Is that all right?

DR. DUTCHER: Sure.

DR. GULFO: Could I ask our statistician to

discuss the predictive value of a complete response in the issue of stratifying patients for positive outcome, negative outcome, and using that as a basis to decide who we can treat less aggressively, who we can treat more aggressively.

DR. DUTCHER: Identify yourself for the record.

DR. KIRSHNER: Ron Kirshner, Anthra.

[Slide.]

What we are attempting to do here is address in Dr. Gulfo's initial slide, the correlation of this response measure as predefined the protocol, the response as defined by negative biopsies out to six months clearly correlates with these clinically meaningful outcomes, and here time to cystectomy as shown by a significant p-value, reduction in risk of getting a cystectomy.

Also, based on the demographics we have seen, that these two groups, there is nothing to distinguish them demographically or in terms of risk factors that might predict this kind of response.

So, basically, what we have here is a small subset of responders, namely, 20 percent that show response to valrubicin, show negative biopsies, which translates in terms of clinical benefit.

DR. SIMON: I just want to make a comment. I mean you are basically determining when a patient gets a cystectomy based on whether they have a response or not, and

then claiming that doing a significance test as to whether the time to cystectomy is longer for the CRs versus the non-CRs is circular. It is meaningless.

DR. KIRSHNER: The point here, it may be a somewhat more simpler one. The initial question on Dr. Gulfo's slide was to what extent does the clinical response translate to clinical benefit, and just graphically, if you even take away the p-values, you can see visually that the response rate as predefined in the protocol translates into clinical benefit.

DR. D. JOHNSON: That is Basic Statistics 101. I mean that is not true. This has been looked at by numerous clinical investigators over the years, and there is actually classical papers which have compared this type of analysis of response and non-response that have been published. I will be glad to provide them to you, if you would like to read them, but this may simply reflect biology of the disease. I mean that is all that may reflect.

So, it may not be in any way related to valrubicin except that it points out a biologic effect of that subset of patients. That is all that means.

DR. DROLLER: May I address that? I am not a statistician, so I am really ignorant about this, but I am a clinician and I know what prompts us to do cystectomy, and that is the fear of progressive disease.

I fully agree that the biology of the disease is very important in categorizing or separating compartments between responders and nonresponders, and I am familiar with not analyzing or separating the two because it is a circular type of thing.

But what we are trying to address is the issue of what prompts us to advise a patient to undergo cystectomy and what we actually see in the clinical setting. Here we have a certain group of patients where there is some sort of apparent biologic effect which we can't explain. We assume it is related to their having seen the drug, because they have seen something else that was found to be ineffective, and they have done something to indicate that their disease is no longer present.

Can it come back? It can. We don't understand that biologically either, but it is very common for people in the literature to have a complete response and then eventually to have recurrence and succumb to their disease.

Now, the issue then is why not do a cystectomy once you have a treatment failure, and the reality of the clinical setting is, one, we rarely, if ever, see failure to the point of aggressive disease without an indication clinically that disease is present in some way. That is the positive cytology that we were talking about before.

Number two, the clinical reality is that we can't

do cystectomy in every single clinical setting, either because of patient reluctance to have that, or because of the condition of the patient that doesn't permit them to have that.

So, in that setting, what do we have available, and if this provides the availability of something that can be effective, this is something that provides an advantage to the patient, to the physician.

The question is will there be other agents down the road that will enhance that effect or not, obviously, that is future, but statistically, we can't argue from what is statistically important, but from a clinical viewpoint, I think the data almost speak for themselves.

DR. DUTCHER: Dr. Simon.

DR. SIMON: I want to ask Dr. Lange a different question.

DR. DUTCHER: He is just about ready to run out the door.

DR. SIMON: You had indicated that you would expect from a cystectomy series an 18 percent incidence of stage 3 and 4 disease.

Maybe I missed it, but could you clarify where that data comes from and how you would sort of see it so of comparable to this data, and sort of summarize, put together how you see the risks of delaying cystectomy from this

study, whether there are any such risks, not only for the patients who went to cystectomy, but you indicated there were four deaths of patients who hadn't, and were there any other cases of metastatic disease in patients who hadn't gone to cystectomy.

[Slide.]

DR. LANGE: Is this the slide you are referring to?

DR. SIMON: Right.

DR. LANGE: And the question there is -- I am not quite sure what your question was.

DR. SIMON: Well, part of the question was why should we not be concerned about that 18 percent on the left. On the right, what kind of a series of patients is this? Immediate cystectomy at what point, what does immediate mean on that graph on the right there?

DR. LANGE: These are patients who have a variety of indications for cystectomy, either they have invasive disease already, they have CIS. In fact, all of these are CIS.

DR. SIMON: All of these are superficial.

DR. LANGE: All of these have CIS. So, instead of giving another drug or a drug, in the case, some of these didn't have drugs at all, they performed immediate cystectomy. In the other group, they had CIS, and they had

the drug, and then they got the cystectomy, and the point being is that the delay did not result in any change in the ultimate pathological consequences.

DR. SIMON: There are also four patients in the valrubicin group who died of advanced disease who didn't have cystectomy, and were there any other patients who had metastatic disease diagnosed?

DR. GULFO: All patients who had metastatic disease with our follow-up have died. The thing about this slide that is interesting, no patient who responded died, and the cystectomized patients -- I am sorry -- none of the patients who died had a cystectomy.

DR. SIMON: So, it is basically 15 out of the 90 patients at this point have had metastatic disease.

DR. GULFO: No, 4 patients -- well, these passed on, so I would assume they had metastatic disease.

DR. SIMON: I am sorry?

DR. GULFO: They passed on, so I assume they had metastatic disease, but the 4 prior -- can we go back? Let's count any n-positive.

[Slide.]

DR. GULFO: That person had lymph node positive disease, this gentleman. I think I would say 6, 6 patients had metastatic disease.

DR. SIMON: I thought on the 18 percent was 11.

DR. GULFO: That was pathologically advanced disease.

DR. GROSSMAN: That was locally advanced disease, not metastatic disease.

DR. SIMON: Locally advanced disease at a stage that presumably has a bad prognosis, is that right?

DR. GROSSMAN: Yes.

DR. SIMON: That is really what I am trying to get at. How many patients are there here in this series of 90 who wound up having disease at a stage that carries a bad prognosis?

DR. GULFO: Ten. Four patients died, and 6 had, at cystectomy, pathologically advanced disease, and only one of the patients who went to cystectomy and had pathologically advanced disease had cystectomy within a window that Dr. Lange would be comfortable. That is within three months -- this one had it within a month -- of when the protocol said the patient failed, the drug failed.

All of the other patients that had a poor outcome as measured by pathologically advanced disease had their cystectomy significantly delayed after the drug was already shown to have failed.

DR. SIMON: I thought it was 11 out of 63, which was 18 percent.

DR. GULFO: Eleven out of 61 is 18 percent for all

the studies. The FDA, in the write-up to you, focused on the pivotal studies. That includes 10 patients. The percent for pathologically advanced disease is less in that group, but we included everyone.

The concept, if I just may say one thing about the use of the agent to stratify patients, Dr. Grossman made a point during his presentation that the patients who have an incomplete response induced derived benefit, and the patients who don't have a complete response induced derive benefit, too, because now there will be an agent with a profile known and the risk of not performing cystectomy when it should be performed will be known.

So, that is according to the logic that I interpret Schilsky as proposing of benefit, knowing the patients that have to be acted upon quickly is certainly a benefit of the failures. Inducing a complete response in the patients that respond is clearly a benefit.

DR. DUTCHER: I think we should have break.

Thank you for your presentation and your answers. We appreciate it. We are going to have a 15-minute break and then we are going to hear from FDA.

[Recess.]

FDA Presentation

DR. DUTCHER: Dr. Odujinrin, please.

DR. ODUJINRIN: Thank you very much.

On behalf of the FDA, I will be presenting the data on the application by Valstar.

[Slide.]

This and the next slide is a list of people involved in the review within the FDA.

[Slide.]

This slide contains the general information which you have heard a lot about concerning this drug. I will simply point your attention to this item here, which is the proposed indication.

The drug is proposed for us in patients with CIS of the bladder who have failed all available intravesical therapy including BCG. The standard of care in this setting, as has been mentioned, is cystectomy.

AD-32 treatment is intended to be an alternative to cystectomy. The applicant anticipated that the drug would further impact the course of the disease in three months or the patient would be expected to proceed to cystectomy if unresponsive to treatment.

A critical issue in the application is the risk to the patient for delaying the needed cystectomy while undergoing this drug therapy.

[Slide.]

At the last ODAC meeting on June 1st, the following issues were considered and certain conclusions

were reached. The CR achieved with this drug therapy was small, and 19 of 90 patients, or 21 percent, as determined by Anthra, and as determined by the FDA was 7 definite responses and 7 potential responses.

Cystectomy was performed on 37 of 90 patients. Four of the 37 cystectomized patients had advanced bladder cancer or greater than pT3. Four uncystectomized patients died of bladder cancer.

[Slide.]

The Advisory Committee was unconvinced that the CR rate achieved was worth the risk of delaying cystectomy or that the study population was in imminent need of cystectomy. There was also concern about disease progression while patient are on AD-32 therapy.

[Slide.]

Given this information, then, why are we here again? This cartoon is supposed to represent the Agency's meeting with the company on June 1998, as well as the numerous telephone calls and faxes which transpired in the interim period.

[Slide.]

This slide and the next summarizes the substance of the communication which transpired between the FDA and the company.

Anthra request is summarized in this slide, that a

re-evaluation of response rate be provided, a re-evaluation of risk involved in delaying cystectomy, and an identification of a patient population who might be candidates for AD-32 treatment.

[Slide.]

The FDA's comments and suggestions are summarized here. The applicant noted that that response duration was longer on AD-32 than on their previous intravesical therapies. This was in response to one of the issues raised by a member of the committee during the discussion of the application.

The applicant claimed that it could provide this evidence, that among responses in patient, duration of response was longer.

Point number 2 was while cystectomy is the standard of care in this category of patients, there is a population of patients for whom cystectomy is not feasible for medical reasons. The FDA suggested that the applicant should identify this population of patients for whom cystectomy was medically contraindicated.

Thirdly, in the original protocol, failure of AD-32 treatment with only papillary disease and no CIS led to a designation of no response, because such patients do not generally require immediate cystectomy, response rate to this therapy would be increased if such patients were

considered to be responders.

The applicant noted, and the Agency agreed, that it had used more stringent criteria in determining CR than those used by another company in a previous submission.

[Slide.]

These are therefore the issues for consideration at today's meeting - an analysis of duration of response after previous therapies, a re-evaluation of rate of complete response, consideration of the actual risk of delaying cystectomy for three months, and a consideration of whether there is an appropriate patient population for AD-32 treatment.

[Slide.]

Before proceeding to a discussion of the issues, I would like to provide the committee with a brief review of the protocol and indicate where the re-analysis differs from the original protocol.

[Slide.]

The study objective is to determine efficacy and toxicity of intravesical AD-32 treatment in CIS patients who had recurred or failed after multiple courses of intravesical treatment including BCG.

[Slide.]

The treatment regimen is that indicated in this slide, 800 mg dose of AD-32 in 75 cc of diluent was

instilled into the patient's blood with a dwell time of two hours. The treatment course consisted of six consecutive weekly instillations.

[Slide.]

As shown in this slide, the protocol required rigorous re-evaluations both at baseline and at specified follow-up intervals including biopsies of numerous specific sites and urine cytology.

The rigor provides confidence that the disease observed at baseline, if not observed at follow-up, was gone rather than just missed due to random sampling. When patient had less than protocol-specified follow-up evaluations, the reviewer than begins to question the aggressiveness of disease, the appropriateness of follow-up of the therapy given, and whether the drug caused the change seen with the treatment.

Such omission led the FDA to classify some patients as potential CR.

[Slide.]

With the new analysis, recurrence papillary disease does not exclude patients from the CR category, and the CR, as indicated in the protocol, there is no evidence of disease at primary disease evaluation, which is at three months, and at six months.

No evidence of disease is defined as indicated and

the change is as highlighted here, that is, no recurrence of papillary disease and papillary lesions. These are now acceptable as evidence of response.

[Slide.]

Anthra issue number 1 therefore deals with the analysis of duration of response that complete response patients experience with AD-32 treatment. You have seen versions of this slide many times today, and I will just go briefly over what we think of the slide.

The slide shows the 19 patients who responded to AD-32 treatment, and the same set of patients in terms of duration of response to the last therapy, second to last therapy in 19 patients each, and then the third therapy in 12 patients.

[Slide.]

Complete response patients appear disease free longer on AD-32 than on prior intravesical therapies. The number is small, 14 of 90, but the analyses are exploratory.

[Slide.]

Data and graphs of time to cystectomy as measure of clinical benefit was shown in several slides by the applicant. The date on the 90 patients showed 19 patients had a longer time to cystectomy than 71 patients with no response.

The applicant provided the analyses as

statistically significant.

[Slide.]

We believe that the analysis, even though exploratory, results suggest an association may be exist between CR and time to cystectomy.

[Slide.]

The second issue that the applicant raised deals with re-evaluation of disease response criteria. This slide represent Anthra's list of 10 patients who were originally classified by the company as nonresponders due to failure with papillary disease only.

Duration os response to AD-32 treatment is provided on each of the 10 patients. As a result, the company would like to increase the complete response rate to 29 of 90 patients, or 32 percent.

[Slide.]

The FDA analysis of these 10 patients is presented in the next three slides. There were two definite CR and 8 no responses. The two definite CR patients both show positive cytology at baseline with change to negative at three months post treatment.

Bladder mapping was well documented in these patients, and they changed from Tis to Ta at the sites were provided. The duration of benefit was 8 months and 6 months respectively.

[Slide.]

Among the nonresponsive patients, two patients were not evaluable because the history of CIS was not convincingly demonstrated. Review of available pathology reports was not convincing, and in one patient, cystectomy was performed, and the specimen still showed no CIS.

[Slide.]

This slide therefore represents the Agency's summary of re-analysis using the expanded DR criteria, which includes the 10 Ta G1/G2 patients. The CR rate increases to 9 of 90 patients, or 10 percent, and the potential CR remains unchanged at 7 of 90 with a definite and potential CR rate of 16 of 90 patients.

Median duration of response depends on the method of calculation, being 12 months until the time of last biopsy, or 21 months to recurrence.

[Slide.]

The third issue raised by the applicant deals with medical contraindication to cystectomy. This table represents the company's list of 16 patients who are not considered to be candidates for cystectomy due to medical complications.

The medical contraindications associated with each category of patients is listed in the slide. Four of these patients are classified as responders by the applicant,

while the FDA classified two patients, two of the 16 as responders.

[Slide.]

The point of this slide is that this is not a unique group of patients, but a representative sample of the patients in the study. Response to AD-32 among the 16 patients is similar to overall response in the study. Demographic and other baseline characteristics were also similar.

Radical sensitivity was safely performed on two of these elderly patients. Both patients had deep muscle invasive disease.

[Slide.]

This slide represents a summary of four studies that was published by Stroumbakis and Herr at Memorial Sloan-Kettering. They deal with very elderly patients older than 75 years. The summary represents the range of zero percent to 5.3 percent mortality.

Given that two of the studies have very small number of patients, 9 each, one can estimate the mortality rate to be less than 5 percent. The overall mortality rate in patients of all ages, as has been previously mentioned, with cystectomy is 2.5 percent.

The morbidity rates determined by length of hospitalization and other complications, postoperative

complications, similar in three of the studies, and somewhat higher than in patients that are younger than 75 years.

[Slide.]

It would appear as if cystectomy can be performed in octogenarians, but with a mortality that is slightly higher, of 5 percent compared to 2.5 percent.

Mortality rate varies by surgeon, institution, and the decade of the publication.

Morbidity and mortality rates improve for all patients with improvement in surgical procedures, as some of the urologists here have indicated.

Mortality rate in this study, in the 44 cystectomized patients, is zero. At least none has been reported to us. The morbidity information is not available.

[Slide.]

On the issue of approval of AD-32 due to patient refusal of cystectomy, this may be affected by assumption of the availability of a safe and effective alternative treatment. There is a need for patient education about the disease and available treatment options, and I cannot agree more with the gentleman from the association who spoke at the beginning of the session.

The next set of slides deal with safety issues, regulatory considerations, and a summary of the presentation.

[Slide.]

Ten of 90 patients had adverse outcome, 6 of 44 cystectomized patients had deep muscle invasive disease, 4 of 46 uncystectomized patients died with metastatic bladder cancer. Most patients did not have immediate cystectomy.

The median delay between treatment and adverse outcome was 17.5 months with a range of 1 to 36 months. This is in comparison with the expected delay of three months in the protocol.

[Slide.]

The regulatory policy has readily evolved in the division over the last eight years, and consists of the following. A med treatment capable of delaying cystectomy with durable CR rates in a substantial proportion of patients is a worthwhile clinical benefit.

However, such therapy should not place patients at unreasonable risk of developing metastatic bladder cancer while undergoing this treatment.

[Slide.]

Non-randomized clinical trials could be adequate to support approval of such treatment if a sufficient response rate and duration are observed.

[Slide.]

In summary, then, expanding the CR criteria to include Ta G1/G2 patients adds two patients to the CR

category, for a total of 16 patients.

The median duration of response depends on the method of calculation, and as previously mentioned, 12 months to time of last biopsy or 21 months to recurrence.

Patients responding to AD-32 treatment appear to experience a longer duration of response than to their previous intravesical therapies.

[Slide.]

Ten patients had adverse outcomes with 4 deaths from metastatic bladder cancer in 46 non-cystectomized patients and no deaths in 44 cystectomized patients.

Six patients at cystectomy had deep invasive disease including one patient with lymph node metastasis. In all 10 patients, the actual delay after failing AD-32 treatment was much longer than the expected delay of three months.

Improvements in surgical procedures have decreased the risks involved in cystectomy for all patients.

[Slide.]

In concluding this presentation, I would like to highlight what has changed and how much is the change for any re-analysis of data presented by the applicant since the last meeting of ODAC.

I shall relate these changes to the issues raised at the beginning of this presentation.

The first issue is re-evaluation of response rate. The complete response rate increased from 7 definite and 7 potential to 9 definite and remains at 7 potential. The patients' experience in complete response had a longer response duration on AD-32 treatment than on prior therapies and a long time to cystectomy than nonresponse patients, and this may be an issue of patient benefit.

The second item deals with re-evaluation of risk. Seven of 90 patients in the trial remain in CR until the time of data cutoff, and 4 patients were lost to follow-up. The denominator is therefore different from the number presented the last time, on June 1st, so only the enumerator can be compared.

Notice the number of cystectomy patients increased from 37 to 44, and stage progression increased from 4 to 6 patients. That is two more patients had deep muscle disease at cystectomy.

Change in adverse outcome is with the two cystectomized patients with deep muscle disease, which changed the number of patients at risk from 8 during the June 1st presentation to 10 at this presentation.

[Slide.]

Delay in cystectomy in the 10 patients was 17.5 months. The risk to the patients in this study was not due to the three-month delay from drug treatment. It would

appear that most of the patients delayed because they did not want cystectomy even though they had failed treatment.

If there is a population of patients who absolutely cannot tolerate cystectomy and for whom this drug is a viable alternative, there may be such a population. It would be highly conjectural to estimate the size of the population.

Should the drug be considered for patients who fail or refuse cystectomy, or cannot have cystectomy for medical contraindications?

This is a philosophical question with regard to patients who refuse cystectomy. The Division would like the input from the committee. I am concerned that patient refusal of cystectomy might be fueled by hopes that a safe and effective alternative is available.

Until it is determined by this committee and the regulatory process that AD-32 is safe and has a reasonable efficacy, I believe that one cannot make a recommendation for this indication.

DR. ALBAIN: Repeat your last statement.

DR. ODUJINRIN: I believe that one cannot make a recommendation for the indication of patient refusal until this committee and the regulatory process makes a determination as to the efficacy or safety of this drug.

Questions from the Committee

DR. DUTCHER: Dr. Margolin.

DR. MARGOLIN: I have a couple questions for you. The indication that you read here, I believe was the same as the one in June. That was not revised to be what we are supposedly talking about today, that the drug is indicated for patients who have a contraindication to cystectomy?

DR. ODUJINRIN: Well, the new indication is for patients who for medical reasons cannot tolerate surgery or who refuse surgery.

DR. WILLIAMS: Dr. Margolin, you are actually going to be asked all the questions. You can pick an indication, but I think the specific one the company applied for was either medical or refused, either of those options.

DR. MARGOLIN: Can I ask another question? I don't know whether you know the answer or whether it needs to go back to the company. What I haven't seen in all this presentation is the time between -- we have seen these plots of time to cystectomy in complete responders or time to cystectomy in patients with clinical benefit versus time to cystectomy in nonresponders.

Do we know what the time to cystectomy is following failure, following redevelopment of a positive cytology or positive biopsy in patients who were CRs? That would be the time that we are comparing with really versus the nonresponders at least in terms of what is the delay

after the indication that they have malignant cells back in their bladder.

DR. ODUJINRIN: Time to cystectomy information that we have is what is provided by the company, and that is 24 months in patients who are complete responders. It is 24 months in nonresponders and it has not been reached in responders, but we believe that the data are exploratory, and the statistical significance that is claimed need further clarification.

DR. DUTCHER: Dr. Simon.

DR. SIMON: I think there is some information about that point, because on the sponsor's figure on figure 3 on page 11, this was the Kaplan-Meier curve of duration of CR, and it shows that by two years, about 60 percent of the patients have relapsed from their CRs, but on page 16, on time to cystectomy, we see that most of the patients, most of the CRs still have not gotten cystectomies.

DR. ODUJINRIN: Right. That is what I said.

DR. SIMON: So, there is a long time delay between it looks like failing, you are relapsing from your CR, and getting a cystectomy.

DR. ODUJINRIN: I will let the company respond to that.

DR. GULFO: Yes, I can answer Dr. Margolin's question. On the four complete responders who upon failure

ultimately underwent cystectomy, their cystectomies were one year and three months after failure, three months after failure, five months after failure, and three months after failure. Their stages at cystectomy were pathologic stage T1 Grade 2, pathologic stage T1, pathologic stage T0, which happens, and pathologic stage TIS, all superficial.

DR. DUTCHER: Dr. Scher.

DR. SCHER: I was wondering if you can discuss your interpretation of the curve which shows the differences in time to failure on previous therapies and valrubicin. I didn't get your conclusion beyond that this was an exploratory analysis.

DR. ODUJINRIN: Well, we had 14 patients of the 19 patients as responders, and the 14 patients, the analysis that we had suggested that the 14 patients had on the duration of response on AD-32 treatment than on the previous therapy. We didn't have the raw data as such on these patients.

DR. SCHER: And your interpretation of that?

DR. ODUJINRIN: Interpretation is that it appears as if on these as if these patients did derive some benefit, but again, the data as I mentioned are exploratory, and the significance of the information cannot be determined from the --

DR. SCHER: What would convince you in this

setting?

DR. ODUJINRIN: Pardon me?

DR. SCHER: What would convince you short of a randomized trial? Intervention A doesn't work twice, or A and B sequentially have essentially the same time to progression curves overlap and medians, a few outliers, then, a different intervention in patients who are proven to recur, then shows approximate doubling in time to progression. So, what else could that be?

DR. ODUJINRIN: Oh, what we are saying is that we do believe that the change is real.

DR. SCHER: Right, but you are not convinced.

DR. WILLIAMS: Dr. Scher, let me answer as part of the team, but I was impressed by this analysis because, in discussing with the statistician, I don't think we can put p-values on it, but if you look at the potential biases, I believe they are biased against AD-32, because your follow-up is not likely to be as rigorous as they are in this trial, therefore, you are likely to overestimate the previous duration. You might not even have a full diagnosis. You might re-treat based on something else.

So, they were just measuring treatment to treatment, and I think the bias would be more likely against AD-32. Therefore, some of the things we labeled as potential CRs were because maybe we didn't have the full

second biopsy to fit protocol criteria or we might believe that they snipped out the disease and it wouldn't have even been there, but knowing that you have another set of data that suggests that you have changed the natural history of disease led me to believe that indeed this other group we are calling potential were actually real, and we just didn't have the data from the protocol.

So, I did find it somewhat convincing that it helped to solidify that there is an enumerator of some size here.

DR. SCHER: Can I ask the same question of Dr. Simon, if he could discuss that point, because he was concerned about progression, altering natural history to a point where a clinically relevant endpoint is affected.

DR. SIMON: Well, to me, I mean I don't deny -- I mean clearly there are those regressions here, about 15 percent, and they seem to be pretty durable. I guess the question is whether if you did nothing with those patients, or you treated them palliatively with more BCG or whatever all these patients were getting while they were waiting to get their cystectomies for many months, whether they would have basically had the same stage at cystectomy as what they did.

Now, I think sort of operationally, you know, people are more comfortable, as Dr. Schilsky pointed out,

observing a patient who seems to have had a CR, but from this type of a study, I don't think you can really say whether that really contributed.

DR. SCHER: You can speculate de novo a population that is not destined to invade or progress based on p53 status, for example, and you may have an imbalance, but when a patient proves that their history is to progress --

DR. SIMON: I am just saying that the patients who didn't have the CR, basically, had a long time until their cystectomy, and they didn't have advanced stages either, so what could we conclude about that delay, that causing regression and permitting the patient to be observed a little bit longer than that, or longer than that, substantially longer than that is really --

DR. SCHER: But then you would interpret a recurrence endpoint as irrelevant.

DR. SIMON: Well, I am not sure we really know what is happening in a real subclinical, you know, at a real detailed level. I guess for myself, what it comes down to is it seems like a reasonable -- it causes regressions -- it seems like a reasonable approach. There is a tradeoff, and I think the risks are not well defined and for the patient it is going to be a touch choice.

So, for the patient who has to make that decision, if there is not a medical contraindication to cystectomy, I

think given the data here, it is very tough choice. It would not accurate I don't think to say that there are no risks from the delay of progression to advance disease.

DR. JONES: If I could make one comment. Brian Leland Jones, McGill University, a member of the Scientific Advisory Board from the good old days when my life was filled with novel anthracyclines, but anyway I wanted to refer to a comment that Dr. Rick Schilsky made earlier, and to me, I just want to spend one minute on what to me is the crux of the question.

If you have a patient that has failed BCG two or three times, and is not cytologically and/or pathologically positive, whether persistent or gone from negative to positive, what else is there to do but cystectomy, and how else can a surgeon become comfortable in recommending anything other than cystectomy, and what has been presented here I think is a clear drug that has some biological activity in converting cytological and/or pathological positive to negative with an 18 or 19 percent CR rate.

Now, if we come to the issue of does AD-32 alter the natural course of this disease, I think, as Dr. Sledge and Dr. Simon have very clearly pointed out, no, we absolutely cannot be sure. If, on the other hand, we ask the question does a trial of this drug defer cystectomy in all of the patients, the answer is yes.

Does a response to AD-32 in the responding patients, does that make the surgeon absolutely comfortable in deferring a cystectomy, the answer is yes, and is the patient placed at an undue risk by deferring the therapy, It think we are agreed it is no, and that to me is the issue.

DR. DUTCHER: Dr. Raghavan.

DR. RAGHAVAN: I was just going to comment that I think one of the points that somewhere along the line has been lost, I think one of the urologists spoke to this point, but it was perhaps lost in verbiage, was the fact that carcinoma in situ eventually kills people, and we got tangled I think a little in the fact that the patients who were not complete responders didn't obviously do badly, and the corporation got stuck because they were trying to demonstrate that there wasn't risk in being exposed to the drug, and that was then turned around to imply that because there wasn't risk, therefore, the drug wasn't doing anything, and it is sort of you are damned if you do and you are damned if you don't.

But the reality is if we look at the literature and the wealth of clinical experience from Drs. Lange and Droller and Grossman, the reality is what each said, is that this disease eventually progresses and kills people if you wait long enough.

While one would take as a reasonable point Dr.

Simon's contention that maybe there isn't evidence that this drug is having a biological effect and that it is for the comfort of the urologist that CRs are being sought, the reality is that absence of cancer until proven otherwise is probably a good thing, and if we come back to the basic tenet of today's meeting, which isn't supposed to be the same as last time, but which is meant to be focusing on patients for whom cystectomy is medically contraindicated and then maybe as a secondary issue those who refuse cystectomy, then, we have actually seen some reasonable data to suggest that there is some biological impact from this drug.

The one thing that struck me is that the company, it seems like they made a whole bunch of mistakes in doing the wrong study, but they have done one thing very well, which is they have set the most incredibly stringent criterion for complete remission, they have had a six-month gap. It is very, very -- I don't think we have ever seen it at this committee, a criterion of complete remission that requires a six-month time interval, and that has kind of been glossed over, and I think my guess is they have done that so that they wouldn't get into the trap of us saying, well, what was the remission and how do you know you biopsies the right spot, and so on.

I think that was the point Grant Williams was

making. So, they have stacked the deck against themselves. They have tried to compare duration of response with patients being sort of randomly and maybe cavalierly treated with BCG without stringent endpoints versus their own trial, which has stringent endpoints and have come out with at least the implication of disease free interval, and they have set a very rigorous criterion of complete remission.

That implies to me at least that Dr. Williams' contention might be reasonable, and I just would not like to dismiss those two points. I am not sure that I share the concern that we don't have enough evidence to grant an approval in this context, particularly in the context of patients who would be medically inoperable.

If we then set that criterion, it is probably not the business of this committee to define whether a patient has the right to choose if they are given appropriate information. Then, the key is to make sure that there is appropriate information in the package insert.

DR. DUTCHER: Are there any other questions for FDA? Go ahead.

COL SCHULTZ: Was there a criteria in determining when BCG was refractory? I mean was there a time length, months? We are talking six months here for AD-32. How did the physicians determine BCG was refractory and how many times?

I have undergone four different sessions of BCG, and I am still here, I still have my bladder. I just need to get settled in my own mind --

DR. ODUJINRIN: I think I will let one of the surgeons answer that.

DR. GROSSMAN: In the study, 70 percent of the patients received two inductions. An induction is generally classified as a six-week course of BCG. In addition, there were another 8 patients who also received maintenance or started an induction and were stopped because of toxicities. So, that brings it roughly to around 78, 79 percent of patients received essentially an attempt at two cycles of BCG, and the data in the literature suggest that that is a reasonable point to stop induction therapy.

There are other ways of giving BCG with an induction and a whole series of maintenance treatments, but that is a different issue.

COL SCHULTZ: I am still not clear. I am looking for what time between the end of the BCG course of treatment and then recurrence of the tumor or disease was used as a measuring point or was there one?

DR. ODUJINRIN: The way the protocol was written, a patient should at least have failed BCG by three months.

COL SCHULTZ: Three months.

DR. ODUJINRIN: Yes.

DR. DUTCHER: You mean be away from BCG for three months.

DR. ODUJINRIN: Right, be away from.

DR. DUTCHER: The difference between having failed a course and it being a period of time later and refractory are not necessarily the same thing. I mean if there is an 18-month interval, is that refractory?

DR. GROSSMAN: There is no absolute definition of that item when you come right down to it in the literature. These patients on average had three recurrences in the period of 24 months, which suggest rapidly recurrent refractory disease. That is not what one would expect if you see a new patient with carcinoma in situ walking in the door being treated with BCG.

DR. DUTCHER: Any other questions for FDA? Dr. Droller, did you want to make a comment?

DR. DROLLER: BCG acts in a way presumably that is different from intravesical chemotherapy. The theory is that an immune response of some sort is involved.

Depending upon the timing and these studies are currently really underway, and a recent South West Oncology Group suggested that a booster to the immune response may reinforce or maintain the efficacy of the BCG, and that is, if the induction response obtained a complete response initially and you want to maintain that response with

booster treatments.

Someone who has repetitive treatments, either that is because there has been a lengthy interval between one treatment, the diagnosis or documentation of a disease-free status, and then recurrence at some time hence, or because there has not been documentation of disease-free status and the physician feels that perhaps a second course may achieve that disease-free status, and then if it does, to have periodic booster treatments or maintenance treatments.

For someone who does not respond, they are at risk in an undefined time period for the development of more aggressive disease. Now, we get into the molecular biology which we are only now learning more about. There may be some forms that don't have the biochemical ability to penetrate and extend, but in a majority of what we are finding, they certainly have the molecular changes that portend that potential activity.

So, what happens is if someone has no documented response, they are probably more at risk for recurrence. Those who have a response, but then recur or are detected clinically probably don't have the same risk for progression in the immediacy of follow-up until they show a more rapid recurrence pattern.

In looking at the patients that were presented in this series, the ones who had demonstrated a pattern of more

rapid recurrence were the ones that were focused upon in some of these slides as showing the response to valrubicin, and that was the most impressive part. They were people who clinically we, as urologists, would consider at greater risk for the potential of progression, and they were the ones whom we would urge to undergo cystectomy, or if they were not candidates on a medical basis or a cystectomy, we would all be losing a lot of sleep as to what is going to happen.

DR. RAGHAVAN: One of your early slides, you summarized the FDA discussions with the applicant, and the second point that you listed was the FDA suggested that the applicant identify the population of patients for whom cystectomy was medically contraindicated, and that was just left hang.

Have you or the applicant defined exactly what that population should be, so if this committee were going to approve for this indication, what are we actually talking about?

DR. ODUJINRIN: Well, I did show a slide of 16 patients provided to us by the applicant. The company, unfortunately, did not show that slide today. I commented on the slide. I indicated that the 16 patients did not represent a special population.

DR. WILLIAMS: Certainly, these were criteria suggested by the applicant. They were not at all detailed,

and I don't think we should really consider them criteria. There is a precedent for leaving it up to the physician. At least in our recent approvals we have done with this [photophrin], we talked about when in the judge of the physician, laser wasn't indicated. We did that for I guess esophageal disease.

So, I think this is a good point for discussion if you decide to undertake that indication as something to consider.

DR. DUTCHER: Thank you very much.

Committee Discussion and Vote

DR. DUTCHER: We are going to proceed with discussion.

Dr. Williams, it was suggested that we narrow Question No. 1. Do you want to make a comment?

DR. WILLIAMS: Question No. 1 actually was hard to word because I guess in my mind, it was meant to originally say is there any efficacy which might be useful for any indication, but since other questions follow, it is sort of hard to do, so you don't want to ask it too big and too little, and I think for now why don't you answer it let's say for a limited indication, is there efficacy here as it applies to a limited indication of medically contraindicated or patients who refuse.

You can actually construct it any way you want.

Why don't you go ahead and take a shot.

DR. SIMON: I thought the way you did construct it was, No. 1 was medically contraindicated and then when you get to 4, you get to for patients who refuse.

DR. WILLIAMS: Okay. Why don't you do that.

DR. DUTCHER: There was some concern that it was a little wide open-ended, but anyway what we have done is revised Question No. 1 to specifically say: Does the committee agree that these data demonstrate efficacy in this setting, i.e., carcinoma in situ refractory to BCG and for whom cystectomy is contraindicated?

DR. SCHER: That is the way you want to discuss it, lumped or separate?

DR. DUTCHER: I think we should discuss it for limited indication, for limited patient population.

DR. WILLIAMS: Actually, the way it was worded was to mean for BCG-refractory CIS, because efficacy is efficacy. The question is, is it enough as applies to each indication. The intent was is there any efficacy here basically, and then you can apply it to the other indications as you wish, is it enough for these settings.

If you don't think there is any efficacy at all in any of these limited indications, then, it would be no. I mean if you would like to do it that way.

DR. SCHER: Let's focus on the efficacy question

first.

DR. DUTCHER: So, we should focus on efficacy to start with.

DR. BEHRMAN: We are really in a way asking three separate questions. We are asking -- because you have to make a different risk-benefit assessment for those in whom it is contraindicated, those for the general population, those who refuse. The segments are very different.

I think our feeling was during the general discussion, it did get a little bit confused, so it would probably be best to start with the most limited indication, which is those for whom it is contraindicated and work our way up, so that we don't get bogged down.

DR. SIMON: I really agree with that. I think to sort of discuss it in general for efficacy, I mean there is different levels of evidence of efficacy, and I think it is going to get really bogged down.

I think it would be best to interpret it the way you read it, that No. 1 is for patients who are medically contraindicated for cystectomy.

DR. DUTCHER: Who don't have other options.

Dr. Margolin.

DR. MARGOLIN: Just to make sure we are all on the same level here, if we do go on to broaden this, we are revisiting what we visited in June, and I want to just make

sure that I understand correctly that the only two additional pieces of information or analyses that were done to differentiate the September meeting from the June discussion of this drug was the difference in time to cystectomy in responders versus nonresponders, and the -- what was the other one --

DR. SCHER: Antecedent history.

DR. MARGOLIN: Right, and this retrospective, unrandomized comparison of a poorly defined BCG response versus the AD-32.

DR. WILLIAMS: And there were a couple of others. One was that we sort of solidified our CR rate to maybe be 18 percent, and the other is the risk analysis really wasn't well discussed, that is, if you attributed the full 10 percent of the risk to delay for AD-32 versus if you come to grips with the fact that, in reality, the three months for delay for AD-32 was only a fraction of the actual delay of these patients.

So, I mean there are three or four issues, and if I think a revote is indicated.

DR. DUTCHER: Dr. Schilsky.

DR. SCHILSKY: Sorry to prolong this, but my own view is that we really should discuss efficacy as a separate issue because the issues are efficacy and risk-benefit, and they are not the same, and the risk-benefit is going to be

influenced by the population that is the focus of discussion more than is the general issue of efficacy.

DR. DUTCHER: All those who want to discuss efficacy first?

[Show of hands.]

DR. DUTCHER: Okay. Half and half. Limited indication? Four. Abstaining? Let's talk about efficacy. Dr. Scher.

DR. SCHER: I will make a stab at actually doing it both at once. I think we will all agree that the natural history of in situ disease is one of progression to a more advanced stage, in some cases metastatic disease without an invasive component.

So, what you are really addressing is when do you lose the window of curability, i.e., presumably if you did a cystectomy on all patients at first diagnosis, the overwhelming majority of patients in that setting would be cured.

The median duration of in situ disease in this population was 25 months, and to my read, three additional months of treatment with investigational agents really seems quite small within the natural history, and I think it is very important to have alternatives available because there clearly are patients who benefitted for the following reasons.

The next question that come up is, is a retrospective analysis of time to cystectomy definitive? The answer is no, it is retrospective, but it certainly is highly suggestive in a trial where patients are meticulously followed, and I guess I have confidence in my urologic colleagues that they will know when it is appropriate to, as Dr. Lange likes to say, hold them versus fold them, particularly when there are rigorous criteria.

You then get into the question of what proportion of patients need to show benefit for a drug to be approved, and the FDA's interpretation of 18 percent, is that enough? To my view it would be. Can you necessarily say that this is a clear cause the effect? The answer is not necessarily, but when you do see an antecedent history of patients who clearly have shown biological aggressiveness in terms of recurrence, and then they don't recur, I think it is reasonable to use their patients as they own control in that situation, and that to me would be a measure of benefit.

It was also of interest, however markedly consistent, that time to failure was on the previous therapies in many cases up to three.

Also noted was the response in patients who were clearly BCG-refractory, and these are patients, 8 cases who had failed on BCG in what appears to be less than six months. The question is how do you interpret the pathologic

upstaging? I think that is very difficult, particularly when the time to cystectomy was not uniformly conducted, but in the patients, again as presented, in whom the interval was short three months, no patient had invasive disease, so I think the risk-benefit ratio is really a non-issue.

You are essentially dealing with a situation where you can develop more aggressive disease at any point in the natural history and three months in the natural history for a patient to try an alternative seems to me to be quite small.

DR. DUTCHER: Other comments? Dr. Raghavan.

DR. RAGHAVAN: I agree with everything Dr. Scher said except perhaps for his last statement, because I think that it is not clear when the window of safety in the management of invasive bladder cancer is actually opened and closed. The reason I was sort of hoping we could discuss limited indications first is that I think, to my mind, that is a no-brainer. If you have a person who is not well enough to have a cystectomy, from the data we have heard, I tend to be impressed that this gives them an alternative. It is not air-tight, but it is an alternative.

For the patient who has failed BCG and who is eligible for cystectomy, I am not sure that the data are strong enough just to say, well, why don't you try for a period of time, because the reality is that out in the open

world, a three-month trial as done on a clinical defined protocol study, often kind of lengthens out, and we have seen that happen with BCG, we have seen it happen with thiotepa, and so on, that the rules for clinical trials don't necessarily apply in clinical practice, and therefore, I think there is a risk that the well-intentioned, but maybe less educated clinician can continue to try an "experimental drug," hoping it will work without really understanding the risks.

So, to my mind, the fact that this has come back in its current context makes a lot of sense to readers of the discussion of last June, which I didn't participate. I am not impressed that there has been a great change in the available data.

So, I agree with everything you said, Howard, except that I am not personally convinced that this is ready for prime time with no qualifications.

DR. DUTCHER: Dr. Simon.

DR. SIMON: I think in terms of is there evidence of efficacy, I don't think this can be a yes or no sort of thing. I think there are different levels of evidence of efficacy. I think there is some evidence of efficacy here. It is not the level of evidence we would like to see in general.

It may be I would think that a level of evidence

that you would accept in a clinical situation where there are no alternatives, so that is sort of my take on it.

DR. DUTCHER: A glimmer.

Dr. Ozols.

DR. OZOLS: I tend to agree with Dr. Scher. I think the situation where you have got a disease that has a variable natural history, with a bad endpoint, but still can be very benign for relatively long periods of time, you tend to re-treat these patients, as we have heard from Colonel Schultz that he has had it four time, a three-month delay to try to see if AD-32 works, I really don't think -- I mean we don't have hard data, but I don't think that puts a patient at significant risk.

DR. DUTCHER: Have we got the sense of the group on that one? Oh, Dr. Sledge, sorry.

DR. SLEDGE: I hate to play ping pong here, but I tend to agree with Dr. Raghavan on this. I don't view this as being particularly a question of toxicity or loss or opportunity, because I would agree, I think three months is relatively minimal from what we have heard of the natural history of this disease.

On the other hand, I think we do have a responsibility to try and decide whether or not there is real clinical benefit with this drug, and clearly from this study, we don't have that clear evidence of clinical benefit

that I think most of us would be comfortable with for most drugs.

So, while I am reasonably comfortable allowing this for a very limited indication, I would be very uncomfortable about opening the floodgates on this drug.

DR. SCHER: This is not a floodgate population. I mean seriously, if you are trying to design trials for this population, to give you a sense of the difficulty, the number of centers involved, the number of urologists involved, many of whom are working in academic centers with large practices, the majority of these patients don't go on to second and third line therapy. It is probably the minority.

I don't view this as a floodgate. It is really a highly selected population. I think the urologist feels comfortable they can monitor the situation and clearly, if you see explosive disease within the bladder, diffuse in situ, I would suspect that most urologists would not fool around with that.

DR. SLEDGE: The problem I have, though, is this idea of comfort with the urologist's clinical judgment. We heard Dr. Lange here today say that he was distinctly uncomfortable with the clinical judgment that was applied in this trial. I mean he pointed out several cases where he said he would have done a cystectomy immediately. So, if

there is that level of disagreement, I don't know why we should feel a level of comfort.

DR. MARGOLIN: I agree strongly with Dr. Sledge on that. I tend to be often pointing out practical situations that don't necessarily help us, but I can just see -- it is very hard to feel comfortable regulating approval of a drug for a group that we don't have a definition for.

I mean I just think of the situation where you have an elderly patient in an HMO setting, you do not have academic urologists. You have urologists who don't feel comfortable with the complications of a high quality cystectomy and for whom repetitive intravesical therapy is very appealing and for whom perhaps that degree of precision and knowing exactly when to cut bait, as it were, or send them out of the HMO where there is all sorts of issues about capitated care could get in the way, and I think this could get out.

I mean it is not floodgate numbers, but the judgment here is something you ought to be very, very careful about, and so I think we want to be sure this is a highly active drug before we start saying we are going to release it for a small fraction of patients because we are not sure it really benefits the whole group, but it may benefit just enough to be for a slice of patients, but without really defining what that slice is.

DR. DUTCHER: Dr. Justice.

DR. JUSTICE: We may get into this later, but Dr. Raghavan asked earlier about defining medical contraindication. In thinking about that, I think that is going to be very difficult to do in labeling. I mean we can try to put some parameters on it, but unless the committee has some suggestions, we are happy to listen to them, but I mean I think it all comes down to the practicing physician making decisions, and there is a limit to how much we can actually put in the labeling.

DR. WILLIAMS: You are not saying that we can't put it in the labeling that it is the judgment of the physician.

DR. JUSTICE: No.

DR. BEHRMAN: But that, in fact, is what we as an agency typically do. Although you are right that it is discomforting to approve a drug for a narrow population, which is typically almost impossible to define, that is, in fact, what is more often done than not, because a drug that is safe and effective, and, in fact, very important for a certain population, can be very hazardous in another population, and other than the example of thalidomide where there is a very strict distribution system, in general, the Agency does put the faith in the system, and there aren't a lot of alternatives to that.

DR. DUTCHER: Dr. Schilsky.

DR. SCHILSKY: Just a couple of points. I guess I am persuaded that there is a population of patients who benefit from this drug. I wish I knew how to decide who they were, and it would be nice if there were some biological marker that you could check in urine cytology that would be predictive of who would respond and who wouldn't.

But in the absence of that, I think you just have to try it and find out. I don't think we know really very much at all based on these data about what the risk of delaying cystectomy is by three months, because, in fact, nobody had a cystectomy at three months, or very few did, and the ones who did have superficial disease determined.

All the patients who had deeply invasive disease had cystectomy that was long delayed, you know, much longer than would be recommended, so I don't think that we really know what the risk of delaying cystectomy is, but it doesn't seem to be very high.

So, I don't think that is such an issue. I am concerned about trying to limit the patient population with respect to the indication, because, first of all, I am not sure I understand the intent, and frankly, I think trying to do so is sort of ridiculous and not likely to be anything that can actually be accomplished in practice.

I agree completely with what Kim Margolin just said about that, because if you try to limit the indication to patients for whom the treatment is medically contraindicated, well, who is that? We can't agree on what population that is, and frankly, a patient for whom the cystectomy is medically contraindicated tomorrow, you know, and three months from now might be buffed up enough to be able to undergo a cystectomy, strange as that may seem.

The issue of also trying to limit the indication to patients who refuse cystectomy, I think is fraught with danger and is not something that we should attempt to regulate.

So, my own view is that if we believe that there is sufficient efficacy to recommend approval, that we should just recommend approval for BCG-refractory carcinoma in situ.

DR. BEHRMAN: Can I address that for a moment from the Agency's point of view? Limiting the indication does a couple of things, one of which it does restrict the promotion. In other words, if there are concerns that we really don't understand what this would do in the general population, it can't be promoted in that population, and that is fairly important.

The other point is that it does help to convey to the practicing physician the limitations of the database,

where the risk-benefit ratio was felt to be appropriate. So, it is something actually that we think is relatively valuable.

DR. DUTCHER: Dr. Margolin.

DR. MARGOLIN: Just a follow-up on that, I mean I don't pretend to really understand exactly how the FDA works in terms of these final decisions and the package inserts, but there is a difference between limiting a drug to patients who cannot undergo what would otherwise be the standard alternative versus limiting a drug based on a risk-to-benefit ratio that may make it a little too toxic for a population of patients with the disease.

You know, we are not talking about a risk-benefit toxicity issue of the drug, we are talking about of the alternative, which kind of turns it around in a way.

DR. DUTCHER: Dr. Ozols.

DR. OZOLS: As I recall, one of the major concerns we had in June was really this whole issue of efficacy. I mean at that point we were talking about a response rate, and it was down to 7 percent, and there was a lot of debate between Agency and the sponsor about responses, and so forth, and now we have come to a conclusion that it is a consensus at least that it is somewhere double that, maybe triple that, so around 20 percent.

I think that adds a significant amount of comfort

level if we are talking about 20 percent of the patients who had progressive disease on BCG getting a complete response to therapy, I think that is a much stronger indication of clinical benefit and activity than a 7 percent response rate, which we were talking about last time.

So, I think the situation has changed when we are talking about general demonstrated efficacy in this patient population.

DR. DUTCHER: Dr. Raghavan.

DR. RAGHAVAN: I think we are getting into a forest and trees problem here, because there are a number of drugs that can be given intravesically. There is thiotepa, there is doxorubicin, et cetera, et cetera.

When the debate and discussion started, I was really quite concerned that predicated on Dr. Simon's concern that related to definition, and so on, that approval would be totally turned down because there wasn't finite data, and in the last five minutes we have gone right to the other end of the spectrum where now we are going to force patients to have this and deny them cystectomy -- which is fine -- but I just want to get back to reality for just a couple of seconds.

A 20 percent response rate in BCG-resistant disease is substantially less than maybe an 80 percent, if you can call it, or maybe 100 percent response rate that is

achieved by cystectomy. I just want to keep a certain perspective. I personally don't have any difficulty in understanding why someone would want to retain his bladder. I also understand that if you had superficial bladder cancer and it had resisted the impact of BCG, a patient should understand that there is a proven treatment with a high chance of permanent cure, and a very promising treatment, with a not completely defined chance.

I think the point that FDA seems to me to be making is that the decision we make here will allow the appropriate level of information to be presented to patients who wouldn't otherwise necessarily get it.

In the practice that I have with advanced bladder cancer -- I would be interested in Howard's experience -- I see tertiary referral cases who unfortunately have gone way too long on programs of intravesical treatment, patients who have had BCG and then have tried a little of this and a little of that, and so on, under the aegis of trying to preserve the bladder, and during which time the window of opportunity has completely closed and a cystectomy is no longer possible because the patient has metastatic disease.

So, I think we need to be cautious. I certainly admire the fact that this drug seems to have activity. I definitely admire the fact that the company has been quite stringent in assessing a criterion of complete response, but

this is recycled data from the previous meeting, and it hasn't suddenly changed to become a standard of care, and I would hate to see it thrown out based on what I have just said. I am also not sure that we know enough about the drug to have it just out there in the community ready to replace cystectomy.

The risk is that the way things work, an indication does not equate to the stringent requirements for protocol-driven care as per protocol, and people will certainly use the drug for more than this magical three months that people have conceived.

I think the point that we need to define very clearly is what we think we are doing.

DR. DUTCHER: Dr. Ozols.

DR. OZOLS: That is sort of the same question about BCG use in general. I mean if you want to get rid of this disease, you do a cystectomy immediately, and it is clear that that is not the standard of care. I mean patients don't want that, and urologists don't want that.

So, to dismiss a 20 percent response rate and say you can get 100 percent response rate with cystectomy, that is the same issue you could raise with BCG, then, why give BCG.

DR. RAGHAVAN: Except BCG has actually gone through the process where survival data have shown that is a

safe thing to do. The response rate is higher. Now, I am not trying to set a higher standard for this product because this is BCG failures as I understand it.

What I am saying is that we haven't really quantified the level of risk because the study wasn't designed to do so. Grant Williams' suggestion that we relook at a product and say, look, there is a window for use here, let's let it in, and at the same time bet more experience, I think that is sensible.

To suddenly just say, oh, fine, we have another one, let's go with it, and give it an indication, I think we haven't quantified what the risk is from the data that are available.

DR. OZOLS: But I think the message we are hearing is that it is probably unlikely that we will ever get a trial which will get us that information, and who is fault for that inability to do that trial is something that we can't resolve here, but we may not have that information, and I think we should have that option out there on the basis of what we have right now.

DR. DUTCHER: Dr. Margolin.

DR. MARGOLIN: Sort of a two-part comment or perhaps rhetorical question to the FDA again. I wonder if the possibility of an expedited-like approval that requires some postmarketing studies from the company and reporting

back with data has been considered, and as part of that I want to point out one of things that at least one of my esteemed colleagues and former professor, Maury Markman, has been popularizing -- I know Dr. Ozols knows -- in the area of ovarian cancer, and this issue of defining refractoriness.

I think a Phase III trial, for example, of AD-32 versus BCG intravesical therapy in second-line therapy, those who failed one round of BCG therapy might be just what we need to really know the activity of this drug and carefully define the endpoints, and perhaps that would function a proper postmarketing study if we were to allow this with the very limited indication as an expedited type of approval.

DR. WILLIAMS: Certainly, I don't think we are thinking about accelerated approval in this case, you have the population, I am doing the study to look at some other endpoint that shows clinical benefit, I don't think is really practical.

In terms of a Phase IV study, sometimes we do have Phase IV commitments, but the company is investigating this in superficial bladder cancer. I don't know if there are any other CIS studies, but certainly I am not sure that at this point I can think of the study that would answer the questions that you want answered except for a large

randomized, controlled trial, and I don't know that that is doable. The company might want to comment on what trials they are doing and whether they are going to do anymore in CIS.

DR. GULFO: There is one thing that I would like to say. The Eastern Cooperative Oncology Group is just starting a trial right now with this agent. Having seen the data in carcinoma in situ, they decided, well, let's look at papillary tumors that are proven refractory to BCG and have the same characteristics, proven refractoriness, and they are not doing a randomized trial, they are doing a 80-patient study, and I asked why don't you randomize it, and they said to me what are we going to randomize to, nothing has proven effective.

The other point I would like to make about that request -- and Dr. Grossman and Dr. Droller can help me out with this, please -- BCG, despite the level, its use is changing the way it is used. It is now used in a maintenance regimen ala SWOG data that have been published in abstract form a couple of years ago. I don't know if the publication is out yet.

So, to do a single induction and then when the patients fail, do a trial versus valrubicin, I agree with Dr. Williams 100 percent. The numbers to do that trial, it already took us four and a half years to get 90 patients,

would be prohibitive, but even the way BCG is being used, it is being used now in a maintenance booster fashion. I don't even know if that trial could be done.

DR. DUTCHER: Dr. Justice.

DR. JUSTICE: Dr. Margolin, could I ask you to clarify your question about accelerated approval? Which indication were you talking about, were you talking about the broader indication or are you talking about the indication for patients who have medical contraindications to cystectomy?

DR. MARGOLIN: Actually, that would make me more comfortable with the broader indication, although I am not really comfortable with either one.

DR. JUSTICE: It would make you more comfortable with the broader?

DR. MARGOLIN: More comfortable with the broader one because I still think the practical constraints on the limited indication make it difficult to really --

DR. JUSTICE: The question would be what trial would be done to confirm that benefit, and there have been some discussions. You know, it is very difficult to randomize versus cystectomy.

DR. WILLIAMS: This trial is already in the full population. I mean this trial was in the population that you would want your final trial to be done in. It would

just have to be a different design, I guess.

DR. DUTCHER: Question No. 2 I guess is where we are. We are not voting, we are discussing. We discussed No. 1. Well, we can vote. Do you want to vote? Okay.

Does the committee agree that these data demonstrate efficacy of Valstar in this setting?

DR. SIMON: I really object to that phrasing because it deals with efficacy as a binary yes or not, and that is just not the nature of efficacy. There is different levels of evidence, and it is just a very naively worded question.

DR. WILLIAMS: Is there any efficacy for any setting?

DR. SIMON: There is levels of evidence of efficacy, and the level of evidence that is appropriate depends upon the clinical setting.

DR. WILLIAMS: How would you like to word it?

DR. SIMON: I would prefer to word it the way it was before, that it is asking about the narrow indication. We gave you a discussion of efficacy, but I think to vote on a binary definition of efficacy is meaningless.

DR. DUTCHER: What about if we go through the next three questions and add efficacy, based on the efficacy demonstrated, and then it defines the population to be considered?

DR. SCHER: Is there sufficient benefit?

DR. BEHRMAN: We have three votes, for medically contraindicated, for --

DR. DUTCHER: General population.

DR. BEHRMAN: -- and for those who refuse.

DR. DUTCHER: Is that more reasonable?

DR. SIMON: What is it?

DR. DUTCHER: The next three questions are subpopulations, and we could basically ask does the risk-benefit ratio, as defined in the study, permit approval in this population.

DR. SIMON: Where is the question for the population with a medical contraindication?

DR. DUTCHER: No. 3.

Let's start with No. 3. In patients with a medical contraindication to cystectomy, relying on physician judgment, treatment with Valstar is not associated with an additional risk of delaying cystectomy; therefore, the benefit to risk ratio of treatment with Valstar is increased in this group. Given the evidence of a reasonable complete response rate and no added risk, the Division believes the case for approval is strong in this population. Does the committee agree?

Discussion? Dr. Margolin.

DR. MARGOLIN: It is very unusual that the

Division writes in the question how we should vote. Do you really want us to vote on that question as it stands that way?

DR. JUSTICE: We are just giving our opinion these days.

DR. MARGOLIN: It may be quite different than Dr. Odujinrin's opinion.

DR. DUTCHER: No, his was for the refusal. His opinion was on the refusal. Am I right? You opinion that you stated had to do with those that refuse?

DR. WILLIAMS: If you are asking is there a spectrum of opinion, yes, there is, from the reviewer to the office director.

DR. SCHER: Can you rephrase this to risk-benefit ratio would support the approval, because none of these can be quantitated. What you are really doing is you are basically asking for a judgment on risk-benefit ratio based on the data presented. If the question were written in that way, since none of these, the absolute risk of delaying cystectomy by three months is unknown.

DR. DUTCHER: In patients with a medical contraindication to cystectomy, does the risk-benefit ratio of Valstar support approval for this population? That is the question.

Does the risk-benefit ratio for Valstar presented

in this study support approval for this population -- I am sorry -- in the patients with medical contraindication to cystectomy, does the risk-benefit ratio for Valstar support approval for this population? Dr. Schilsky.

DR. SCHILSKY: Before you answer the question, just one comment, I guess, which is that as far as I can tell, we actually don't have a study that was designed to answer this question in this population. We only have a few patients in this broad study that might be interpreted to have a medical contraindication by some people.

DR. BEHRMAN: That is correct, but again that is not unusual because if you believe that there is evidence of an effect, that these tumors did not regress on their own, but you are uncomfortable with -- you don't have a comparison to cystectomy, that is clear, so you don't want this drug to be approved and potentially promoted as an alternative to cystectomy in the whole population.

Then, one approach that we, the Agency, take is to limit the indication, acknowledging that you are absolutely right, that this is how we see the data as a package.

DR. DUTCHER: Dr. Raghavan.

DR. RAGHAVAN: Rich, you know, even though we haven't tried to define the population, you and I both know the patients that are going to die on the table when you do a cystectomy. It's the patient with an MI within three to

six months. It's the patient who has just had a CVA. It's the COPD'er who can't climb a flight of stairs.

It seems to me that the question that keeps getting turned around, but that I think I understand very clearly from the director down to the office boy, is in that group of patients, however they may be defined, is this stuff going to let them stay alive with a bladder that is quiet for longer.

I think at this committee we are making this very, very complicated despite their strident attempts to make it simple.

DR. DUTCHER: Dr. Ozols.

DR. OZOLS: But that is why we have to go back to general efficacy. I mean if you talk about medical contraindications and patient refusal, you really get into, you know, again what is medically contraindicated in New York City may be totally different than in San Francisco, and so you really get down to very subjective things, and somebody just has to tell an HMO that this guy has got chest pain on walking up a flight of stairs, I mean you can conjure up any sort of scenario you want if you try to really legislate too specifically this kind of indication. Either it works or it doesn't work, is this an active agent, and let the physicians use their judgment, and the patients have the option to talk about it and decide whether they

want to use it.

We are never going to get the perfect trial in this situation. We have gone through this now two meetings in a row, and we are not going to get any more information. We accept the fact that we come to some better agreement, that the response rate is at least reasonable, instead of being 7 percent in CRs, this disease doesn't go away by itself, we are talking now about agreeing that there is about a 20 percent response rate. That means something.

DR. DUTCHER: But I think the issue for all of us that is creating this is that there is an alternative in this setting for the general group of patients, which can cure them.

DR. MARGOLIN: We are not voting on the general group right now.

DR. DUTCHER: I know, but he wants to go back to general efficacy, and I think that the problem there is that we have an alternative treatment that is 100 percent or 90 percent.

DR. SCHER: It is still a very narrow group.

DR. DUTCHER: Which?

DR. SCHER: The BCG failures, the true refractory BCG patient, it is still a very narrow group. Just look at the difficulty in getting patients on the trial, 40 centers, five years, 90 patients. It is a very small group.

DR. SIMON: I am very comfortable with the way we are doing it here, with these three questions. If we proceed in this way, it may send a message that we think there is a certain level of evidence of efficacy, it's not the kind of evidence we generally like to see, there are certain risks that we are not completely comfortable with, have not been adequately defined for the patient to really make it totally open, and I think doing it this way is very appropriate and sends the right message.

DR. DUTCHER: Dr. Droller.

DR. DROLLER: We have spoken about the heterogeneity of bladder cancer, and there is a heterogeneity of carcinoma in situ. We see in those patients who have a bad response to BCG who fail, who have symptoms of urinary irritability that they are at profound risk. Only those patients who are terribly poor medical candidates do not undergo cystectomy, and that is very clear to urologists across the country.

Having a method of curing patients with that form of this disease within the narrow window that is available prompts cystectomy. Patient refusal for cystectomy is largely seen among those who have the kind of indolent, for want of a better term, disease that we were seeing and have been discussing this afternoon.

The predictability of that disease in terms of its

progression is only when progression will occur, and I believe Dr. Raghavan or Dr. Scher mentioned that. It is not that it won't occur, eventually, it will.

Those are the candidates I think whom we are discussing in terms of options for alternative therapies because we might just have an agent with a durable response.

I don't think any urologist is willing to put a patient at risk who is recognized as curable in a narrow window of time to avoid cystectomy at all costs. That patient is going to be told you need a cystectomy.

So, I don't think that is really the issue, and I think the issue really is do we have an agent that has efficacy, can we apply that agent in a patient population that is not at risk for immediate progression of disease and then failure for cure by cystectomy, and does the use of that agent identify a group of patients that can then be urged to undergo cystectomy at some point because they failed this additional potentially valuable option.

DR. DUTCHER: Dr. Margolin, comment?

DR. MARGOLIN: No.

DR. DUTCHER: I think our colleagues from California are a little more concerned about other issues related to pressures from other sources of not doing cystectomy from what you just both said.

Anyway, I think we should vote, and I think we

should vote on the limited indication, No. 3.

In patients with a medical contraindication to cystectomy, does the risk-benefit ratio for Valstar support approval for this population?

Those who would vote yes?

[Show of hands.]

DR. DUTCHER: Nine.

Those who would vote no?

[Show of hands.]

DR. DUTCHER: Two.

Abstain?

[One hand raised.]

DR. DUTCHER: One.

No. 4. Cystectomy has a significant effect on quality of life and some patients are very reluctant to undergo it. The applicant proposes that Valstar be approved for intravesical therapy in patients with BCG-refractory carcinoma in situ who refuse cystectomy.

If this approval were contemplated, a patient package insert could be created to inform patients of the risk of delaying cystectomy and of the limited efficacy demonstrated for Valstar.

With this in mind, should Valstar be approved for intravesical therapy in patients with BCG-refractory in situ carcinoma of the urinary bladder who refuse cystectomy?

Any comments? No comments. We have commented.

Dr. Schilsky.

DR. SCHILSKY: I mean I just think this is a ridiculous question. Surely, there should be a package insert that provides information to the patient, but how on earth is any doctor going to discuss this with the patient? Mrs. Jones, you should have a cystectomy at this point in your illness. Gee, Dot, is there anything else that I might consider? Well, there is this Valstar stuff. Okay. I don't want a cystectomy, I will take it.

I mean how can you possibly have this written as an indication? It doesn't make any sense.

DR. DUTCHER: Do you want to vote to get rid of the question? All those in favor of getting rid of this question?

[Show of hands.]

DR. DUTCHER: Okay. No. 2. Should Valstar be approved for intravesical therapy in the general population of patients with BCG-refractory carcinoma in situ?

Any comments? All those in favor of the general population?

[Show of hands.]

DR. DUTCHER: Five yes.

All those not in favor?

[Show of hands.]

DR. DUTCHER: Five.

Abstain?

[One hand raised.]

DR. SCHER: I think there were 6 no's. You might want to check.

DR. DUTCHER: Six no? Will the no's put the hands up?

[Show of hands.]

DR. DUTCHER: Six no's, 5 yes, 1 abstained.

I think we thank you all for your in-depth comments, discussion. We have two announcements.

DR. TEMPLETON-SOMERS: The committee members can leave things they don't want to keep on the table. We can get rid of them. If you want to keep them, take them with you. Also, I have some more questions for tomorrow afternoon, so I will be handing those out. You have some new additions to your folders for tomorrow morning in case you haven't noticed.

DR. DUTCHER: Thank you.

[Whereupon, at 5:50 p.m., the proceedings were recessed, to reconvene on Wednesday, September 2, 1998, at 8:00 a.m.]

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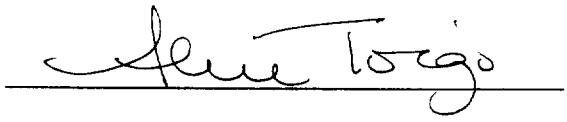
CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.



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