UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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ONCOLOGIC DRUGS ADVISORY COMMITTEE

73RD MEETING

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Tuesday,
December 17, 2002

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The above-entitled meeting was convened in the Versailles Room of the Holiday Inn Bethesda, 8170 Wisconsin Avenue, Bethesda, Maryland, at 12:30 p.m., Donna Przepiorka, Chair, presiding.

MEMBERS PRESENT:

DONNA PRZEPIORKA, M.D., Ph.D. Chair
DOUGLAS W. BLAYNEY, M.D.
OTIS W. BRAWLEY, M.D.
JOHN T. CARPENTER, Jr., M.D.
STEPHEN L. GEORGE, Ph.D.
DAVID P. KELSEN, M.D.
SILVANA MARTINO, D.O.
JODY L. PELUSI, F.N.P., Ph.D. Consumer Representative
GREGORY H. REAMAN, M.D.
SARAH A. TAYLOR, M.D.

ALSO PRESENT:

KAREN M. TEMPLETON-SOMERS, Ph.D. Executive Secretary
JAMES DONALD BRIDGES, M.D. Bexxar Consultant
JAMES E. KROOK, M.D. Bexxar Consultant
SUSAN KRIVACIC Patient Representative

ALSO PRESENT: (cont.)

GEORGE H. OHYE		Industry Representative
SATISH MISRA	FDA	
STEPHEN LITWIN	FDA	
GEORGE MILLS	FDA	
PATRICIA KEEGAN	FDA	
JAY SIEGEL	FDA	

I-N-D-E-X

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

12:38 p.m.

CHAIRPERSON PRZEPIORKA: Good afternoon. Welcome to the 73rd meeting of the Oncology Drugs Advisory Committee. I just want to state for the record and to clarify that this Committee is not a decision-making or a policy-making body but rather we sit as consultants to the FDA, and we will use the information presented here as well as our own individual knowledge base to address questions asked specifically by the FDA regarding the product being presented this afternoon to us.

The agenda has been handed out or is available at the tables outside. We will start with a conflict of interest -- well, actually, we'll start with the introduction of the Committee members, the conflict of interest statement and open public hearing, the Sponsor presentation, the FDA presentation, and for those folks who registered to present at the open public hearing, if you so choose to actually hold your presentation until after hearing the data presented, we will be very happy to

accommodate you at a second chance for an open public hearing later this afternoon. Thereafter, we will have a discussion of the questions that the FDA has submitted to the Committee and take votes, then adjourn.

I'd like to start then by having introductions for the Committee members, starting with Mr. Ohye.

MR. OHYE: I'm George Ohye, industry representative.

DR. MARTINO: Silvana Martino, medical oncologist.

DR. PELUSI: Jody Pelusi, oncology Nurse Practitioner and consumer representative.

DR. BRAWLEY: Otis Brawley, medical oncologist.

DR. TAYLOR: Sarah Taylor, Medical Oncology, Palliative Care.

DR. BRIDGES: James Bridges, Radiation Oncologist.

MS. KRIVACIC: Susan Krivacic, patient rep.

CHAIRPERSON PRZEPIORKA: Donna Przepiorka, Chief Hematology and Transplantation, University of Tennessee Cancer Institute.

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

DR. KELSEN: David Kelsen, Medical Oncology.

DR. CARPENTER: John Carpenter, Medical Oncology.

DR. KROOK: Jim Krook, Medical Oncology.

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

DR. BLAYNEY: Doug Blayney, Medical Oncology.

DR. MISRA: Satish Misra. FDA.

DR. LITWIN: Stephen Litwin, Medical Reviewer.

DR. MILLS: George Mills, FDA, Medical Reviewer.

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

DR. SIEGEL: Jay Siegel, Office of Therapeutics, Center for Biologics, FDA.

CHAIRPERSON PRZEPIORKA: Thank you to all, and our Executive Secretary, Karen Templeton-Somers, will now read the 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 the meeting. Based on the submitted agenda for the meeting and all financial interests reported by the Committee participants, it has been determined that all interests in firms regulated by the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, which have been reported by the participants, present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

Dr. Bruce Cheson and Dr. Bruce Redman are excluded from participating in today's discussion and vote concerning Bexxar.

Dr. Silvana Martino has been granted a

waiver under 18 USC 208(b)(3) for unrelated consulting for a competing firm on unrelated matters. She received less $10,001 a year. And for the review of a manuscript for a competing firm, she received less than $5,001 a year.

Dr. Douglas Blayney has been granted waivers under 18 USC 208(b)(3) and 21 USC 355(n)(4) Amendment of Section 505 of the Food and Drug Administration Modernization Act for ownership of stock in competitors. The first stock in a competitor is valued between $25,001 and $50,000. The other stock holding is valued at less than $5,001.

Dr. Sarah Taylor has been granted a waiver under 21 USC 355(n)(4) Amendment of Section 505 of the Food and Drug Administration Modernization Act for ownership of stock in a competitor valued at less than $5,001.

A copy of these waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building. We would also like to note for the record that George Ohye is participating in this

meeting as an industry representative acting on behalf of regulated industry. Mr. Ohye has reported that he owns stock in Eli Lilly, Schering Plough, Amgen and Merck.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record. With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon. And I'd also like to announce that copies of the disclosure statements are available for your viewing at the front desk if you're interested. Thank you.

CHAIRPERSON PRZEPIORKA: Thank you and let us now proceed directly to the open public hearing. We have a number of individuals who have registered to make comments at this open public hearing. I would ask that they come forward, beginning with Thom Jones

from Pittsburgh, Pennsylvania, and I would also ask that any of the speakers at the open public hearing also provide their financial conflicts of interest if they have any. Mr. Jones?

MR. JONES: Good afternoon. I have nothing new to say to you, no stories of the drug, other than the fact of my own experience. The most important thing I do for people, I believe, in this community and in my hometown of Pittsburgh is simply show up every day. I am, for better or worse, undeniable proof of the efficacy of Bexxar. It was four years ago this past Thanksgiving that I was discharged from the University of Pittsburgh Medical Center, and my doctor said, as I said, "I'll see you in three weeks," because my cancer was recycling every three weeks, he said, "Don't come back," and I said, "Excuse me?" He said, "Don't come back." He said, "We can't do anything for you."

I was extremely fortunate. I had a great friend who heard a news broadcast and called a friend of his, and I met Dr. Armitage when I was looking into a bone marrow transplant at the University of

Nebraska, and I called him and he said, "Yes, we're testing Bexxar and you're a perfect candidate, Thom." When I said, "I won't make the four weeks for the study," he said, "Yes, you will." I was privileged to get Rituxan to buy me the four weeks, and I went to the University of Nebraska on Christmas Eve, 1998, got my first dose of Bexxar.

I tell this story to a lot of people. I even had a gentleman fly me to Denver on a plane just to kick my tires to make sure I was telling the truth and so he could look in my eye when I tell him. Most people who've been through chemo and anyone -- I'm sure most people in here who's seen people go through chemo have seen the ravages. When I tell them that I went out to Nebraska and that evening my sister and I went out and celebrated together, although we had to stay at opposite ends of the table because I was hot from Bexxar, we had a heck of a Christmas Eve. Turned around and my therapeutic dose fell on New Year's Eve, so we went out and partied again on New Year's Eve. This time we took a table for six and sat far enough away so that we could keep partying. I tell about

that, that I did that the same night that I had the drug and people don't believe me. I tell people all over that I took the drug and it has had no worse side effect than a glass of water.

I show up in my community, I'm a volunteer fire fighter, I'm a paramedic, I contribute to my community every way I can. I work with my friends and neighbors and the greatest pleasure it gives me is simply to show up and watch the look in their eyes when they try and compute this. I look at people who call me all the time because the word gets out about Bexxar, and they call and say, "Can I get this drug," and I used to say, "It will be there in a minute." I don't say that anymore.

I don't know what has slowed it down. Every year when I go see Dr. Armitage again, I walk in the door and I say, "Well, how close is it," and it's gotten non-verbal now. He just shrugs and we go on about the business of getting me checked out. I don't know what I can do. I do know what patients -- what we all do is we try and make it evident to everyone else just how undeniable it is what the drug does. I

could not be here, I would not be here. I had three weeks to live and without pain or suffering Bexxar brought me back. And everything I do for anyone or with anyone is because of that drug. Thank you all who worked on Bexxar. I appreciate your time.

CHAIRPERSON PRZEPIORKA: Thank you, Mr. Jones. Next is Erica Hertz from the Wellness Community.

MS. HERTZ: Good afternoon. My name's Erica Hertz, and I'm the Director of Patient Education and Outreach for the Wellness Community. For the record, the Wellness Community receives unrestricted educational funding from GlaxoSmithKline; however, I receive no funding or compensation for my presence here today.

By way of background, the Wellness Community is a national non-profit organization, and we provide free services to people with cancer and their loves ones by way of support, education and hope. Our programs include professionally facilitated support groups, educational seminars, nutritional workshops, exercise, mind-body programs and many

others. Our aim is to help people with cancer and their loved ones regain a sense of control over their lives, feel less isolated and restore their sense of hope in the future regardless of the stage of their disease, and we've worked with over 25,000 people last year alone.

At the Wellness Community, we see a wide range of diagnoses and provide direct services to thousands of people with lymphoma. We've learned a great deal from these patients and believe in the importance and value of an educated and empowered patient. People with cancer often feel stigmatized, alone and overwhelmed with grief. They feel stronger and more hopeful when they have more options available to them for the treatment of their disease. With more than 56,000 individuals diagnosed with non-Hodgkin's lymphoma each year in the U.S., we're in great need of improved treatment options and better access to those treatments. We have the opportunity to expand the chances that these families have for a better life with new treatment options, and we feel very strongly about supporting that opportunity, especially when

treatment promises limited side effects, has potentially long-term efficacy leading to remission, improved quality of life and other positive outcomes.

I ask today that you carefully consider the plight of patients with lymphoma and endeavor to understand the psychological and physiological issues that they face daily. So please take a leadership in approving a broader range of treatments and then encourage patients to be informed, empowered and optimistic about the possibility of longer, healthier lives. Thank you.

CHAIRPERSON PRZEPIORKA: Thank you, Ms. Hertz. We appreciate you being here today. Next, Patricia and Joseph Bashaw from Brookfield, Wisconsin.

MS. BASHAW: First of all, neither of us have received any reimbursement or compensation for being here. I entitle this, "One Bexxar Patient's Perspective."

Thank you for giving me the opportunity to speak to you. The reason why I'm here is that I was treated with Bexxar in a phase two clinical trial and went into complete response. I have relapsed, and I

have been told that I cannot have Bexxar again unless the FDA approves it. I will soon need retreatment and I beg you to recommend Bexxar's approval so that it will be available for me and others.

I retired from the federal government in January 1996 after 28 years of service. I have four children, two are to be married in the next two years. I hope and pray that I will live long enough to see and enjoy my grandchildren. I do live in Wisconsin near Milwaukee. I have no medical background. Whatever I have learned about lymphoma comes from dealing with the disease. Obviously, I'm not an expert in disease; however, with respect to Bexxar, I consider myself pretty knowledgeable in that I am only one of a few people in this room who have actually had Bexxar coursing through their bodies.

In October 1995, I had a mammogram which showed enlarged bilateral lymph nodes. After appropriate testing, I was diagnosed with stage IV, low-grade B-cell follicular non-Hodgkin's lymphoma. The first and only treatment I have received is Bexxar in February 1999 as part of a phase 2 clinical trial

of previously untreated patients. Bexxar put me into complete response for two years. I am HAMA-negative, I went from PCR-positive to PCR-negative. Unfortunately, I went out of remission, but it has been approximately four years since the treatment, and I've remained stable.

I know what it is like to have Bexxar. I have experienced being hooked up to an IV and having the tracer dose enter my bloodstream. Through scans I saw how the antibodies were initially aimless, and then I saw how they began to target my lymphoma. I took the treatment dose. I experienced the restrictions that were in place during the treatment phase and a few days following treatment. I took precautions at home as I was instructed. These were not burdensome. I had weekly blood tests, I saw the counts drop off and then return to normal. I experienced some fatigue, and this was not a problem. My recovery was uneventful and very tolerable.

Before my treatment, I spoke with a fellow lymphoma patient who had numerous chemotherapies and then Bexxar. He told me that if I have Bexxar without

having had chemo, I would not have had any real cancer treatment experience. He was right. During the entire treatment period, which was two infusions a week apart and recovery, I would never have known I had been treated for widespread cancer.

With respect to Bexxar's possible thyroid toxicities, I've already been taking thyroid replacement hormones since the 1970s. This has not been a problem. For patients who require thyroid replacement because of Bexxar, a one-a-day tablet is easy to handle. Taking a pill a day is a lot better than death.

As you know, the nature of this disease is that it is progressive and terminal. Without proper treatment, I will die. There is no cookie cutter recipe in the treatment of lymphoma. Lymphoma responds to treatment such as chemotherapy, how eventually the lymphoma cells learn to reject, eject treatment poisons from the tumor cells. Eventually, treatments become ineffective, the tumor cells grow uncontrollably and the patient dies. Chemotherapy drugs wreak havoc on healthy cells, and they create

long-term disabilities and problems. Because of its toxicities, I would like to stay away from chemotherapy drugs as long as I can.

We need more treatment options now, not years from now. It is very important that treatments be given in a proper sequence and timing so that bridges are not burned and opportunities lost. This must be individualized. Until the molecular differences between low-grade lymphomas and differences in immune systems are identified, this will remain the case. People search for a perfect cure. This is great, but as far as I'm concerned, if I were kept stable for the rest of my life, I would consider myself cured. I assume all lymphoma patients share this sentiment. Stable does not kill.

During the clinical trial, I faithfully followed the instructions I was given and had what I thought an excellent result. I consider Bexxar to be an ace in the hole in fighting this disease. I was shocked to find out that even though I tolerated Bexxar so well and had excellent results that I could not be retreated with the drug because it was not

approved. I cannot have Bexxar even though it is my choice of retreatment and that of my oncologist.

It makes absolutely no sense to me that I may be forced to take a probably more toxic therapy or therapies for which I have no experience, but I cannot take the drug that I have already had and which gave me good results. I feel like I have been used to help provide an answer in a Phase 2 trial and then summarily abandoned and discarded when no longer useful. How is it right that I am prohibited from taking a drug that is effective? A two-year remission is not nothing.

It is now almost four years since my Bexxar treatment. These past four years have been wonderful. I've been able to see all of my children graduate from college and be successful in their careers. From my patient perspective, Bexxar is non-toxic, and, I may say, a breeze to take. I know it can work.

Since I was treated with Bexxar, I am no longer an untreated patient, and therefore I do not qualify for many of the other treatment possibilities,

the promising drug trials going on now. I understand that the FDA may have certain questions they would like answered, possibly through Phase 3 trials. I would also like questions answered but at what expense? Am I to die sooner and thousands of others while waiting for the answers? We need options now. It's bad enough coping with this disease but worse knowing that there is an effective treatment that I cannot have. I need this drug. Please do not fail me and thousands like me.

From my perspective as a lymphoma patient, Phase 3 clinical trials with their randomization take advantage of desperately ill people fighting to stay alive. They make patients succumb to treatment protocols that they may not want only to be given the possibility of getting a desired drug. They may wind up burning bridges. The randomization means that patients wanting a certain drug which is shown to be effective may not even get the drug after all after going through the whole protocol. Why is it necessary to randomize double-blinded studies in non-Hodgkin's lymphoma since the results of the treatment can be

objectively found on CT scans, bone marrow biopsies and blood tests?

I believe that at some point, even before all questions are answered concerning an effective drug, the drug should be available for use. I do not believe that oncologists and their patients are stupid and unable to make reasonable choices regarding treatments for their terminal illness. Please don't kill me and thousands of others of us while the research community is getting questions answered.

I think that the whole study of lymphoma would benefit from a lymphoma registry similar to that of bone marrow and children's cancer registries. Oncologists could enter data on their patients' diseases, treatments used and results so that researchers can study the data and make recommendations on the overall effectiveness of treatments.

When I was first diagnosed with cancer I did not know if I had months or years to live. I promised my family, as upset as they were, that I would do whatever was humanly possible to stay alive

and be with them. I want to keep this promise. Please recommend that Bexxar be approved so that I and countless others can benefit from this effective drug. We need more treatments to fight the disease now.

MR. BASHAW: Good afternoon. Thank you very much for the opportunity to speak to you. You just heard my wife tell you about her fight with lymphoma and her personal experience with Bexxar. She was diagnosed seven years ago. I have accompanied my wife to all of her doctor visits, tests and treatment visits as well as to a large number of conferences conducted by lymphoma specialists. Two years ago something changed. I was diagnosed with low-grade lymphoma. I became a lymphoma patient also.

I was with my wife throughout her Bexxar treatment and recuperation. I saw the good results from Bexxar and felt confident that if the disease came back she would be able to be retreated. Because of these good results, she had four excellent years. We were told that some patients who were treated with Bexxar and then relapsed had been retreated with Bexxar with excellent results. My wife will need

treatment soon, but she has been told she cannot get Bexxar because it is not FDA- approved, even though the drug worked well for her. All drugs do not work the same on all people.

After I was diagnosed with lymphoma, I had radiation treatments because I was stage II. Most oncologists and radiologists tell me that it may be only a matter of time before my lymphoma comes back and I will need treatment. I had thought Bexxar would be an excellent choice for me because of what I observed for what it did for my wife. Now I cannot get Bexxar.

As you know, low-grade lymphoma is unique. First of all, it is terminal. Life expectancy is about eight years from diagnosis, on average. These statistics have changed little, if any, in the past 30 years. Every low-grade patient tries the same treatment options, because there are only so many, and each time one is treated the remission is for a shorter period. We are just trying to stay alive. Bexxar may keep us alive a few extra years. Two to three years may not seem like much to some people, but

when one has an average of an eight-year life expectancy, two to three extra years is huge.

I am 62 years old, and I have had a good life. I have seen my four children grow up. As bad as the disease is for wife and me, it is much worse for many young people who have it. We were recently at a lymphoma conference in Los Angeles, and we met several people with lymphoma who were in their 30's, 40's and even in their 20's. They have new spouses, young children and in some cases just starting careers. They all talked about their treatment options so they can stay alive. Bexxar might give them another option.

The lymphoma specialists who have spoken at conferences we have attended have usually spoken about Bexxar as though they expected that the drug would soon be available. I have never heard a negative word from any of these physicians about Bexxar. We have asked several of them why they thought Bexxar had not been approved, and they all said they did not know. None of them spoke of any negative side effects or any other reasons they knew

why Bexxar had not been approved.

Please recommend that Bexxar be approved. We need it now, not several years down the road when many of us are dead. It may help thousands of patients stay alive longer and if we are real lucky help us stay around until a cure is found. Thank you again for me giving me, a patient, an opportunity to speak to you.

CHAIRPERSON PRZEPIORKA: Are there any questions?

(Applause.)

CHAIRPERSON PRZEPIORKA: Thank you, Mr. and Mrs. Bashaw. Next is Kent Halbach from White Bear Lake, Minnesota.

MR. HALBACH: Hello. First of all, I'd like to thank the Committee for the service that they perform and for giving me a chance to talk about my experience with Bexxar. My name is Kent Halbach, and along with my wife and two teenage daughters, I live in White Bear Lake, Minnesota. I'm here on my own behalf. I do not represent any company or organization. I have no financial stake in any

product of company related to this discussion. I've paid all my own expenses.

When I was diagnosed a little over six years ago with low-grade lymphoma, I was told that my disease was chronic, incurable and uniformly fatal. It took a little while before the reality of that statement sunk in. I was 41 years old, and I was going to die. That reality permanently changed my decision-making process, and primary among those decisions would be what treatment to seek. I was told that regardless of which treatment I selected my life expectancy was likely to be short. With longevity not attainable, quality of life became a top priority. So I began my search with that in mind.

After spending countless hours studying clinical trial abstracts and other data, I decided that Bexxar had the capability to provide what I was looking for: a treatment that wasn't worse than the disease itself. In March of 1998, my turn came to participate in a clinical trial at the University of Michigan. By that time, without a CT scan, I could count well over a dozen tumors in my neck, armpits and

groin. Several tumors in my neck were approximately the size of a half an orange. In addition, my spleen was heavily involved and had become very enlarged.

The treatment was so simple I could hardly believe it. A tracer dose one week, some gamma scans on ensuing days to track the antibodies? migration path and absorption rate, a personally tailored therapeutic dose the next week, a couple days watching TV and then go home and back to work. I didn't lose any hair, I didn't throw up.

Two weeks after the therapeutic dose my platelet count began a one-month process of dipping down and then going back to normal. A week following the platelets, the white blood cells did the same thing. These lowered counts did not result in any infections, illnesses, transfusions or any other complications. I haven't experienced any thyroid problems or any other long-term side effects so far. My tumors shrank slowly over a period of a few months, and my spleen returned to normal. A complete remission was the result.

The before and after CT scans paint a

truly remarkable contrast. I set out to find a treatment that would allow me to maintain a high quality of life and with Bexxar I achieved that. I have been able to serve as a volunteer coach for both my daughters' basketball teams. I have been able to enjoy a quality of life that I didn't think was possible when I was diagnosed with cancer.

But Bexxar has come with an added bonus: durability. To this day, I have not required any additional treatment. From my point of view, as a patient, Bexxar is simple, patient-friendly, effective and durable. It allows patients to maintain quality of life, dignity and hope. It allows those who administer it to create a personalized dose for each patient to achieve maximum effectiveness and minimum collateral damage. The combination of these attributes make Bexxar a unique option for those of us who need all the options we can get.

Since I was treated with Bexxar, more than a quarter million others have been diagnosed with non-Hodgkin's lymphoma. A large number of them have been told that their disease is chronic, incurable and

uniformly fatal. We're told that some day we can expect this disease to be treatable, that we might have a chance at a normal life. The trick, we're told, is to stay alive long enough to see that day. Please allow Bexxar to be among our treatment options so that we might be able to see that day. I can't prove that it will keep us from dying, but I can tell you that it has allowed me to keep on living. Thank you.

(Applause.)

CHAIRPERSON PRZEPIORKA: Thank you for your comments, Mr. Halbach. Next is Pat Haut from Auburn, Michigan.

MS. HAUT: Hi. I want you first off to know that no one paid for me and my sister to come here. I did this on my own. This is so extremely important to me.

In 1985, I was diagnosed with non-Hodgkin's lymphoma. I went through eight years of chemo, radiation, massive doses of vitamin A. My oncologist has sent me to MD Anderson in Houston three times, because he didn't know what to do with me. I

also was at Harper in Detroit twice. The first time I went there they wanted to do -- it was four years into my chemo. They wanted to do a bone marrow transplant, they thought I was a good candidate. When they ran all the tests they found out that my first chemo damaged my heart. I had 35 percent heart function, so I was not a candidate for a bone marrow transplant, so I went back home.

And then a few years later, I was on every kind of drug you can imagine. I spent numerous days in the hospital. I kind of thought I owned Midland Hospital, that's how I much I was in there. Anyway, then my doctor sent me back to Harper because he thought things were going quite well and that maybe I would be a candidate for the bone marrow transplant. So I went back there. I talked to the doctors, went through all the tests, and they had decided that, well, maybe they could do the bone marrow transplant on me, my chances were not good. And I turned around and looked at them and I said, "The first time you rejected me. What changed it?" And they said, "Really nothing." I said, "Well, thank you very

much," and I walked out.

The last time I went to MD Anderson Hospital. My doctor suggested that I have my bone marrow taken out, and maybe I would change my mind. I had up to five years, they could freeze it, and I could change my mind. Well, I never did. But in the meantime, in 1992, in October, I went to the U of M Hospital and seen Dr. Kaminski, and he -- there was three of us that went there, three women, and he looked at us and he said, "Which one of you is the candidate?" I was never very -- I didn't look like I was sick, but I was. But, anyway, he said I was not sick enough to go through this, it was not a desperate thing. At the time, my lymph nodes were so enlarged that I could not wear jeans, my left leg was so swollen. I had a lot of problems with that. Otherwise I was pretty good.

Anyway, so I went there, and then I didn't hear from him for quite a while, and my oncologist said I had a -- I was not getting any chemo because there was nothing that he felt would do me any good. I had the best of the worst drugs. Anyway, in '93,

Dr. Kaminski called me and told me to come down the next day, and I was a candidate for this experimental drug. I was the 20th patient to have it, and I have not had another treatment since. I am cancer-free. I go down to see Dr. Kaminski now once a year. All my tests are done. And at one time, I believe I had over 200 CT scans in my life. I cannot -- they cannot get blood out of me because my veins are no good, but I am still here, and if it was not for Bexxar I would not be here. I know that. It has given me life, and that is the most important thing.

People do not realize how sick you get with chemo or anything. With Bexxar I was never sick. When I took it I was the 20th patient, and I was there for three weeks. I stayed right in the hospital for three weeks, but the only time I was in my room was when they did the treatment, which was one day a week, and then I had to have a scan for an hour a day for five days. And other than that I was never in my room. Dr. Kaminski used to leave me a note on my table saying, "I was here to see you, but you must be doing well." And then I came home for a week and a

half and I went back for a week and then I was in isolation for one day, but it was wonderful. No one can imagine what you go through when you go through plain old chemo. Thank you.

(Applause.)

CHAIRPERSON PRZEPIORKA: Thank you, Ms. Haut. Next is Frank Burroughs from the Abigail Alliance for Better Access to Developmental Drugs. Mr. Burroughs.

MR. BURROUGHS: Good afternoon. I'm Frank Burroughs, and I'm President of the Abigail Alliance for Better Access to Developmental Drugs. First let me make it clear that I do not represent in any way or our organization represent in any way the pharmaceutical industry nor do I or our organization own any pharmaceutical stock. We represent cancer patients and only cancer patients and other people with life-threatening illnesses.

First, I'd like to dedicate my talk today to Johnny Clark. Texan Johnny Clark died two weeks ago while he was waiting to get Iressa and Erbitux that had a significant chance of saving his life like

Abigail. You may have heard of the Abigail Alliance for better access to developmental drugs in three recent Wall Street Journal stories, the New York Times, the LA Times and Fox Cable News and other places, and you're going to hear more about us as we move forward to help save lives.

I'm here for two reasons. One is to urge the rapid approval of Bexxar and to make a very important point about Bexxar and other drugs. They need to be approved sooner, at least conditionally approved sooner for people who have run out of options. And it's not being done. Where's Iressa? People can't get Iressa except in a very limited expanded access program. The slow access to new drugs is nothing short of a tragedy -- a tragedy. What if it was your daughter?

Bexxar is another example of a drug that's been around for a long time that needed to get to people sooner. Bexxar's been available since 1990 -- yes, 1990. A few people were able to get it in an expanded access program for a few years, but a lot of people who could have benefitted from it couldn't get

it. They ran out of options, they couldn't get it. Their last option was the loss of their lives. Bexxar should have been at least conditionally approved years ago. Come on, these people are out of options. It showed efficacy and safety. There was maybe -- certainly, there was more things to learn about the drug, but imagine if you had run out of options.

If there is a bad car wreck down the road, guess what happens? Right, they send out ambulances, they send out the paramedics and they try to save the lives of those who are in the car wreck. But we're not making an emergency response to cancer patients. Come on. Again, I repeat, Bexxar should have at least been conditionally approved years ago.

What's going on is wrong and it's tragic. There are cancer patients out there that we're leaving by the side of the road to die. There's one. I'm not the only one with this position, though I may be more vocal than a lot of people. This is just one example, this is a March letter to the FDA by the ODAC representative back last winter urging the approval of Bexxar. He also urges better information about new

drugs get to patients and to the public.

In closing, let me say let's get Bexxar approved. It should have been approved conditionally years ago. We have lost lives with Bexxar, Iressa, oxaliplatin and other drugs that waited and waited to be approved. We need changes now. We are talking about people's lives. That's Abigail one month before she died. She was 21. Iressa had a significant chance of saving her life. We could not get it. Let's conditionally approve, early conditionally approve, and I'm not talking fast track, drugs like Bexxar and Iressa for people like Abigail. Thank you very much.

(Applause.)

CHAIRPERSON PRZEPIORKA: Thank you for your words, Mr. Burroughs. And next Mr. Tom McDermitt from Glenside, Pennsylvania, please.

MR. MCDERMITT: Thank for the opportunity to speak here today. I have to say like the other folks I have not been financially reimbursed by anybody. I have come here from near Philadelphia, I would have come from Alaska.

I've been a professional social worker for 26 years, I've been a professional cancer patient for almost that long -- 21 years. I was diagnosed with non-Hodgkin's lymphoma in October of 1981, 34 years old, stage III, follicular small-cleaved and large cell. My tumor was inoperable, the size of a soccer ball. It had been previously misdiagnosed as an abdominal hernia. A nine-month protocol of C-MOPP CHOP radiation resulted in a three-and-a-half-year remission, but the protracted throwing up was overwhelming, the fatigue was devastating.

My first recurrence in the spring of 1985 presented in the chest and spine. I was successfully treated with MACOP-B. Side effects: Extensive nausea, hand burns, mouth sores, intense fatigue. That bought me two and a half years more. Over the next seven years, I had three more recurrences and a change in pathology in 1988 to diffuse large cell and diffuse mixed. During that time, those seven years, I underwent eight more different regimens of chemotherapy and two different cycles of radiation. The worst were the sisplatin regimens, the side

effects were even more damaging and included life-threatening infections and very debilitating fatigue and dizziness, requiring six months of recovery each time.

During those seven years, the remissions lasted anywhere from six months to two years, with only a couple of months each of reasonable health. For the most part, my life had come to a halt. Life had become synonymous with struggle and survival. By 1992, my body could simply not take anymore intensive chemotherapy. There was no quality to my life. I was worn down, I was worn out. I asked my oncologist to simply put me on less toxic palliative drugs and see how long I could keep the lid on. Clearly, I was prepared to die rather than endure any more intensive treatment, and I mean that. My pathology must have been fluctuating slightly at that point back and forth as I was able to comfortably survive two more years on the palliative drugs before the cancer became pretty much resistant.

I was literally in the process of trying to accept that my time was up when my doctor heard

about two different antibody trials. After researching the information, I decided to go with Bexxar with Dr. Kaminski at Michigan. Sure I was apprehensive, but I wanted to try it because of the compelling early results and certainly for me the allure of few side effects. I was surprised by how well I treated the anti-B1 radioimmune therapy. I experienced only slight nausea and moderate fatigue.

Following my return home, my platelets were diminished but not seriously. I enjoyed 14 months of remission with a return to health. But, hey, when the cancer returned during the summer of 1996 I was only too willing to go back to Michigan and try again. That August again I only experienced some very minor discomfort with the treatment. After my return home there was the usual platelet loss, a few weeks of moderate fatigue for about two months. As of now, I am very pleased and touched to say that it's been six years, four months and counting since I have been lymphoma-free. That's almost twice as long as I've gotten from any other remission by chemotherapy. I never thought it was possible, I never thought I

could get that kind of extended remission.

I say lymphoma-free because I developed significant side effects -- excuse me, I developed significant bladder problems, bladder cancer in 1995 from all the toxic chemotherapy. That has required minor surgery every year as well as bladder installations. Thus began a parade of long-term side effects from all those regimens, including very severe damage to my bladder as well forcing me over the last two years to remain fully catheterized at least 85 percent of the time, some loss of hearing and balance, a compromised immune system, recent diagnosis of osteoporosis.

You know, I think we all have come to realize that the definition of survivorship has expanded significantly. It's not just about physical survival and longevity anymore. Now we survivors are just as concerned about the quality of our lives during treatment. New choices in treatment have allowed us to pretty much get beyond that old notion of, "Look, just quit complaining and be grateful your cancer can be treated." We've moved beyond that,

folks.

In addition, we know that survival is not necessarily a single stage or outcome. Quite often it is a chronic illness extending over periods of time with remissions, not cures, and it may lead to secondary cancers as well. So coping with the physical and emotional effects may extend over several years now. Accordingly, using the least invasive, most tolerable yet effective treatment is even more vital now. So, yes, we do want choices, and we are grateful for them, and we do welcome the opportunity to have the alternative of Bexxar.

So this is my story with cancer and with Bexxar and 131. Back in 1995, it literally gave me life, another choice other than dying. Over the last seven years, it has given me the opportunity to have a productive and gratifying life and the realistic hope for more. But, you know, probably more than anything for me just the sheer pleasure of being able to have a successful treatment without the grueling side effects and the tremendous worry, anxiety, fears they generate, both in the short-term and the long-term.

My work consists entirely now of counseling cancer patients, running support groups, conducting coping seminars. I know the terrain of cancer recovery. I know what patients struggle with. I know their stories, and their stories are not unlike any stories that you've heard here today, except there's one difference, and that difference is those people would absolutely crave the opportunity to have the kind of treatment we were blessed with.

All the stories, all the cancer stories you hear are going to move you. You know that, I know that and only hope that they go beyond that today and provide some real impact, and along with the consideration of the other data you have, move you to strongly recommend approval of this treatment. Thank you.

(Applause.)

CHAIRPERSON PRZEPIORKA: Thank for being here, Mr. McDermitt. Next is Leonard Greer from Rye, New York.

MR. GREER: Good afternoon, ladies and gentlemen. My name is Leonard Greer, I'm 64 years of

age, and I live in Rye, New York. I participated in the clinical trials for Bexxar in January 2000. I'm appearing at this hearing at my own expense.

My appearance today is because of as a result of receiving one treatment of Bexxar almost two years ago, I am in complete remission. This was achieved after multiple chemotherapy sessions failed to successfully treat my cancer.

In September 1998, I was diagnosed with stage IV non-Hodgkin's lymphoma. I was advised that my form of lymphoma was incurable but could possibly be controlled by shrinking it with chemotherapy and if successful, additional treatment would not be necessary for years, if at all. I began chemotherapy in 1998. My lymphoma responded to the chemotherapy both clinically and diagnostically. The scan in January 1999 showed that the size of the tumor had significantly decreased. However, scans eight months later, in September 1999, showed that my lymphoma had recurred and thus needed to be treated again. My oncologist suggested investigation of treatment options such as Bexxar, and I thank God today that the

decision was Bexxar.

In January 2000, my baseline scans for the clinical trial showed that my lymphoma was more prominent in January than it had been just four months prior in September. I received Bexxar at New York Hospital in January 2000. I had virtually no side effects during or after the treatment, whereas I did have negative side effects from the chemotherapy, such as fatigue, nausea and low blood counts that could lead to life-threatening infections. In April, 13 weeks later, most of the lesions had been resolved, and all of the others had major decreases in their sizes. Quarterly scans showed that Bexxar continued to reduce the size of my lymphoma during the first year after treatment. Today, almost two years later, according to my latest scan in September, I continue to be in complete remission.

I believe that there are many people who have a similar form of lymphoma and they could be successfully treated with Bexxar similar to myself. I hope and pray that the Panel will look favorably upon the approval of Bexxar, as I believe it saved my life

and can save many others. Thank you very much.

(Applause.)

CHAIRPERSON PRZEPIORKA: Thank you, Mr. Greer. Next, Alida Diab from Princeton, New Jersey.

MS. DIAB: Good afternoon, ladies and gentlemen. My name is Alida Diab, and I'm here today to tell you about my experience with Bexxar, the drug that saved my life. From my perspective, Bexxar is the greatest breakthrough in the history of modern medicine, and I stand here today as proof of its success.

I received Bexxar in October of 1998 at New York Presbyterian Hospital under the care of Dr. John Leonard. At that time, I was in a poor situation and honestly it wasn't looking good. Before that I had received an aggressive chemotherapy regime in 1995, ten rounds of CHOP, and that was the maximum that I could ever take. After relapsing two years later, I was one of the first people to be treated with Rituximab after it was approved in January of 1998. Six months later I was in need of treatment again.

I had done extensive research on the Internet, and based on everything I read felt positive that it would be the radioactive iodine in conjunction with the monoclonal antibodies that would save my life. Three months after receiving the drug in January of 1999, there was no sign of disease and I thank God every day for Bexxar. I believe so much in Bexxar that a couple of months later I bought a few shares of Coulter Pharmaceuticals in my IRA retirement account. Four years later, virtually unscathed, I'm a successful business executive leading a team of 15 employees. I would like to take this opportunity to convey to the decision makers that the isolation associated with Bexxar treatment is a minuscule price to pay for being able to live a normal life with no sign of disease.

Chemotherapy treatment lasted for nine months, caused me to lose all my hair, made me constantly exhausted and still was not a complete success. Rituximab treatment was administered over a period of one month and then six months later failed for me. With Bexxar, the isolation period was only

two days accompanied by some mild flu-like symptoms. This is in direct contrast to the debilitating effects of chemotherapy. The very same month I received Bexxar and the following two months after that in the same year I won prizes for being the top advertising sales person each of those three months. I beat all those other completely healthy people in my office.

I would like very much to help others have the same opportunity to receive the gift of life. I'd also like to mention that I received no financial assistance whatsoever for travel or other expenses. I used my frequent flyer miles to get here. Thank you for listening and in closing I ask for the speedy approval of this miracle called Bexxar.

(Applause.)

CHAIRPERSON PRZEPIORKA: Thank you, Ms. Diab. That ends our registered speakers, but I would like to ask if there is anyone else who would like to make a comment during this period?

DR. BRAWLEY: May I?

CHAIRPERSON PRZEPIORKA: Yes.

DR. BRAWLEY: I know this is unusual for a

member of the Committee to speak so early, but I just --one minute of talking to the folks who just addressed us. I want to say I appreciate those of you who talked to us rather than down to us, and I have an open mind on this issue right now, but I think we need to explain why we're here and why this is a question, and I think the advocates and the survivors deserve that explanation.

Very briefly, there are diseases where therapy, although causing a partial or a complete remission, don't make a patient live longer. Indeed, several of the stories that I heard suggest that those individuals didn't necessarily need Bexxar even though they went to complete remission and are doing well. There can be, by the way, an advantage to treating someone who has symptoms from the disease in improving their quality of life even though you don't live longer from getting the disease.

And so there's a group of drugs that sometimes the only thing that people get from them, they may seem to get a benefit but they only get the inconvenience of that treatment and sometimes they

even get harmed or even get killed from getting that treatment that seems to be beneficial to some folks. And, unfortunately, too, there are some folks out there who are dishonest and just want to take advantage of sick people to make a buck. I'm not talking about anyone today at this meeting.

So we have to rely upon the scientific method. Sometimes that involves randomized trials to actually see if people benefit and to see if the drug really is as good as it appears to be. We have to look at the entire forest as opposed to one tree in the forest, and so that's why we're here and I, again, want to say I appreciate the advocates and survivors who spoke to us as opposed to down to us. Thank you.

CHAIRPERSON PRZEPIORKA: Thank you, Dr. Brawley, and if there are no other comments, I want to express the gratitude from the Committee for all of the individuals who made comments at the open public hearing, and we will proceed now to the presentation by the Sponsor on Bexxar anti-B1-I-131, Corixa. Dr. Zaremba, please.

DR. ZAREMBA: Madam Chairperson, members

of the Advisory Committee, ladies and gentlemen, good afternoon. Actually, I am not from Corixa, I'm from CBER. There would seem to be a little bit of confusion in the program. And I am the Chairperson and the product reviewer for the product under consideration today, tositumomab therapeutic regimen from Corixa Corporation.

First, I would like to introduce you to the other members of the Review Team. The clinical reviewers were Drs. Litwin, Mills, Luksenburg and Shastri; the biostatistician was Dr. Misra; Pharm/Tox was performed by Dr. Green; radiochemistry by Dr. Epps. Dr. Andrich was the bioresearch monitor; Debbie Trout is the facilities specialist, and I especially want to thank the work of Karen Jones, Craig Doty and Mike Noska, who is no longer on the Committee but did quite a bit of work.

Now, we heard a number of impassioned pleas for the approval of this product and some suggestion that the FDA has dragged their feet in this approval, so with that end I would like to present some highlights of the timeline, and I say highlights

because if I put all of the things that were submitted and considered by the FDA, we would be here until six o'clock, so these are just the highlights.

First of all, the BLA was submitted on September 14, 2000. I might add that it was originally submitted in 1999, but after consideration, the Center decided to not file it because there were really quite a lot of missing data. But then eventually on 2000 it was submitted and accepted. Now, there were quite a few study reports submitted. These all have numbers so I'll give you an idea. The 004 was in chemo-refractory patients, and that was one of the efficacy studies, but it only contained data up to 5-31 of 2000. A couple of final study reports were submitted for studies 000 and 01. One was the MTD study, the maximum tolerated dose, and the other was a dosimetry study. Then there were some other interim reports submitted for hot antibody versus cold antibody. That was the 002. And 003 was used as first-line therapy.

Now, in December 14 of 2000, the CP98-020 interim study report, that was the expanded access

study. They also -- oh, I should point out that there were 286 subjects in the first safety report, and then in December they increased it to 308 subjects for our consideration. Now, in March 16, we issued an action letter which addressed a number of issues that we had found after review. One was that for the product there was really insufficient data on comparability since it was manufactured under three different manufacturing schemes plus the current one for licensure. Also, there were some questions about some of the testing that was performed.

In addition, there was some inadequacy in the efficacy databases. There was a single pivotal trial which had substantially different efficacy in the transformed versus the non-transformed patient group, and some supportive data was submitted as interim rather than final reports. There was also apparently an inadequate safety database where there was substantial missing data for acute hematologic toxicity and delayed hematologic toxicity, and there was also thyroid and HAMA events that were not always entirely clearly explained.

Now, in August 27 of 2001, this 003 second interim report was submitted. That is the first-line therapy. But this only went to December 20 of 2000. They also updated the safety update with another patient, bringing it to 309 now. Then in September of 2001, a final study report for 97-012 was submitted. I believe that was the first time that the Rituximab refractory patients were submitted, and this was the second efficacy study. Let's see, then there was another amended study report for 002 which was the hot versus cold protocol, and now we saw a MIRROR Panel review which was the first time for that, which was an independent review, and now the data cutoff was January 2001.

Okay. In September 10, 2001, Corixa responded to the FDA letter of the March 16. And then on December 11 of that year, this 004, the chemo-refractory protocol was an amended final study report, including more data up to January 2001 and now more data from the MIRROR Panel, up to September of 2001. Then there was another safety update, which now was up to 620 patients, which included 387 from the expanded

access study. There were long-term responders also that were from various studies and the MIRROR Panel review. And, again, there was now additional information for the study 020, the expanded access.

On March 5 of this year, there was another safety update which was corrected for errors and gave additional hematology data collected from audit at the clinical study sites for about 620 patients. March 12 of this year, FDA gave to Corixa another action letter. They really needed to demonstrate a meaningful therapeutic advance over existing treatment because now in February Zevalin was approved for the same indication and same patient population and additional safety data were needed.

On July 2 of this year, case report forms and report tabulations for long-term responder subpopulations were submitted. And then in July 11, a revised proposed indication was submitted to the FDA in which they requested accelerated approval for chemo-refractory patients and standard approval for Rituximab-refractory patients. In addition, another amendment to the final study report for the Rituximab-

refractory patients was submitted at that time.

On October 4 of this year, amendment to the Rituximab-refractory group was submitted, and on October 30, the independent review for additional patients in that study with transformed histology was submitted. Now, on October 31, Corixa completed their response to the FDA letter from March.

December 10, one week ago, Corixa responded to the Bi Mo inspectional findings. We really didn't have a lot of time to review that before this meeting, I might say. There were outstanding issues on the clinical trial. There's identification of the dose delivered versus the dose prescribed for patients in efficacy studies, and the FDA will need to confirm the safety profile of the proposed dose. In some cases, apparently, some sites had patients they knew exactly what dose they got; in others, they just wrote down the prescribed dose, so this is something that we have to sort of work through.

All right. Well, now I'm going to talk a bit more about the product itself, or tositumomab therapeutic regimen. I will call it TTR, it's a

little easier to pronounce. Actually, it consists of both unlabeled and I-131 labeled antibody. The antibody has also been called in anti-B1 in a lot of literature of the past. It's a Murine IgG2a -- it showed me Lambda on the screen. It was a Lambda light chain, I don't know why it came out like that. It recognizes the CD20 determinant on B cells.

To give you an idea of the characteristics of the antigen it recognizes, it's a transmembrane phosphoprotein with a molecular weight between 33 and 37 kilodaltons. It's present on the surface of pre-B and mature B cells, and it's expressed on greater than 90 percent of B cell lymphomas. It is now, however, present on stem cells, mature plasma cells or other non-lymphoid normal tissues, and it is not shed or internalized upon antibody binding.

To get back to the characteristics of the antibody, it's manufactured by standard tissue culture and purification techniques and the iodinated with I-131 as radiolabeled by the IODO-GEN method. The mechanism of this is by electrophilic addition of the iodis ion to tyrosine residues. Approximately eight

tyrosines are iodinated and no hystodines.

The components of TTR, the unlabeled antibody is prescribed in two vial sizes, a small one with 35 milligrams and a larger dosage vial of 225 milligrams, both of them at 14 milligrams per mil. The labeled components also are supplied in two forms. One is a dosimetric vial, which contains 12 to 18 millicuries of I-131, and a therapeutic vial, which of course is more powerful, containing approximately 112 to 168 millicuries.

The TTR procedure is two-fold. Step one is imaging, in which an unlabeled portion of antibody is first given, IV over 60 minutes, followed then by the dosimetric form of the iodinated antibody, which is given over 20 minutes and contains approximately five millicuries. Approximately seven to 14 days after the imaging dose and imaging sessions, then the therapeutic dose is given, and this is also -- first there is an unlabeled dose given over 60 minutes, followed by a therapeutic dose, which is patient-specific and it depends on the -- it's by the whole body clearance rate. This ranged also from about 112

to 168 millicuries.

In addition, the TTR procedure involves the thyroid protective agent, which is given beginning about 24 hours prior to the first infusion of the iodinated antibody, the dosimetric dose, and continues for 14 days following the last infusion of the iodinated antibody, the therapeutic dose.

There are a few remaining chemistry manufacturing and control issues. A number of manufacturing issues do still remain to be resolved, and one of the contract facilities needs to be inspected. Thank you for your time. Now, I guess Corixa Corporation will take the stand.

CHAIRPERSON PRZEPIORKA: Thank you, Dr. Zaremba, and I do apologize for misspeaking regarding your affiliation. I'm certain your colleagues at CBER will welcome you back with open arms right now.

(Laughter.)

And so we will then move on to the Sponsor presentation. The first speaker listed is Dr. Fisher. Dr. Jacobs, will Dr. Fisher be introducing the presentation? Okay. Dr. Jacobs will be introducing

the presentation from Corixa.

DR. JACOBS: Dr. Przepiorka, Dr. Siegel, members of the Committee, FDA and guests, good afternoon. My name is Cindy Jacobs, I'm the Senior Vice President of Corixa Corporation. On behalf of Corixa Corporation, we'd like to thank you for the opportunity to present and review the data from Bexxar.

The proposed indication for Bexxar is the treatment of patients with relapsed or refractory low-grade non-Hodgkin's or transformed low-grade non-Hodgkin's lymphoma. This includes patients with Rituximab-refractory NHL. We requested accelerated approval for the relapsed or refractory low-grade or transformed low-grade non-Hodgkin's lymphoma patients last year upon completion of our first response to the complete review letter. We then, in addition, this year, asked for conventional or standard approval for Rituximab-refractory non-Hodgkin's lymphoma patients. The accelerated approval is based on the existence of long-term durable responses in patients who have relapsed in refractory non-Hodgkin's lymphoma. The

request for conventional or standard approval is based on demonstrated efficacy in patients that have Rituximab-refractory NHL.

In addition to Dr. Fisher and Dr. Armitage who will be speaking this afternoon, we have with us today a number of lymphoma experts, independent reviewers and clinical investigators who were involved in the development of the clinical process of Bexxar as well as the independent review of the data and as advisors. They are here with us today to assist in answering any specific questions that you might have on the interpretation of the data.

This will be our agenda for the presentation: Dr. Fisher will first present the disease, the outcome and therapy for low-grade and transformed non-Hodgkin's lymphoma. I will then present the efficacy and safety overview, the basis for approval. Dr. Armitage will then finish with the risk/benefit analysis.

I'd now like to introduce Dr. Fisher who is the Samuel Durian professor of medicine and the Chief of the Hematology/Oncology Unit and the Director

of the Wilmott Cancer Center at the University of Rochester. He's also the Chairman of the Lymphoma Committee at SWOG.

DR. FISHER: Good afternoon, everybody. Thanks, Cindy. You wonder what I do with my spare time after that introduction. What I wanted to do today was really take a few moments of your time and help bring everybody together in terms of the diseases we're going to talk today about, in terms of the treatment options, in terms of what we can expect. And in sitting back and listening to the moving testimony of the patients who talked before, I was reminded of something that I see regularly in the clinic, which is that our patients with lymphoma become lymphoma experts as they go through. So my job is much easier, because they've actually told you much of this as they went through.

The low-grade non-Hodgkin's lymphomas are a group of indolent or chronic diseases, as you've heard about, diseases that are not curable but that are not uncommon. The annual incidence in the United States is well over 15,000 cases. Because these are

chronic diseases and because patients live for a prolonged period of time, the prevalence is significantly greater than the incidence. And in the United States recently there are about 64,000 cases at any one time in the year. So that's the potential group of patients with indolent lymphoma alive.

As I said, unfortunately, it's a chronic disease, and as many of the patients said, it's an incurable disease. Median survival from the time of diagnosis, and we'll talk about different survival figures so we'll try and be precise about when we're starting the clock, at initial diagnosis is eight to 11 years in multiple series.

Why do these patients die, ultimately? Well, frequently, at the end of their disease, about a third or more will have a malignant transformation to a more aggressive presentation, frequently a large cell lymphoma, and that histologic transformation with aggressive clinical disease will be associated usually with a median survival of less than one year and will frequently require more aggressive treatment.

As you heard from the FDA just a moment

ago, we're talking about therapy directed at CD20, and probably most of you are aware why CD20 is such an ideal target for treating these indolent lymphomas. First of all, it's not expressed on the stem cells so that when you knock out CD20, as the anti-CD20 antibodies do, you take out the CD20 positive B cells, you will repopulate the repertoire from the stem cells.

Secondly, it's not expressed in the majority of plasma cells. That's the immunoglobulin factory that makes immunoglobulin. And, therefore, there are no significant changes in the circulating immunoglobulin. Therefore, the immunodepression is not significant and not really a problem in these patients. And most of all of these patients express this CD20, which can be removed, as I said.

Now, how do you treat these patients? Unfortunately, it's now a very complicated diagnosis and treatment. The discussion is not easy. It would be easy if we had one therapy to cure patients, but we don't at this time. Patients frequently present asymptomatic after a lymph node biopsy, and some of

those patients can be given a treatment called watch and wait, which is really no initial treatment. That means they can go a prolonged period of time, sometimes a couple years, without anything other than perhaps some local radiation therapy. Other patients, and even the watch-and-wait patients, ultimately, will inevitably develop symptom management progressive disease, and then they will require treatment.

Almost all of these patients are chemotherapy sensitive at the time this happens. What does that mean? They can be treated with alkaline agents, they can be treated with CVP, combinations of alkaline agents, they can receive CHOP, they have a variety of different chemotherapy options. However, the responses are all relatively limited. More recently, as this group knows well since the advent of Rituxan on the market, essentially every patient in this country who has access to the health care system, has insurance, will get Rituxan at some point and frequently multiple times, and they will be responsive. But, in fact, those responses, as you well know, are also of short duration.

Toward the end, we get the relapsed or transformed manifestations, and then as I said, frequently very aggressive chemotherapy, even stem cell transplant is advocated often. The patients who don't show that clinical transformation become refractory to chemotherapy and antibody, and symptom management may be the only thing we currently have to offer them in the latter stages of this incurable disease.

Now, this is a very important slide, because it sets the basis on which the data will be presented today on which you will evaluate some of the efficacy of this potential drug. This is data from St. Bartholomew's Hospital, published in the JCO, which shows what happens when you treat the patients the first time, the second time, the third time and the fourth time. What is not shown on this slide are the response rates, and not surprisingly they go down every time they relapse and every time you retreat them. What is shown very well is that at one treatment the median response duration, how long they stay in remission, is about 16 months, the second time

down to 11, ten, and if you have four relapses, the median response duration, the 50th percentile is three months, and the response rate is low. This is not a surprise to the medical oncologists. As you get later in the disease, the disease becomes increasingly more refractory. And this is what will also be confirmed when we show you data from the patients who entered the Bexxar studies, have a similar pattern prior to Bexxar showing the same thing: More and more relapses, less and less response, less and less duration.

Now, this is, unfortunately, where we show our failure. I've been doing this for over 25 years in terms of lymphoma treatment. A number of us, the experts we have a lot of years of work on this disease and to date, unfortunately, we have not changed the natural history of this disease based on survival. This is data from Stanford over a variety of periods and different regimens of their treatment, but what it shows you is that the median survival is again in the range of seven to ten years, and there is no apparent plateau or curability of these patients in that

regard.

Okay. Well, why did we turn to radioimmunotherapy? What do we think is happening? Well, if you'll -- this is now only Powerpoint possible. Now you're going to see modern technology at its best. When you have Rituxan available, you had an unlabeled cold antibody, and if it could bind the CD20 antigen, it could kill the cells, maybe by complement, maybe by ADCC, maybe by intracellular single invade optosis. But there are cells that are not reached by the antibody, and they're unaffected, and so the cells that are in contact with the immune system and antibody die.

With the Bexxar treatment, you have an antibody again going to CD20 binding those same cells but you have a cross-fire effect from the radiation tag on the antibody that can result in more death of the cells, and this is the theoretical underpinning by which this happens.

Well, really, why radiation therapy? Jokingly, the other day we were saying when I first started out in this field I was told by my

predecessors the major, most effective drug treating lymphomas is radiation therapy. The problem is that disseminated lymphoma, which is what the majority of these patients present with, is not amenable to local fields and cannot be encompassed with acceptable toxicity. Bexxar is a way to target radiation to the site of the disseminated tumor.

How about the rationale for iodine? Well, there's an enormous safety record in this country and the world over 50 years. The fact that there's a gamma radiation allows you to do patient-specific dosimetry. You can do scans and calculate doses. And the fact that the real radiation therapy is coming from beta with a short path length will limit the toxicity outside of the area where the antibody is actually present.

Now, this is one of the complicating features of this discussion we're going to have today. Everything is a bit of good news/bad news. The good news: This is not a new product, this is not new in development. It started in 1990, so you are seeing data that has follow-up as long as 12 years for some

patients. The phase 1/2 study and then the first phase 2 multi-center study in the '90s. The patient control trial you'll hear more about starts in the last '90s, a trial of the cold versus the hot antibody. A trial of phase 2 looking at Rituxan failures, and then finally expanded access.

So the good news is there's a lot of time to see the long-term effects of this particular drug. The bad news is, of course, that the world changes during that time, and so things that you might have said in studies that were needed here might not have been known there or might not have been available, so you have to balance those two effects.

Corixa took over this program in '01, and today no matter how we got there, the efficacy is not on a small number of patients, it's on 250 patients for data, and the safety and toxicity data is in over 600 patients. So that is a sizable database for us to deal with.

Now this is one of the most important slides and I'd like you to focus on this, and I suppose if you remember one thing from my talk, I'd

like you to try and think about this slide, remember this slide, because this is what you heard about from the patients who were talking today. Some of them are shown on this slide. This is long-term durable response, event-free survival plotted for all five trials, and the scale here is not months, not weeks, but years. And out here beyond two years, two, three, four and five years, what you see is a significant number of patients in each study with between ten and 20 percent predicted to be alive, disease-free, off all therapy with one treatment that took two weeks out of their lives, and as you heard, did not result in major toxicity that they perceived. This is something that those of us who have been in this business for a long time have not seen in this kind of circumstance, remembering that these are patients who on the average have about four prior treatments. This is a new observation for us and one that I think makes us stand up and take note of the efficacy of this product.

Hopefully now with us on a common page and with that introduction, I'll turn it back over to Cindy, and she's going to present the actual data to

you. Thank you for your attention.

DR. JACOBS: These are the agenda items that I will follow, both of which will be to review the individual studies. The first two studies evaluated the development of the dosimetry and the MTD of radiation, followed by then the validation of the dosing methods at multiple clinical sites.

This first study showed the pharmacokinetics, the tumor targeting and the dosing methods, the pre-dose of the unlabeled antibody to block non-specific binding sites and optimize the distribution was determined. The maximum tolerated dose of radiation was also determined. The second study was designed to show the reproducibility of the whole body dosing methods at multiple centers and again preliminary safety and efficacy for patients with relapsed and refractory low-grade non-Hodgkin's lymphoma, with or without transformation.

Results from these two studies defined the Bexxar treatment regimen as follows: First, a thyroid protective agent is started on day minus one and continued through day 14 after the therapeutic dose.

On day zero, the dosimetric dose is given as 450 milligrams of unlabeled tositumomab infused over one hour followed by 35 milligrams tositumomab radiolabeled with five millicuries of Iodine 131. Total body counts by gamma camera scans are taken on day zero, again on day two, three or four, followed by day six or seven.

From these total body counts, the total body clearance is derived, and the patient-specific activity in millicuries is calculated to give a total body dose of 75 centigrade. Thus, on day seven to day 14, the therapeutic dose can be given as 450 milligrams of unlabeled tositumomab infused over one hour, followed now by 35 milligrams tositumomab radiolabeled with Iodine 131 to deliver the 75 centigrade total body dose. Thus, Bexxar treatment is administered as two doses over this one- to two-week period.

Other results from these two studies are represented in the next three slides. As was already stated, the unlabeled pre-dose of tositumomab gave superior tumor targeting. We determined the clearance

of radioactivity which was dependent on tumor bulk, spleen size and bone marrow involvement. This allowed the patient-specific dose to be calculated and can be easily delivered in nuclear medicine departments by personnel. The dose living toxicity was myelosuppression. The MPD was 75 centigrade total body radiation dose, which was attenuated to 65 centigrade for those patients who had platelet counts less than 150,000 at time of study entry.

This slide shows the preliminary efficacy for those patients who had low-grade or transformed low-grade NHL in the studies. For the first study, 42 patients had low-grade or transformed low-grade non-Hodgkin's lymphoma. They had failed four median numbers of prior regimens. Thirty-three percent had transformed histology. The overall response was 64 percent, and the CR rate was 38 percent. In the second study, again the median number of failed prior regimens was four, 30 percent of the patients had transformed histology, the overall response rate was 49 percent and the CR rate was 26 percent.

This is a time to progression curve for

both of these studies. Durable responses were observed for both studies, as shown in this figure. This is an important finding in that the four- to eight-year Kaplan-Meier estimate is 13 percent, which is not expected after a single treatment in this refractory patient population.

Based on these early results, the pivotal study, 004, was designed in 1996. Sixty patients were enrolled at eight sites. These were for chemotherapy-refractory. The study designed used patient-as-own-control comparing the results following Bexxar compared to the last qualifying chemotherapy. In 1996, there was no suitable comparator for this refractory patient population. Patient-as-own-control designs have been recognized as appropriate for registration. They are particularly useful in disease settings like low-grade non-Hodgkin's lymphoma when previous responsiveness in patients can predict future outcome.

All efficacy end points were reviewed by an independent panel, the Masked Independent Randomized Radiology and Oncology Review Panel,

referred to as the MIRROR Panel. The procedures for the MIRROR Panel were coordinated by an independent CRO. It was a masked reviewed by two independent teams, each with an oncologist and a radiologist. For each patient, the review of the last qualifying chemotherapy was randomly assigned to one team and the results following Bexxar to the other team. This included redacted radiographs and redacted medical notes.

This is a list of the last qualifying chemotherapies that were prospectively defined in the protocol required to be appropriate for multiply relapsed low-grade or transformed low-grade non-Hodgkin's lymphoma. The primary end point was the comparison between the number of patients with longer duration of response, defined as greater than 30 days following Bexxar, to the number of patients with longer duration of response after their last qualifying chemotherapy. Secondary end points were overall response, complete response, duration of response and time to progression.

To be eligible patients had to have

chemotherapy refractory disease defined as follows: they had to have had at least two prior qualifying chemotherapy regimens; there had to be no response or progression within six months after completion of their last qualifying chemotherapy. Also, complete documentation for that last qualifying chemotherapy had to be available. The ANC had to be greater than 1,500, platelet count greater than 100,000, less than or equal to 25 percent bone marrow involvement in bidimensionally measurable disease.

Patient characteristics for the 60 patients are represented here. The median number of the prior failed regimens was four, the range was two to 13 prior regimens. Thirty-eight percent of the patients had transformed histology. There was one patient that was retrospectively reclassified as having mantle cell lymphoma. This patient is included in all the efficacy analyses as an attempt-to-treat basis. There is a high frequency of other poor prognostic factors known in this disease, and as stated, patients were refractory to their last chemotherapy. The overall response was 12 percent

with only two percent complete response and no response longer than six months.

This bar graph illustrates the primary end point. The x axis shows the results for each of the 60 patients. The y axis shows the duration of response in months. The yellow bars show the duration of response for the last qualifying chemotherapy for the 60 patients. As you can see, only seven patients responded to their last qualifying chemotherapy. The blue bars illustrate the duration of response in those same patients following Bexxar therapy. The plus signs above here are showing those patients in continuing or ongoing response at the time of their last assessment.

So, for example, this patient had almost a six-month response to their last prior chemotherapy compared to 36 months following Bexxar treatment, and that response is still ongoing. The side-to-side orientation is simple: Those patients who had a longer duration to Bexxar are to the right; those patients who had a longer duration to their last qualifying chemotherapy are to the left; those

patients who did not have a response or an equivalent response are presented as E's in the middle of the bar chart. As you can see, the primary end points for comparing the number of patients that had a longer response to Bexxar compared to the response to the last qualifying chemotherapy was highly significant in favor of Bexxar.

This slide shows the overall response, and complete response was also significantly different in favor of Bexxar. The overall response following Bexxar was 47 percent compared to 12 percent; for the CR rate, 20 percent following Bexxar compared to two percent.

This slide illustrates the time to progression following Bexxar compared to that following the last qualifying chemotherapy. Although the curves overlap initially, you can see that 20 percent of the patients had long-term durable responses following Bexxar therapy, some out to four years.

This study is a randomized study comparing Bexxar to the unlabeled tositumomab. This study was

designed to show the relative contribution of the radiolabeled antibody compared to the unlabeled antibody. Seventy-eight patients were enrolled at nine sites. Again, they were chemotherapy-relapsed refractory with or without transformation. As stated before, patients were randomized to receive Bexxar or the same amount of unlabeled tositumomab in the same manner. All of the assessments of response were independently reviewed by the MIRROR Panel. The primary end point was the comparison of CR rate; secondary end points, response, duration of response and time to progression.

Both arms were balanced for patient characteristics, both arms patients had a median number of two prior failed regimens. They were similar in the frequency of poor prognostic factors. Seventy-three percent and 77 percent of patients responded to their prior chemotherapy, but the duration of response was a median of six months.

The primary end point CR rate was 33 percent following Bexxar therapy compared to eight percent with unlabeled tositumomab, which was

statistically significant in favor of Bexxar. The overall response following Bexxar was 55 percent compared to 19 percent with the unlabeled antibody.

Time to progression as the secondary end point was also statistically significant in favor of Bexxar compared to the unlabeled antibody. Again, there were a number of long-term durable responders with a four-year Kaplan-Meier estimate of 35 percent. Thus, the addition of Iodine, I-131, to the antibody did contribute to the overall response and the time to progression in this study.

The protocol also allowed patients who progressed with the unlabeled tositumomab to cross over to receive Bexxar therapy. There were 19 patients who did cross over. Of the 19 patients, 68 percent had an overall response and 42 percent had a complete response. More details of that information is presented in the briefing document.

The last study to be summarized is a single-arm study evaluating Bexxar in patients who are refractory-relapsed following Rituxan. Forty patients were enrolled at three sites. These patients had

disease which failed to respond or progressed after Rituxan therapy. Again, all of the efficacy end points were independently reviewed by the MIRROR Panel. These 40 patients had a median number of four failed prior regimens. Thirty percent had transformed histology. Again, a number of poor prognostic factors were seen. Eighty-eight percent of the patients had no response or the response was less than six months to the prior Rituxan. The overall response following Bexxar treatment was 68 percent. The median duration of response was 16 months. Thirty-three percent of the patients had a CR with the median duration of the CR not yet reached. The median time to progression was one year.

This bar graph again illustrates the comparison of the duration of response following Bexxar compared to the patient's response to Rituxan. The x axis shows the results for the 40 patients; the y axis, the duration of response. Again, the yellow bar shows the duration of response for patients to their prior Rituxan therapy. The blue bars illustrate the duration of response for those same patients after

Bexxar treatment with again the pluses showing those responses that are still ongoing at last time of assessment.

When using a patient-as-own-controlled analysis comparing the number of patients with longer duration of response to Bexxar compared to the number of patients with a longer response to Rituxan, again, it was highly statistically significant in favor of Bexxar.

This figure summarizes the time-to-progression curves for all patients from the five studies that you have seen. The time to progression is defined as the start of Bexxar therapy to the first documented progression. In summary, all five individual studies consistently showed a number of long-term durable responses after this single treatment.

Let's now turn to the integrated efficacy population. The integrated efficacy population consists of 250 patients enrolled from the five studies that you have just seen that had low-grade or transformed low-grade non-Hodgkin's lymphoma and

received Bexxar therapy at any time. The patient characteristics again showed that the median number of prior failed regimens was three. Twenty-eight percent of the patients had transformed histology. Again, a high number of poor prognostic factors. Eighty-four percent of the 250 patients had no response or less than six months response to their prior therapy and were refractory to their prior therapy.

The overall response was 56 percent with a median duration of response 13 months. The CR was 30 percent with a median duration of CR almost five years. This is the time-to-progression curve for the 250 patients in the integrated efficacy population. The dotted blue lines show the 95 percent confidence intervals. The timeline goes out to eight years with an eight-year Kaplan-Meier estimate of 13 percent.

From the integrated efficacy population, two subpopulations were further analyzed: the long-term durable responders and the transformed low-grade patients. We will first review the Durable Responder Population. Upon consultation with our lymphoma experts, we defined the Durable Responder Population

as those patients who had an independent-assessed response and a time to progression of at least one year or more, again, confirmed by the MIRROR Panel. Thirty-one percent, or 78 patients, met this definition. Two patients were removed due to confounding factors regarding their response to Bexxar. Seventy-six patients then are retained in this Durable Responder Population. The median follow-up is 44.6 months.

The demographics for this 76 subpopulation are patients that have a median number of failed prior therapies of three, 20 percent were transformed, again, there were a number of poor prognostic factors, and 75 percent of them were refractory to their prior therapy. Seventy-six percent of these patients had a complete response following Bexxar. The overall response and the complete response approached five years. The median time to progression is five years.

This is the time-to-progression curve for those selected 76 patients who had a time to progression greater than or at least one year as the Durable Responder Population. We then analyzed that

the long-term durable responders were present in patients who had poor prognostic factors and found that patients who were refractory to their prior therapy had bulky disease or had a high IPI score and could achieve long-term durable responses, as shown in the next three slides.

As seen in the chemotherapy-refractory population in 04 and the Rituxan-refractory population, these durable responders can be seen in patients refractory to their last chemotherapy as well as relapsed from their last chemotherapy. Patients with bulky disease, defined as lesions greater than five to ten centimeters, also you can see that there are long-term durable responders in those patients. Patients who were intermediate high-grade or high-risk based on IPI score could also have durable responses following Bexxar therapy. In summary, patients who still have well-documented poor prognostic factors can have durable responses following Bexxar.

Let's now look at the transformed low-grade subpopulation. There were 71 patients of the 250 who had transformed histology by the

investigators. These are the investigator-assessed histologies. At the request of FDA, we had the histopathology reviewed by a retrospective Central Pathology Review. Of the 71 patients, 53 patients had sufficient material available for this retrospective pathology review of their original low-grade diagnosis as well as their diagnosis of transformation. The majority of the other 18 patients we were not able to get sufficient material of their original low-grade diagnosis. Of those 53 patients, 47 patients were confirmed by Central Review as having transformation. Five could not be confirmed and one was classified as an intermediate grade.

I will focus on presenting the data for the 47 patients. Of these 47 patients, the median number of failed prior regimens was four, the range was one to nine. Again, there were a number of poor prognostic factors. Sixty-five percent of the patients had bulky disease, and 56 percent had an elevated LDH. The overall response in these patients was 40 percent with a median duration of 14 months. The complete response rate was 23 percent, the median

duration of CR was 36 months, or three years.

This is the time-to-progression curve for both the 71 total patient subpopulation as well as the 47 that were confirmed by Central Pathology. The time-to-progression curves are similar and again show durable responses out to five years.

You've now seen the efficacy profile from the individual studies as well as the integrated efficacy population. We will now review the safety data from the integrated safety population. The integrated safety population consists of 620 patients. Two-hundred and twenty-nine were from the five studies that you have just seen with patients that had received the prescribed 65 or 75 centigrade total body dose. The other 21 patients had received less than 65 centigrade total body dose and were removed.

Three hundred and eighty-seven patients were included from the expanded access program that also had low-grade and transformed low-grade non-Hodgkin's lymphoma and had at least 13 weeks of follow-up. There were also four compassionate use patients that had long follow-up and had been

monitored by the Company.

Eighty-nine percent of the patients had any type of adverse event at any time. Sixty-five percent of them were Grade III/IV, 23 percent were serious adverse events. And, again, these are serious adverse events regardless of relationship to study drug. Eighteen percent, hospitalizations; infection and fever, 6.8 percent; 8.6 percent of the patients died within 90 days of Bexxar; 1.3 were not related to progressive disease. Again, all the adverse events that we will be showing will be regardless to any relationship to Bexxar.

The infusions were well-tolerated. Most common were the Grade I/II adverse events. Fever and pruritus were the most common for the dosimetric dose, and chills and nausea were the most common for the therapeutic dose. Grade III/IV adverse events were less in approximately two percent of patients. Infusion rate adjustments was only five percent following the dosimetric dose and four percent following the therapeutic dose.

This shows the non-hematologic adverse

events, and as you can see, the majority were Grade I/II adverse events, with asthenia, nausea and fever being the most common. The Grade III/IV adverse events were less frequent. The most common was dyspnea followed by asthenia, nausea, fever and pain. Twenty percent of patients had one or more serious non-hematologic adverse events, again, regardless of the relationship of study drug. The most common were fever at three percent, sepsis, pneumonia and dyspnea at two percent. Grade III/IV hephanic and renal toxicity occurred in less than one percent of patients.

Decreased thyroid function was defined as an elevated TSH or initiation of thyroid medication. The four-year cumulative instance was 12 percent. Of note, 11 percent of patients were identified with a diagnosis of hypothyroidism at the time of study entry. Those patients are not included in this analysis. And as you're aware, hypothyroidism is easily diagnosed and treated as long as patients are monitored annually. The two-year cumulative incidence of HAMA was ten percent. Some patients did have

delayed HAMA. This is most likely due to delayed immunologic recovery. In summary, the infusion-related in other non-hematologic toxicity was not remarkable.

Let's now review the hematologic toxicity, as myelosuppression was the dose-limiting toxicity. The median time to nadir ranged from day 34 to day 47. Grade III/IV neutropenia was 42 percent; Grade III/IV thrombocytopenia, 36 percent; and Grade III/IV anemia, 11 percent. The median duration for the Grade III/IV cytopenias ranged from 19 days to 30 days. Five percent of the patients did not recover to Grade II. The majority did recover to their baseline grade.

Twenty-six percent of patients received one or more hematologic supportive care measures at any time during recovery. Supportive care measures are a surrogate for the severity of the hematologic toxicity. Fifteen percent of patients had red blood cell transfusions; 12 percent, platelet transfusions; 11 percent of patients received G-CSF; and seven percent erythropoietin.

The consequences of neutropenia and

thrombocytopenia were infrequent. Less than two percent of patients had a Grade III/IV infection with neutropenia, neutropenic fever or bleeding with thrombocytopenia. Thirty-eight percent of the patients had any infection within six months following Bexxar. Six percent of those patients had a serious infection. The majority of these infections were Grade I/II that were viral rhinitis, pharyngitis and flu-like symptoms. The six percent of serious infections were predominantly sepsis and pneumonia. Twelve patients died with a serious infection within 90 days of Bexxar therapy. Nine had concomitant disease progression and three did not.

Eight point five percent of patients had bleeding events. One point six percent of those were Grade III/IV bleeding events. Four patients died with bleeding events within 90 days of receiving Bexxar therapy, three with disease progression and one without.

In these studies, there was missing data mainly due to patient withdrawal for progressive disease or death. Corixa did additional analyses with

FDA such that if data were missing during the key nadir time, the occurrence of Grade III/IV toxicity that were assumed to have occurred to provide a conservative or a worst-case analysis. So, for example, 42 percent of patients had a documented Grade III/IV neutropenia; 15 percent of patients had missing data during the key nadir time and were assumed to have Grade III/IV events that were missed, thus giving a total conservative or worst-case analysis of 57 percent Grade III/IV neutropenia. If one looked at any hematologic toxicity using this conservative analysis, 65 percent of patients would have had a documented Grade III/IV neutropenia/thrombocytopenia or anemia in these studies.

The potential long-term safety concern for radioimmunotherapy is MDS in associated leukemia. There were 19 reported cases in the 620 patients with accrued incidence of 3.1 percent and annualized incidence of 1.7 percent per year. Of the 620 patients, 387 were from the expanded access program which had shorter median follow-up of only one and a half years and are less informative regarding the

incidence of MDS. So in looking at only the 233 patients with a median follow-up of 2.4 years, 18 reported cases occurred.

A centralized independent masked review by Dr. Bennett was performed for these cases in the remaining 233 patients. It was determined in retrospect that four patients had evidence of preexisting MDS prior to receiving the Bexxar therapy and are removed from the analysis. One additional patient had no morphological evidence that could be confirmed by Dr. Bennett of having MDS. Thus 13 cases out of 229 patients gives a crude incidence of 5.7 percent and an annualized incidence of 2.2 percent per year.

The combination of extensive chemotherapy and external beam radiation treatments has been well documented in association with the development of MDS and acute leukemia. It is not possible with the experience to date to know what extent Bexxar may contribute to the incidence of MDS in this patient population.

There is one other study, 003, which had

Bexxar treatment to previously untreated patients. Seventy-six patients were treated. The median follow-up is 3.6 years, and there is yet to be any incidence of MDS in this study. All patients are being continually followed for MDS, or acute leukemia. As an update, through September 13 of this year, five additional cases of MDS have occurred in the 387 patients on the expanded access protocol, thus giving to date a total of 24 out of 620 patients with an annualized incidence of 1.8 percent per year.

There were no infusion-related deaths. Time from the dosimetric dose to death was 38.7 months. Two hundred and fifty-four patients, or 41 percent, have died during the studies, 31 percent primarily due to lymphoma progression, five percent due to complications from their lymphoma or additional non-Hodgkin's lymphoma therapy, one percent for incidental causes, two percent due to the MDS or acute leukemia, 12 patients died with other causes, of which three were attributed to study drug. Eight of these deaths, or 1.3 percent, occurred within 90 days of Bexxar therapy.

In summary, there is a low incidence of Grade III/IV infusion-related adverse events, no infusion-related deaths. The non-hematologic AEs were predominantly Grade I or Grade II. The four-year cumulative incidence for hypothyroidism was 12 percent; HAMA, ten percent. The AEs were primarily hematologic. There was limited need for supportive care and a low incidence actually serious infections in Grade III/IV bleeding events. The annualized incidence of MDS is 2.2 percent per year and still being followed, and non-lymphoma deaths within 90 days was 1.3 percent.

I will now again summarize the basis for our request for approval. As stated, we requested for accelerated approval last year for the relapsed or refractory low-grade or transformed low-grade non-Hodgkin's lymphoma patients. The basis for accelerated approval is defined as follows: Clinical trials must be adequate and well-controlled, they must establish that the product has an effect on a surrogate end point that is reasonably likely to predict clinical benefit, the product must provide a

meaningful benefit over existing treatments, and the Company must commit to subsequent trials to confirm that that surrogate end point does predict clinical benefit.

Thus, our request for accelerated approval is based on the 004 pivotal trial demonstrating longer duration of response compared to the prior chemotherapy. Bexxar has induced long-term durable responses, and we have done additional follow-up data at the request of FDA with these submissions over the last year. No other single treatment to date has been shown to induce extended responses out to five to eight years. Corixa has also committed to additional trials. One trial is a SWOG study that is already ongoing. The other trial is a randomized trial comparing Bexxar therapy to Rituxan therapy. The primary end point for that study is event-free survival.

We are requesting conventional approval as of this year. For Rituxan-refractory patients based on a safety profile that is predictable and manageable. The efficacy is based on the patients

enrolled in study 012 showing that more patients had a longer duration of response to Bexxar than their prior Rituxan therapy, which was highly significant in favor of Bexxar.

Dr. Armitage will now describe the potential role for Bexxar in this patient population. Dr. Armitage is the Dean of the University of Nebraska College of Medicine and is the Past President of the American Society of Clinical Oncology and the American Society of Blood and Marrow Transplantation.

DR. ARMITAGE: Thank you. As you heard, my task today is to try to take all this information and put it in a clinical perspective. Now, in addition to the administrative responsibilities you heard a minute ago, I have for more than 20 years and do, spent a significant portion of my time treating patients with lymphoma, and I'm involved in clinical research in this disease.

The reason I agreed to make this presentation is that I've actually treated several of the patients on the data being considered and have found this drug to be the most active agent that I've

seen in patients with multiply relapsed or refractory low-grade B cell non-Hodgkin's lymphoma.

Now, certainly, the most striking bit of data incorporated in this slide that you've seen before is the fact that in addition to a high response rate a significant and surprising proportion of these patients remain well for extended periods of time, particularly striking given the comparative simplicity of the treatments, certainly from the patient's point of view.

Now, as we look at the data, what I'm going to do is consider toxicity and the response -- the activity of the drug, Bexxar, and try to, when possible, consider it in light of what might have been expected or what could be accomplished with other available agents. Certainly, the group of patients we're going to talk about represent an unfavorable population. These are people with multiply relapsed, usually refractory lymphoma; certainly not a group where you would expect to see a significant number of patients with long-term durable remissions.

I believe the data you've seen does in

fact illustrate an acceptable safety profile. I'll talk about myelosuppression and myelodysplasia in just a moment. The hypothyroidism, while it does occur, occurs at a much lower incidence than we're used to seeing, for example, in patients with Hodgkin's disease who receive mantle radiotherapy, and of course this is an easily manageable condition.

This is the hematological toxicity, the primary toxicity with this agent. Now, I think it's worthwhile remembering what this means. Thrombocytopenia means less than 50,000 platelets that have Grade III toxicity. Neutropenia is less 1,000 neutrophils and anemia is hemoglobin less than eight grams. First of all, these are not striking numbers to the medical oncologists in the room, and ones that we would see fairly regularly with other intensive therapies that we would use to treat patients with this or other diseases.

And you remember that you saw before that this number is larger than that number, because there were some patients, usually because they for one reason or another, dropped out of the study and whom

there was a number not measured that could have been a higher grade of toxicity. And so a reasonable interpretation of this, it seems to me, is that this is the lowest and this is the highest toxicity level we could have and most likely it would really be somewhere in the middle if we had every bit of information.

Now, how to put this in perspective because this isn't an easy thing to try to judge but it's what we would expect. Now, what I've chosen to do is to compare this toxicity with that reported for the other radiolabeled antibody, the yttrium labeled ibritumomabtiuxetan. Now, let me caution you: It would be absolutely inappropriate or unfair to try to use this sort of a comparison to try to argue that one or the other drugs are better. What I want to use this for, though, is what I think we need to be doing now, is trying to see if there's a red flag raised to suggest that the agent being considered today, Bexxar, has an unusually high toxicity that suggests that it might be dangerously worse, and my interpretation of this data would be that's probably not the case.

Now, hands down, the most concerning toxicity in the treatment of patients with cancer beside toxic agents is the occurrence of myelodysplasia and acute myeloid leukemia. Now, keep in mind two things here. One is that to have this toxicity you actually have to live long enough to get it, so you had to receive a therapy that benefitted you. And, secondly, that the occurrence of myelodysplasia or acute myeloid leukemia is related to the number of exposures to marrow-injuring agents, the duration of exposure and the age of the patients, with patients over 60 years seeming to be at particularly high risk.

You can see that in the data you just saw a few minutes ago that in the patients on studies, 18 were originally thought to have this condition, 13 really did, with four having developed it subsequent to the Bexxar, with four having had both morphological and cytogenetic evidence for the condition before they were treated, not surprising in these group of people with multiple exposures to marrow-injuring agents. And one apparently really didn't have it. This leads

us to this 2.2 percent per year annualized incidence. While I suspect the statisticians in the room can use that data, I also suspect that some of the hem/onc people in the room, like me, don't know exactly what you do with a 2.2 percent annualized incidence. And so for me, and I suspect for some of you, this is more valuable, which is a cumulative incidence curve.

And you can see that in the area where we can still be reasonably confident as you get farther to the right, of course, with smaller numbers of subjects, you can be less confident about it. But in the area where you can still be pretty confident of the result, we have about a 6.5 percent cumulative incidence of this condition.

Well, how do we put it in perspective? We know that that's less than what's been described for the occurrence of this condition subsequent to autotransplantation using total body containing therapy regimens. I'm one of the authors on a manuscript that will soon be published in JCO where we actually reviewed the occurrence of myelodysplasia and acute leukemia in patients treated for non-Hodgkin's

lymphomas and in patients with low-grade B cell lymphoma in various series, the incidence has been on the order of somewhere between three or four percent to about ten percent. So this number seems to fall within that range.

Perhaps the most comforting thing to make you believe that Bexxar is not unusually likely to cause acute myeloid leukemia is what you heard a minute ago, the zero percent incidence in patients who had this as their initial therapy and a group of patients who have been not, for the most part, repetitively treated with agents that we know are potentially leukemogenic.

Now, currently, the two big questions in somebody with relapse or refractory lymphoma, other than transplant, is should they receive another cytotoxic regimen or should they be treated with an antibody? So, first, let's consider what evidence there is that Bexxar might be particularly beneficial to patients who now with multiply relapsed disease would be a candidate for another cytotoxic regimen. The pivotal trial addressed this issue where patients

with disease refractory to their last chemotherapy regimen they had received somewhere between two and 13 with a median of four and then received Bexxar, addresses this issue. This uses a patient-as-their-own-control analysis, which isn't that unusual in this sort of a setting. I'm actually not aware of any randomized trials comparing new agents in patients with multiply relapsed or refractory low-grade B cell lymphomas.

Now, one thing we have to worry about is that these patients might still have been selected in some way to make them particularly good patients where you expect a higher response rate might have been seen. And I'll look at this in a few ways for you. One is this data. Now, this is a complicated slide, and what this is is the response rate in those patients that participated in the pivotal trial to their first or second treatment, this is the average response, third or fourth treatment, fifth or sixth or more than sixth. Remember, some patients had only had two, a minority, some patients had as many as 13, but this looks at what their response rate was when they

were treated the first and second time, the third and fourth time and so forth.

So this is the first data which I'm aware that tries to reproduce the Gallagher data that you heard from Dr. Fisher, the study from St. Bartholomew's Hospital that was published sometime ago in JCO. And you can see, as expected, these people became less and less likely to respond to sequential chemotherapy regimens what you would have expected to see.

And this shows, similar to the curve that he showed you earlier comparing to the old St. Bart's data, the fact that the responses became increasingly brief as the patients were repetitively treated. These responses actually are a little bit shorter than the St. Bart's data, but that's not surprising, I think, in that those patients had almost all received only chlorambucil where these patients had almost all received multiple agent chemotherapy. It's interesting that in none of these groups did the remissions last as long as a year.

Well, another trap might be that the

people had as their last qualifying chemotherapy some really simple, not very aggressive regimen, but in fact the last qualifying chemotherapy in about a quarter of patients each was an alkylator-based regimen, an anthracycline or anthracenedione-based regime, a fludarabine-based regimen or a platinum-based regimen, the typical sort of salvage chemotherapy that those of us who treat these patients have been used to utilizing.

Now, the response rate in this refractory group of patients is high. Just slightly less than half of them had an objective response which to me is an encouraging number, and don't forget this means the patients might have benefitted, their symptoms might have gone away. Fourteen patients had at least a year free of progression of their lymphoma, and seven patients, or about one in eight, remained continuously well all beyond three years.

Now, you might say -- again be concerned with those patients that remained well for a long period of time were just the ones who got the least therapy, and what this slide illustrates is that

chemotherapy history for those 14 patients who remained free of progression for a year following the Bexxar in the pivotal trial, and you can see that these are not undertreated patients at all, and most are fairly heavily treated. Interestingly, the highlighted patients are those patients that currently -- that remained well longer than three years, in complete remission, well, for at least three years.

The alternative approach other using another cytotoxic regimen in these patients with multiply relapsed low-grade B cell lymphoma is today Rituximab, the unlabeled antibody that's an extremely popular therapy. A study was done on 40 patients who had progressed after Rituximab, but 35 of those patients met the definition of refractory, that is no response or response within six months. That has been used in previous similar studies. Of those patients, 63 percent then, after failing Rituximab, responded to Bexxar, and 23 percent of those patients, or eight of the 35, remained well for at least two years. This is that same data in tabular form showing the high response rate and then the median duration, the

proportion of patients achieving a complete remission and the time to progression for all the patients.

Now, again, how do we put that in perspective, and there we have a study that's been previously reported using the yttrium labeled Zevalin. And once again, I would caution you, this is not a way to decide one or the other drug is better; it's a way, for our purposes today, to be sure there's not a red flag raised that the drug that's being considered today is shockingly worse, that it has some problem we should consider. And I would again argue that one wouldn't likely to conclude that there's an obvious problem.

All right. So how do we then conclude, put this all in perspective? Well, this is certainly an active drug in refractory low-grade B cell lymphoma. Both patients who are refractory to chemotherapy and refractory to Rituximab benefit. The most important observation is that a significant proportion of patients, many more than you would have expected in this group of advanced refractory disease, have durable remissions. The treatment has been

generally safe and well-tolerated and does in fact provide an important option for some of these patients, particularly ones who would not be a good candidate for bone marrow transplantation.

The durable remissions are the most striking feature of this data. As I said, certainly, I think, unexpected for, one, short therapy in a group of patients with this chemotherapy history. These really were people where the durable responders had a median of three prior therapies. The majority were refractory to their previous treatment. Patients in all risk groups had responses, and really it's quite unusual to see this, and the only other condition where you see this sort of durable responses in these patients is an allogenic bone marrow transplantation, but that's treatment that would not have been available to most of these patients based on age or availability of a donor. And it's a treatment that's considerably more toxic; it has a whole different order of toxicity.

So, finally, this is, to a great degree, the bottom line. This is the integrated efficacy data

curve showing the number of people here who are alive, free of documented progression and free of another therapy, showing that at five years somewhere between 15 and 20 percent of these patients remain well. And this is an important outcome. As you heard earlier, there are patients on this curve represented by those tick marks who achieved life goals they would not have been able to do and thought they weren't going to when they had multiply relapsed lymphoma. They're someone who got married, they're somebody who had children. The ability to take these advanced refractory patients and induce a complete remission is important, and I believe it would be important that this new drug be available for me and other clinicians to be able to use to try to benefit such patients. Thank you.

CHAIRPERSON PRZEPIORKA: Thank you very much, Dr. Jacobs and colleagues for their presentation. Before we take questions from the Committee for Sponsor, I think we're due for a break. If we can be back here at about 3:20, we will convene and have questions for the Sponsor at that time. Thank you.

(Whereupon, the foregoing matter went off the record at 3:03 p.m. and went back on the record at 3:22 p.m.)

CHAIRPERSON PRZEPIORKA: A number of members of the Committee have come to me indicating that they have burning questions for the Sponsor, so I wanted to actually take questions from the Committee to the Sponsor at this point before going on to the FDA presentation. And I will -- while we are getting a show of hands for who has questions, I'll take the Chair's prerogative and start with the first question to Dr. Jacobs. Do you have any information regarding safety of retreatment with Bexxar as well as information on the delay of salvage therapy after treatment of Bexxar in patients who have not gotten a response?

DR. JACOBS: Okay. The first question if we have data as far as patients who have been retreated, safety. Could I have the slide as far as the 001 patients that were retreated? Do we have any safety data on that? There were 14 patients in the 000 trial that were retreated with Bexxar, and of

those 14, seven did have responses, as you saw; five complete responses. As far as the hematologic, the number of patients again, 14; ANC less than 1,000 was 43 percent compared to our patient population was similar. Platelets Grade III or IV was 21 percent; Grade III/IV anemia, 14 percent. So it was comparable to the 620 patient population. We did have a retreatment protocol that just completed 32 patients, but that data is still being looked at. We just recently completed it, we don't have that.

In regards to patients having additional therapy after Bexxar, we have Dr. Leonard who has the most experience with his patients after receiving Bexxar that have follow-up treatment.

DR. LEONARD: Good afternoon. I'm John Leonard from Cornell. If you could pull up B-111. Great. We looked and presented at ASCO a group of our patients at Cornell who progressed after Bexxar, looking at the issue of what their blood counts were at the time of progression. And of 155 patients, we had 68 patients who progressed. What you see here on this slide is their blood counts at the time of

progression. So on the first row, you see the white count, ANC and platelets. This is pre-radioimmunotherapy and then at the time of progression. And as you can see, the counts were quite similar, both before radioimmunotherapy and after.

Looking at the question of early progressors, the median time from radioimmunotherapy to progression was 180 days, range was 42 to 839. So, yes, there were a few patients that did have early progression, which may have impacted their therapy. But the vast majority of patients, the median again being 180, had their progression significantly later, after the nadir period.

CHAIRPERSON PRZEPIORKA: Dr. Carpenter?

DR. CARPENTER: Do you or do others have open or planned studies comparing Bexxar to Zevalin?

DR. JACOBS: We have actually a protocol that we will be submitting to FDA comparing Zevalin and Bexxar in a patient population that is Rituxan-refractory. The safety end points are the primary end point of that study. That study will be submitted

within the next month. We've had discussions with the FDA for including some additional information and changes to that study.

CHAIRPERSON PRZEPIORKA: Dr. Martino?

DR. MARTINO: I have two questions, the first for Dr. Jacobs and then the second for Dr. Armitage. The first question: I need some clarification as to in 04 what data was available to allow the group to decide what response and what length of response had occurred to the previous standard therapy? In other words, what medical records, what x-rays were available to make that decision, because, in essence, that is the basis for then the comparison.

And the second question is to Dr. Armitage. I want an understanding of the leukemias that occurred. Is there any pattern in the sense of as more time passes are we seeing more leukemias or is there simply a basic underlying rate of so many per year, is there a curve that can be described?

DR. JACOBS: The documentation had to be thorough enough as far as all CT scans evaluating the

last qualifying chemotherapy and all accompanying medical notes. Just for your information, as far as what happened then with the MIRROR Panel review, the radiographs were all masked so there were no dates. All materials from the physician notes were basically put onto standardized case report forms so that the MIRROR Panel, the data that they looked at from the physician, the oncologist, was the same for that following Bexxar as it was for the last qualifying chemotherapy. This was a difficult study to enroll because of the completeness of that data for the last qualifying chemotherapy.

DR. FISHER: And so the question was acute leukemia that occurs after cytotoxic therapy. We know from both the atomic bomb experience and some subsequent data that acute leukemia after a potentially leukemogenic marrow injury has about a ten-year window. It peaks about five years, so the incidence rises for about five years and then tails off and after ten years, is largely gone. Now, some of these patients had subsequent therapies after the radioantibody and so will have further hits, if you'd

like, that would make them at risk. But if this data follows what has been previously described, the fifth year is about the peak of incidence and it should -- incidence, the rate at which it happens, should begin to tail off and patients more than ten years are pretty much past the risk period.

DR. MARTINO: My question actually relates to the existing data related to this drug. Is there a pattern that you can distinguish really is my question?

DR. FISHER: The cumulative incidence curve I showed you and had reached six and a half percent by five years. There are a few patients at risk longer, but I think we can't be as -- you'd be guessing if you tried to be real confident about what's happening to the annual incidence when you get very much past that time period, because there's so few people at risk.

CHAIRPERSON PRZEPIORKA: Dr. Blayney.

DR. BLAYNEY: Thank you. I have two questions. One, do you have any reason to suspect that sequelae of immunosuppression, long-term

immunosuppression might be a problem after this, particularly opportunistic infections that practitioners might get sandbagged for, longer than the six months which you followed patients for infection.

DR. JACOBS: Could I have the B cell recovery? In two studies, the earlier studies we looked at, B cell recovery after Bexxar therapy, this was in the first study 000, and the 003 study. As you can see, the B cells do drop down approximately two months, three months, and most recover by six months, and some patients took 12 months to 13 or 14 months.

The next slide is as far as hypogamma globulinemia, we looked at serum IGG levels, and there really was no hypogamma globulinemia, most likely due to the CD20 expression not being on plasma cells. As far as infections, there were six percent serious infections. There was only one pneumocystic infection and one other shingles that really was probably commonly seen, but no increase as far as encapsulated infections or those types of infections later on.

DR. BLAYNEY: Thank you. In your briefing

document, you talked about dosimetry of the isotope and how you modified that based on body fat distribution. I wonder if you could expand a little bit on -- I didn't hear much about dosimetry in your presentation. I wonder if you could --

DR. JACOBS: Actually, maybe I'd like to have Dr. Wahl come up and go into that, as he was part of those earlier studies.

DR. WAHL: I'm Richard Wahl. I'm Professor and Director of Nuclear Medicine at John's Hopkins but I was at University of Michigan prior to joining the Hopkins faculty and involved in the studies since 1990.

The adjustment for body fat is detailed in the briefing document, but in brief at some time into the study it became clear when we were doing in some patients specked three-dimensional imaging of the patients that there was very little uptake of the antibody in adipose tissue. So the assumption of uniform radioantibody distribution throughout the entire patient which we had made initially under dosimetry was not quite correct.

So in obese patients, we modified it so that if they were markedly obese, we would not assume all of the antibody was uniformly distributed. So there was a reduction or an attenuation in dose in the obese patients, which was basically an adjustment at 37 percent above the predicted lean body mass. We would not give a higher dose than that. We would assume their body mass was not in excess of 1.37 times their predicted lean body mass. And this simply again relates to the biodistribution of the radiolabeled compound in vivo.

DR. BLAYNEY: Thank you.

CHAIRPERSON PRZEPIORKA: Dr. Brawley.

DR. BRAWLEY: Yes. Just a couple quick questions. Can you put up your Slide Number 9 and Slide Number 48 from our packet and explain exactly what the differences are? And then I have a follow-up to that.

DR. JACOBS: Slide Number 9?

DR. BRAWLEY: Yes.

DR. FISHER: I'll take you through this again, Otis, unless you want to be more specific.

This is data from St. Bartholomew's Hospital published in the JCO, and what it shows is a group of patients followed in that large single set of referral base that has basically a significant part of Central London, so it's not quite population-based but it's the same patients repeatedly and it shows what their response duration is the first time they were treated, then they have a relapse, another relapse, et cetera. So this is the median duration of response with sequential treatment.

DR. BRAWLEY: Okay. Now let's compare that to Slide Number 48. That's the same thing but that's for the treatment with Bexxar; is that correct?

DR. FISHER: Well, that's not the same thing --

DR. BRAWLEY: Okay.

DR. FISHER: -- because the prior slide, the zero point starts every time they get a new treatment. So what you could say was that you could compare -- this starts at the Bexxar treatment. This does not take into account their prior remissions or relapses. So if you wanted to see how Bexxar did

compared to a third or a fourth or a second, you could make the comparison, but I'm not sure that's a comparison you'd want to make. This is the result starting on the day you get Bexxar as to what happens to the entire patient population. And remember that behind this curve, before the zero time point, are a median of four treatments for each of these patients, the results of which would have been reflected on the prior St. Bart's curve.

DR. BRAWLEY: Okay. So the Bexxar curve there -- I'm going to make the comparison.

DR. FISHER: Could you speak up just a little, I'm having trouble hearing you.

DR. BRAWLEY: I'm sorry. That's the first time anybody's ever had trouble hearing me.

(Laughter.)

DR. FISHER: I'm getting older, Otis.

DR. BRAWLEY: The people who are on their third treatment on the first slide their curve looks a lot like the curve in this slide. Is that a reasonable statement?

DR. FISHER: Let's look at this slide.

This slide is in years, okay? And so you're saying here that this curve, which is response duration and out at three years, the data only goes out to about three years, if we go back again to the next slide, that's about here on that curve. We have follow-up six or seven years, and this is the number which on this case, I'm sorry, the statisticians will go nuts but I don't know, at five years 25 percent, something like that.

DR. BRAWLEY: Okay.

DR. JACOBS: The other point on the Gallagher slide is that is the duration of response for all responders. So it's not looking at all the patients who responded that received that treatment, so--

DR. FISHER: Duration of response curve, by definition, starts when you are a responder. Time to progression, the zero -- the 100 percent here includes all patients. So non-responders would sink that other curve. If we gave you a time to progression on that other one, it would come down significantly. That's the point you wanted to hear.

CHAIRPERSON PRZEPIORKA: Dr. Bridges.

DR. BRIDGES: First question is another dosimetry question. Was there any specific dosimetry done to look at the dose and sites of bulk disease, for example, if you had an epidural lesion, even though the whole body dose is 75 centigrade, what the maximum might be to spinal cord in an epidural lesion?

DR. JACOBS: We'll get Dr. Wahl back up here.

DR. WAHL: The briefing document gave a range of tumor doses, and probably the highest tumor dose was in the range of just over 3,000 rads. The follow-up in dose with the relatively low energy beta of I-131 is substantially more rapid than with the more energetic beta, so that at about one millimeter, only the dose falls off to five percent of the tumor dose. So at a distance of one millimeter from it, at 0.1 millimeter it's about 33 percent. So those estimates were provided to the Agency. It's a relatively rapid drop-off.

CHAIRPERSON PRZEPIORKA: Dr. Krook?

DR. KROOK: I'd like to go back to this

question that my colleague asked over there about last qualifying chemotherapy. I've generally been involved in randomization studies, and one of the things, as I look at the pivotal trial, we're comparing this, and I had to deal with this as I looked at the data, it's a bit of historical trial although we're using the patient as their own historical control. But one of the things as I look at this is how good are the records, and I realize some of the investigators are in the room. And I'll speak for myself again that commonly when a patient's on study I'm much more diligent at doing things than I am when they're not. So if somebody's from the MIRROR group, I don't know whether somebody's here that looked at this, what were the records like that we're using as the last qualifying -- were they reasonable to look at or was it a difficult task?

DR. JACOBS: We don't have anyone from the MIRROR Panel, but we do have investigators that were on the 004 study. Maybe one or more of them would like to come up and comment. Dr. Press, Dr. Zelenetz, Julie?

DR. VOSE: I'm Julie Vose from University of Nebraska, and I was one of the investigators on many of these studies that you heard presented today. And I can tell you from what they expected us to show from the last qualifying chemotherapy they were very diligent about getting excellent medical records, about getting CT scans that were excellent in quality, and there were many patients that unfortunately we did not have that on and could not go into the study. So for those patients who actually did go on the study, I can you, I personally documented or looked through all the medical records very diligently and also the CT scans.

DR. KROOK: The second part, and perhaps, Julie, you can comment on this also, is that as I look at some of the discussion, and this may come in later, with the FDA and the records there was quite a bit of discussion as when to call a response a response and there were some that at least as I looked at it that were progressions. And then they became a PR. I don't know if you were involved in that or not, but there's a whole discussion that was in there about

that of how you define -- it appears there was a moving target with defining what a response is in the data that I looked at from the Company.

DR. PRESS: Well, I guess I'll begin just by mirroring what Julie said. I'm Oliver Press, I'm a professor of Medicine at the University of Washington and a member of the Fred Hutchinson Cancer Research Center. I've been entering patients on these trials since 1990. And I also contributed patients to the pivotal trial and agree with Julie that this was a difficult trial to accrue patients to because of the strict requirements for detailed records and CT scans. The responses, as has also been mentioned by Cindy Jacobs, were assessed by an independent panel in a blinded fashion, and so if there were difficulties assessing response, that would have come out in the panel. And, actually, the concordance between the MIRROR-assessed responses and the investigator-assessed responses was very good.

DR. JACOBS: I think I know what -- we had -- the Agency, when we had the long durable responses last year, asked that we have ongoing MIRROR Panel

assessment of all the patients that were long-term durable response. So we had another charter to deal with that and reconvened the MIRROR Panel. I believe there was one or two patients that had at the last MIRROR Panel had been thought to have progressive disease but in review of them the follow-up evaluation had no treatment and was assessed as in complete response. So there were a couple of patients with ongoing MIRROR Panel reviews that that happened. We also had then, yet again, a second MIRROR Panel review for those cases more in the earlier trials that had happened or other questions that the FDA had. We re-MIRROR'd the 37 patients, and of those 36 were still as per the original MIRROR Panel.

DR. VOSE: I just wanted to say one other thing too. As you heard from some of the patients earlier, this is a very unusual treatment in that the patients continue to have response over a period of time and in some cases up to nine to 12 months do they continue to respond. So it's a little bit of a moving target, as you mentioned.

CHAIRPERSON PRZEPIORKA: Before you sit

down, Dr. Vose, a question please. Can you give us -- we want to know a little bit about clinical benefit, which sometimes is objective and sometimes is not. Can you let us know a little bit about how difficult it is for patients to receive this therapy and what specifics you have to educate them on in comparison to other radiolabeled antibodies that you have used?

DR. VOSE: Sure. This is a therapy that is very easy to administer, both from the standpoint of the physician, the nuclear medicine technologist, the nuclear medicine physician, radiation oncologist, the nursing staff. We have a very specific team that educates the patient and performs the radioimmunotherapy, both for this agent and for other agents, and it's very easy to administer from that standpoint as well as from the patient's standpoint. They get, as you heard, two therapies a week apart, outpatient, very minimal side effects, and compared to many other therapies they received, chemotherapy agents, or radiation therapy for that matter, it's very non-toxic. The education for the patients is very easy as far as the restrictions that they have,

very minimal restrictions, as you heard earlier from some of the patients. And compared to other radiomenaconjugates, it's very similarly administered as an outpatient, so very easy to administer.

CHAIRPERSON PRZEPIORKA: Dr. Reaman?

DR. REAMAN: In those patients who are assessed to have durable responses, do you have information on the percentage that had documented complete remissions?

DR. JACOBS: Well, in the presentation, it was 76 percent of the patients had CRs that were in the Durable Responder Population.

DR. REAMAN: Okay, 76 of the Durable --

DR. JACOBS: Seventy-six percent of the 76 patients. It is a little confusing, yes.

DR. REAMAN: And in the secondary leukemias, any specific molecular or cytogenetic patterns have been identified?

DR. JACOBS: Actually, we have Dr. Bennett here who reviewed those cases. I'd like to have him comment on that.

DR. BENNETT: Yes. John Bennett,

University of Rochester. We have a lot of information on the cytogenetics, both prior to Bexxar and following, and they all show the typical alkylating agent deletions, minus five, minus seven, plus eight. And of the ones that I picked up that were prior to Bexxar, three that have cytogenetics had chromosomal abnormalities. We have not seen any of the topo-2 type specific translocations.

CHAIRPERSON PRZEPIORKA: Dr. George?

DR. GEORGE: A question I think probably best addressed for Dr. Fisher. Could you describe the SWOG studies that are either ongoing or planned with the randomized studies and how it relates to this discussion?

DR. FISHER: Excuse me. Give me just a minute. We can treat lymphoma, but we can't treat the common cold, I apologize.

It isn't that difficult a question for me to answer either. The SWOG studies are two studies we have done in Bexxar that are of interest. One is completed. It is a Phase 2 study looking at CHOP induction chemotherapy and then at minimal residual

disease, the administration of Bexxar sequentially. That study is still undergoing follow-up, but we can tell you that Bexxar was administered with essentially no major toxicity, no life-threatening toxicity and very good clinical and molecular responses continuing with over about an 85 percent failure-free survival at three and four years now, as we look at that. So that's one study that was completed.

The other study that's ongoing is a randomized Phase 3 study, which was originally going to compare CHOP -- this is in untreated follicular lymphoma, as was the last one I described for you, so this was going to be CHOP versus CHOPO Rituxan versus CHOP Bexxar, with CHOP Rituxan given in the interdigitating way that Chuchman did and CHOP Bexxar given in the way I just described at our prior pilot study.

Unfortunately, unfortunately I say with deep regret, in this country, we cannot randomize patients upfront now to chemotherapy alone without chemotherapy plus an antibody, and this study has accrued very badly. So we have just amended that

study to look at CHOP. We'll be chemo immunotherapy versus chemo radioimmunotherapy, i.e. the CHOP versus the CHOP Bexxar, and that is a Phase 3 study that's ongoing.

CHAIRPERSON PRZEPIORKA: Dr. Blayney.

DR. BLAYNEY: A question again I think for Dr. Wahl perhaps. On Page 86 of your briefing document, you make some dosimetry comparisons, normal tissue tolerance, et cetera. One of the -- two of the tissues that seem to be at risk are the testes in the male and the bone marrow dose. The bone marrow, the red bone marrow doses with your compound looks to be 105 centigrade. How does that compare with total body irradiation that one gets for the immunosuppression in the stem cell transplant setting, first of all. And, second, do you have concern that this might lead to infertility in the male because of the testes dose?

DR. WAHL: Well, the total dose of the marrow -- maybe I can address that first -- is largely delivered by the blood to the marrow and the readout of the toxicity to the marrow is probably best reflected by the peripheral blood counts which were

monitored in the Phase 1 dose escalation. So the patient individualized dosing for Bexxar is designed to give a dose which in the individual patient will be sufficient to cause typically mild, relatively modest bone marrow reversible depression end counts but not long duration toxicity. So I think that this is in the range of other radiopharmaceutical therapies which are designed to be non-myelo ablative.

The dose to the testes of about 100 rads is slightly -- I'm referring to the dose shown on Page 86 -- is slightly greater than the total body dose. I think that it's more than most diagnostic procedures. Certainly, it's less than the doses that Dr. Press would be giving for total body radiation, I believe, potentially, but it would be a consideration and I think issues regarding reproduction would have to be carefully discussed with each individual patient. I doubt if it would lead to infertility, certainly.

DR. BLAYNEY: You say you doubt?

DR. WAHL: I doubt, yes.

DR. BLAYNEY: Okay. The total body dose, I think it -- I'm sorry, the marrow dose has

implications in patients who may have received alkylating agents before, and I point out that the peak incidence of therapy-related myelodysplastic alkylator agent is about six years, and you haven't -- most of these patients have not been followed for that length of time. So I think it is an issue, a safety issue going down the road.

DR. PRESS: Dr. Press again from the University of Washington. I would just supplement those comments by our studies with high dose Iodine 131 labeled tositumomab. We've done a series of studies at the University of Washington which haven't been presented today in which we treated 116 patients with doses of this radiolabeled antibody, which are on the average five times higher than those which have been administered in these studies that you've heard about. Those doses do tend to be permanently myelo ablative and so we give stem cell rescue with them.

Most of the patients on our transplant studies do maintain fertility if no additional chemotherapy is given. We've treated 40 patients with the radiolabeled antibody at myelo ablative doses as a

single agent and another 74 in which they also get cytoxanity topiside. If they get chemotherapy along with it, they're generally sterile, but the majority of patients who get it as a single agent have remained fertile.

In terms of bone marrow dosimetry, we estimate we give about five times the dose to the marrow, and that in our setting is myelo ablative permanently in response to your first question.

DR. KAMINSKI: Good afternoon. My name is Mark Kaminski, and I've been involved in -- from the University of Michigan, Professor of Medicine there. I've been involved with Bexxar studies since 1990. In answer to your question, Dr. Blayney, from the front-line study where previous chemotherapy is not a confounding factor, there are two males who have fathered normal children without bank sperm.

CHAIRPERSON PRZEPIORKA: Dr. Pelusi?

DR. PELUSI: If I can switch gears here for just a minute and ask you were there any quality of life studies that were done on our patients?

DR. JACOBS: Yes. There was one quality

of life study done, and Dr. Mike Hamilton has some of that data to summarize that.

DR. HAMILTON: May I have B-73, 76 and 77. I'm Michael Hamilton from GlaxoSmithKline. I'm in clinical development. So there was a secondary end point of quality of life in the 004 study. Please keep in mind that these are limited data, though. It's very hard to take these too far, because only two-thirds of the 60 patients were able to fill out baseline questionnaires and at least one follow-up questionnaire. You can see that at baseline and at week 13, the patients had scores on the EORTC, quality of life of questionnaire, that were below the normalized general population score. But at week 38, they had recovered to levels that were thought to be statistically improved. So if we can just run through the next two slides.

This is a functional scale where 100 percent would be a normal population, and you can see a general upward trend from the baseline to week 38. And the next slide. A symptomology scale where zero would be no symptoms and a general improvement in

symptomology over that time. But, again, you can see that with very small numbers, the 38 weeks is only 15 cases.

DR. PELUSI: If I can make a comment. You know, we seem to go round and round a lot about quality of life on numerous occasions, and I'm always concerned that many times we miss the true experience of the family and of the patient. And I know that quality of life studies are very difficult to do, but they're not impossible to do. And that's a piece of information I think that becomes very valuable to us in terms of informed consent. If we go forward and we have something to offer to patients, I think it's important to see really what are other people's experiences, not only for us as clinicians to be able to plan for the potential of different issues, but also for patients to make wise informed decisions. And I really wish that we could really start to incorporate whether it's quality of life or even phenomenology studies in addition to this, because you don't need a lot of patients for that.

And the second just comment very quickly

is we always lose the voices of those patients who either don't do well with the treatment or are off treatment. And that is another valuable piece of information for patients, families and clinicians that we really can't lose. And as we heard today, very compelling testimony by many people who are here, and I just always wonder why do we have such a low accrual rate in terms of the quality of life, so it's just a comment. But I think it's something we truly have to look for in the future, because that is the everyday living with or without this drug, and that's important to all of us. Thank you.

DR. HAMILTON: Well, I just want to add that we do fully agree with the importance of the quality of life end points, and in our committed studies quality of life is built into those so that this is not just 40 patients and that's all we look at.

CHAIRPERSON PRZEPIORKA: Thank you, Dr. Pelusi. Dr. Kelsen.

DR. KELSEN: You plan to compare Bexxar to Zevalin, and I wonder if you could tell me a little

bit about the hypothesis that you'll be testing? Will you be looking for superiority and if so in which way, or will you be looking for non-inferiority?

DR. JACOBS: For the study that we have yet to submit to FDA but we have discussed with FDA as of April of this year, the primary end point was really safety Grade III/IV toxicities. The study was powered to look at the possible difference between the safety, but as far as efficacy, it would be a non-inferiority.

CHAIRPERSON PRZEPIORKA: Ms. Krivacic.

MS. KRIVACIC: Do you have any data regarding the use of your hematological supportive care?

DR. JACOBS: I'm sorry, I can't hear.

MS. KRIVACIC: Do you have any data regarding the use of the hematological supportive care products, such as your G-CSFs and how that interacted with the use of the Murine antibody, if at all?

DR. JACOBS: No. I don't believe we have any information regarding the 11 percent of patients who got G-CSF and their inaction; no, we don't.

CHAIRPERSON PRZEPIORKA: Thank you very much. I think that's all the questions that we have from the Committee, and we will now move on to the FDA presentation. Dr. Litwin, the Medical Reviewer. Dr. Siegel.

DR. SIEGEL: Yes. I'd like to interject a quick comment here to clarify some issues. We read -- I read in the Journal of National Cancer Institute, I guess last week, the FDA's interactions with Bexxar have become one of oncology's great political mysteries and one that has no obvious explanation. And we've heard a lot of people here talking about the fact that this drug has been studied for some 13 years and the article actually included an analyst who speculated that, "My personal feeling," at least he indicates it's a personal feeling, "is that it was not a safety dosing or efficacy issue, it was a bureaucracy issue or a process issue." I hope that those here who know the FDA, know my group and other groups in the FDA, know that we don't spend years of time reviewing applications for cancer, important cancer indications for bureaucracy purposes. You may

or may not always agree with us on how we interpret the issues, but I can assure you that we -- and I'd like to assure the patients who spoke, I think, very eloquently of their experience, that we can't always come to the public and tell you why we're -- what's taking so much time, but it's not because of bureaucracy issues.

We can on occasion like this come to the public and tell you a little bit, and I just want to give just a little bit of some of the issues here and not at all in any way to -- I'm going to mention some issues that are resolved and not at all in any way to prejudice against or bias against Corixa who has worked extremely diligently with our reviewers over the last few years to resolve all these issues. And so they are not issues that are important issues in the review, but I think they're important just in terms of the public having an understanding of some of the complexities of a product like this. And it just so happened that a few minutes ago I looked through my files -- not a few minutes ago, an hour or two ago, but during this meeting -- and have seven pages of

handwritten notes from a meeting we had almost two years ago today, December 22. And reading through that was quite interesting.

It's important to note, for example, without going too much into a territory to the extent that it might be getting into commercial trade secrets, that this product over that period of time was manufactured in three different facilities, and there were substantial differences in the product to the extent even in the primary amino acid sequence, so you're seeing data from products with different primary amino acid sequence and with heterogeneity and variability and the amount of glycosylation and with variability in de-amidization and isomerization and other issues.

These are issues that in order to understand whether these data, these data that have been generated over 12 or 13 years are relative to the material that was proposed for commercialization two or three years ago that had had very limited clinical experience but had some -- required some substantial evidence, not necessarily clinical but some

substantial data and was a significant issue for review and concern. And I'm pleased to say, and this isn't true with some of the products that we review, I'm pleased to say that we did get excellent data and we are quite comfortable with that issue, and it's not an issue for discussion before this Committee, but it is a critical issue because it could have turned out differently.

There were important issues at that time in long-term toxicity data, and they simply were not there in the original application. We saw the thyroid imaging in a substantial number of patients. We knew there was a radiation to the thyroid. The TSH was to be measured in the protocol, but about half of the patients had their six-month TSH, and if you went past that, you got the time points where I think it was like 95 or 98 percent of the patients the data were missing. There was no way to know.

If we were here, similar but not as severe issues were occurring with the HAMA data and the HING data. So if we were here two years ago and putting worst-case scenarios up, you would be looking at 99

percent of the patients or 90 percent of the patients with serious hematologic as the worst-case scenario because there were that many where we just didn't have long-term data. Long-term data in antibody responses can be very important with a product such as this because in fact it suppresses the B cells and it suppresses the ability to make antibodies. And sometimes you see the antibodies arising relatively late, and the data simply were not there at the time to address a lot of those concerns.

And so now when you see that the database went from 200 to 600 and you see there's maybe ten or 15 percent range of uncertainty in some of these toxicities, it's worth noting that that ten or 15 percent may have represented half of the patients in the original database in which we simply didn't have uncertainty or more. There were a lot of other issues, not all critical, you know, who had transformed disease and who didn't, who was refractory to the original therapy, who wasn't, and so forth. There were issues in March that we'll get into this year even in terms of regulatory policy related to the

approval of Zevalin.

But, again, my point is simply not to raise issues or concerns nor at all to be critical of the process over the last two or three years, which has I think been a very productive process in addressing some very important issues but simply to indicate that what we're looking at here and what we're discussing here is a culmination of a process of gathering data which allows us at this point in time to assess this product in a way that we felt could not adequately done prior to this point in time. Thank you.

CHAIRPERSON PRZEPIORKA: Mr. Ohye.

MR. OHYE: It seems to me you're saying, Dr. Siegel, that the, as they say in many proceedings, that the jury should not take under consideration the prior statements. Thank you.

CHAIRPERSON PRZEPIORKA: Thank you. I'll call the podium then. Dr. Litwin.

DR. LITWIN: Good afternoon. I'm Dr. Stephen Litwin, and I will present for the FDA the results of our review and analysis of Corixa's

tositumomab therapeutic regimen, and I will refer to it during my presentation by its initials, both for clarity and to save some time, as TTR.

I appreciate that we've had a long afternoon here, and I will try to go quickly over those areas which Cindy Jacobs has so well addressed and focus on those parts of the review which represent differences in terms of our approach or any differences in position.

You've seen the proposed indication. I'll give you a moment to take a look at it. There were two major studies that supported the efficacy claims. The first study was 004, and this was the primary efficacy trial that supported the request for accelerated approval for treatment of chemotherapy refractory patients with low-grade and follicular non-Hodgkin's lymphoma with or without transformation. And this is the same indication or a similar indication for which Zevalin received accelerated approval last fall.

The second major study was 012. This was the primary efficacy trial that supported standard

approval for the treatment of Rituximab-refractory patients with follicular non-Hodgkin's lymphoma, and let me just point out that much of the data on this was as late as July of this present year.

There are three other supportive studies which I will touch on in just a few minutes. Those additional studies were the 002 study, 000 and 001. I'll start with the 004 study. This was a multicenter single arm. It was historically controlled with essentially the patient serving as his own control with the present treatment, TTR, being compared to his last qualified chemotherapy. The primary efficacy end point was the proportion of patients who had a longer duration of response after the current therapy, TTR, as opposed to when compared to longer duration of response after their last qualifying chemotherapy regimen. And the responses were based on MIRROR Panel or a Central Panel assessment.

The secondary efficacy end points have been mentioned. The study population consisted of 61 patients who were enrolled at eight centers. We analyzed those 61 patients. They included one patient

who withdrew consent and did not receive either of the doses. The Sponsor analyzed 60 patients. The results did not significantly differ on that.

Now, among these 61 patients who were registered, there were seven who had responded to their last qualifying chemotherapy, the remainder had not, and the median duration of this response to their last qualifying chemotherapy was 4.1 months.

This is essentially a two-by-two contingency table with the four cells in the center and the totals on the outside. If we look -- not working very well -- if we look at the seven patients who had responded to their last qualifying chemotherapy, we can see that three of those patients had responses to the current regimen, TTR, and four did not. If we look at the 54 patients who had no response to their last qualifying chemotherapy, there were 25 who had a response to the TTR and 29 who did not.

If we break down the categories of these responses, they break down into three areas. Those patients who had -- well, let me point out that in

addition to judging the responses of the patient to his own last chemotherapy, we also took into consideration, the analysis took into consideration the duration of the response. This broke down into three then patient categories: Those patients who had an equivalent duration of response to both their last and the current therapy; those patients who had a longer duration of response to TTR, longer is defined here as at least 30 days or the third category, having a longer duration of response after the last qualifying chemotherapy.

This is the same table taking into consideration a partition for the duration of the response. If we look at the same seven patients who had a response to their last qualifying chemotherapy, we can see that two of them had a longer response to TTR and one had a long response to the last qualifying chemotherapy. There were 29 patients who would be judged as equivalent duration, because they had no response to either the current regimen or to their last qualifying chemotherapy, and I think the other two cells are self-explanatory. Those who responded

to TTR but no response to the last qualifying chemotherapy and more or less the reverse.

Looking at these frequencies then of these categories, there are 29 patients, or 48 percent of patients, who had an equivalent duration of response. Twenty-seven, or 44 percent, of patients had a longer response with TTR, and five, or eight percent, had a long response with the last qualifying chemotherapy. This was statistically analyzed by McNemar's method and by the Sponsor and by the sign-rank test by our own statistical staff. And although the methodologies were different, the results were similar. They indicated a strong favorable outcome for the TTR, which met the primary end point. Secondary end points we've seen. They include the overall response rate of 46 percent.

I'll turn now to the second major study supporting efficacy and that is the 012 study. This was a single arm multi-center study. It was conducted in patients who had relapsed after one or more courses of Rituximab. The end points were overall response rate, complete response, time to progression, time to

treatment, failure and survival.

Because this study did not prospectively have designated powered primary end point and because there were questions about the definition of the timing of a refractory, that is refractory to Rituximab state, we elected to analyze three different populations, both to compare them and to gain some perspective as to the vigor of the results.

The three populations are shown here. The first, or the registered population, is an intent-to-treat population. It's the 43 patients who were enrolled. There were three patients who failed to receive any of the study agent because of progressive disease. This is the treated patient population. It was mainly analyzed for safety. And the last is the indicated patient population of 30 patients which was restricted to those patients who had follicular non-Hodgkin's lymphoma, had a response duration to Rituximab of no more than six months, and it excluded the three patients who had not received any study agent.

Looking at the outcomes of these, this is

the registered, the first population, the intent-to-treat population. We also elected to look at the outcomes by investigator on-site assessment and the outcomes of the Central MIRROR Panel since the investigator assessment was designated as the primary outcome in the original submission. For the overall response rates, the respective values are 60 percent and 63 percent. The median durations of response, 1.9 years and 1.3 years. The complete response is seen below.

I've not touched on the treated patient population but have skipped to the third population, that is the indicated patient subpopulation, which conforms most closely to that indication which is being requested. The overall response rate for the investigator assessment and the MIRROR assessment are essentially the same, although if you keep in mind that the numerator and the denominator were actually different for both of these, 60 percent and 63 percent, the median duration of response was not reached for the investigator assessment. It was 2.1 years for the Central Panel.

We also did an exploratory analysis once again in study 012 to see if patients who had responded earlier to Rituximab would have the same or a heightened or lesser ability to respond to the current TTR therapy. Among the 18 patients who had responded earlier to Rituximab, 11 of those 18 had an overall response rate of 61 percent and a median response duration of 2.1 years. In the 25 patients who had not responded to Rituximab, 16 of the 25, or 64 percent, had an overall response rate 1.3 years median duration. These numbers, these numbers comparing the two, are no different, and they indicate that there appears to be no particular tendency for Rituximab-responsive patients to do better or worse, at least within this unpowered assessment with the TTR therapy.

I'll turn now to the supportive studies, 002, 001 and 000. They'll be much more brief. The 002 study was a two-arm multi-center open label study. It was randomized between the arms, but the randomization was not stratified. Population was the chemotherapy-relapsed or refractory patient group.

The two treatment arms, arm A was the treatment arm, was the TTR therapy, which I'll call hot arm, and Arm B, which is the unlabeled anti-unlabeled tositumomab, referred to as the cold arm. The end point was complete response which differed from the others studies that I've been talking about thus far, with overall response rate being the secondary end point along with others.

There were 78 patients enrolled in this study 002. There were 42 in Arm A, the treatment or hot arm, 36 in Arm B. A series of prognostic variables and demographic variables were analyzed. For the most part, the majority of these were similar with just these three exceptions, which I'll show here but I won't read. I'll let you --

Outcomes, the complete response rate for Arm A was 33 percent versus eight percent in Arm B. I think you've already seen this data. I'll go through it quickly. The overall response rate in this controlled study was 55 percent in the Arm A, or the treatment arm, 19 percent in Arm B.

This is a time-to-event curve. The upper

data is the Arm A, the lower data Arm B for duration of response given in years. The percent responders on the Y axis, these curves do not differ significantly. This is the years to time to progression. Arm A is significantly better than Arm B. The years in time to progression are given in years on the x axis and the percentage not progressing, this is somewhat inverse as some people use, is given on the y. And it significantly different favoring Arm A.

And, finally, the survival in years is compared. There was no difference between Arm A and Arm B. On the other hand, between year one and two, the curves are not together. They come together somewhat later. Patients from Arm B, that is the cold arm, were permitted by protocol within three months to cross over and receive the TTR treatment, and this conceivably could have confounded the results and interpretation of a survival difference between the two arms.

Study 000 was a single-center dose-escalation study. Its purpose was to determine the optimal biologic dose of cold antibody and the maximal

tolerated dose for TTR. There were 59 patients enrolled. This was an earlier exploratory study, and some of these patients had received prior bone marrow transplants and had received different dose regimens. There were 22 without prior bone marrow transplant who were treated at the MTD.

The last study, 001, was a multi-center single-arm study. It assessed reproducibility of the dosimetry methods. There were 47 patients enrolled. The results for the dosimetry were satisfactory.

This is an overview of the study results of the five efficacy activity studies that I've just been describing. The first two were the major studies. I'll just remind you again the 004 being for the Rituximab-refractory group of patients, the 012, for those patients who were -- I'm sorry, I just turned that around -- the 004 for the chemotherapy-refractory patients, the 012 for those patients who had failed Rituximab therapy. The remainder of the three are supportive studies.

All of them have more or less similar median prior chemotherapies with the exception of the

002 study, which is less. The overall response rates are in a relatively constricted range., from 46 percent to 63 percent. The complete responses range from 20 to 30 percent. The median duration of responses from one to 1.3 years. The only data that we don't have that is not reached is the 002.

There were two subset analyses that were done, which have been spoken about but because of the importance of this, I will touch on them again. Those were a long-term responder analysis and a low-grade transformed analysis. The long-term responders were submitted by the Sponsor to show that the TTR, current regimen treatment, provides, and this is actually a quotation from regulations, a meaningful therapeutic benefit over existing treatments in support of accelerated approval.

The low-grade transformed group, or subset or patients, were analyses that we requested to assess the differences in activity in the transformed versus the non-transformed patients since all of the individual studies included both types of patients.

Long-term responders, they were defined as

responding patients who had a time to progression of over a year, a year or over, as per the MIRROR Panel review. We, I think, came up with the same number of 78, down to 76 of the 271 patients we have identified in this efficacy activity group. There are small differences in the numbers of patients that we were analyzing. That's 28 percent of the patient population that were identified by the MIRROR Panel as being long-term responders. And of these, we looked at 68. We removed the eight who had had multiple dosimetric doses, and I should emphasize that these patients were all retrospectively identified across the five-activity efficacy studies, the group starting with 271.

As you might expect, most of these patients were complete responders. There were 21 percent who were partial responders. The median duration of the response was 4.9 years with a range of 0.9 to 7.8 plus years. We did a logistic regression analyses on a number of factors, both predictive and demographic factors. These are the four that were positive. The comparison is between the long-term

responders, the group of 68, which I've just discussed, and the remainder of the population of the 271 patients, that remaining number of patients who did not qualify as long-term responders.

The four variables all deal with the state of entry at the time of entry of the patients. They were less qualified chemotherapy end day to study entry day, the response to the last qualifying chemotherapy in terms of a complete response versus partial response, the duration of the response to the last qualifying chemotherapy and the number of low versus intermediate versus high tumor grades. And I think you can see that all of the -- in all of these four parameters, it seems evident that the long-term responders represent a more favorable initial population. I think this is probably most marked in the first variable or the third.

The second subset were the patients with transformation. There were 71 of the 271, or 26 percent, from these five efficacy studies who were transformed histology. We reviewed and confirmed with sufficient information to document 40 of the 59 we

looked at, and there are a remaining 12 under review. Looking at those 40 patients, the overall response rate was 40 percent, the complete response rate, 26 percent, median duration of response, 1.6 years.

I'm going to turn now to the safety data. The most -- I'm sorry, safety was looked at in five areas. The most severe and serious safety problem was, as we've heard, hematologic, neutropenia, lymphopenia with resultant infections, thrombocytopenia with hemorrhagic events. We looked at infusional reactions. There was gastrointestinal toxicity. The tositumomab protein monoclonal antibody was a Murine protein and we looked at immune responses to the Murine protein. And, finally, delayed toxicity as a result of irradiation, particularly hypothyroidism and secondary leukemias of myelodysplastic disease.

The safety database that was provided included 620 patients. Of these 620 patients, 229 were enrolled in the five efficacy and activity studies, which I've listed here, which I've just described to you, and the remainder of 391 patients

were treated under the expanded access experience in CP98-020 or in some individual trials. I will refer to this at this point as ISS-A and ISS-B. And this shows where these patients came from. Once again, the ISS-A group is comprised of patients enrolled from the five efficacy activity studies that I've just described. The ISS-B is mainly from the expanded access trial plus four individual patients, and I'll call your attention here to RIT-II-003, which is a study I have not talked about thus far. These patients differed substantially from many of the others in that they were untreated but the Sponsor has provided information on them as additional and very useful information. There were 77 patients.

The safety profile in the ISS-A, the five efficacy activity studies, showed a higher incidence for overall adverse events, Grades I through IV. In the first 13 weeks, roughly 90 days, as compared to the expanded access group, of 391 ISS-B, there was a less comprehensive collection of data in the expanded access trial and no monitoring. It was under reporting of the adverse events in the expanded access

trial which was recently confirmed during an inspection. These are the incidence of AEs as Cindy described. These are regardless of relationship to the study agent.

In the first two columns, I compare ISS-A to ISS-B. These are Grades I through IV for various of the adverse events. The adverse events are listed from the top down in order of incidence. And you can see there's a two or three-fold difference, much higher in the ISS-A group for virtually all of these adverse events. I'll show you more in the next slide. This tendency is not as marked for the Grade III to IV comparison between ISS-A and ISS-B.

This is a continuation once again in order of frequency. One can see up to twofold or more differences between the incidence of these adverse events between these two subsets of populations.

This next slide, are serious adverse events. They compare directly ISS-A to ISS-B, 229 patients in the first, 391 in the latter. Once again, there is a marked imbalance; that is there are many more serious adverse events reported, mainly in the

first 90 days in the ISS-A subset as compared to the ISS-B. Now, the only comparison here which probably is confounded is that of Myeloproliferative Disorder since this is a time-dependent event, and the patients from ISS-A were enrolled much before at a much earlier point in time than those in the expanded access trial. Certainly this comparison is probably not fair.

I'll start now with the hematologic toxicity. Complete blood counts by protocol were to be collected at least weekly beginning at week three until the recovery from the nadir to at least Grade III or removal from the study of the patient. Patients who had missing data during the period of the expected data, which is weeks five to nine, or at the time of recovery were assigned a worst-case scenario which Dr. Jacobs has already given you the data on. And I'll show you the data for both the documented Grade III and IV toxicity and the worst-case scenario.

For neutrophils, we had 51 percent Grade III or IV toxicity with the worst-case scenario, that is the imputed values for patients who had missing data during weeks five through nine shown below. For

platelets, 42 percent. Once again, it's a higher figure as you might anticipate for the worst-case scenario. For hemoglobin, 15 percent documented, once again a higher figure if data is imputed. The percentage of Grade IV toxicity is shown and once again worst-case scenario.

The toxicity, the Grade III or IV toxicity began earlier for platelets at day 34, somewhat later for neutrophils. For both of these major lineages it was 30 days in duration. In ten percent of the patients, it was 62 days or more for neutrophils and 102 days or more for platelets. And the maximum observed is shown below.

The target organ for the study agent TTR was a CD20 positive B lymphocyte. These are determinations done by the Sponsor. I'll point out two things to you in this data. First of all, they are selective. They only involve study 001 and study 003, the 003 being patients who were immunologically in much better shape. And I also would like to point out that if you look at the ends, you'll see that many of the patients were no longer available, there's a

rapid decline as we move along, so it makes the data somewhat harder to interpret. If we compare the median at the baseline, there's profound depression of lymphocytes at week seven and week 13, and even at month six, at which time this value falls into the normal range by the CD20 positive lymphocyte determination done in a laboratory, the median value is still well below 50 percent of the baseline value. I should also point out we agree with the Sponsor, with Corixa, that immunoglobulin values did not seem to be altered from the baseline.

Infections and fever. There were 84 patients of the 229, or 37 percent, who had fever. Of those 84 patients, about half of them had fever after study day 14, which would mean that the occurrence of the fever would probably superimpose on the period of maximum neutropenia and thrombocytopenia. And once again, of the 84 patients with fever, there were 15 patients or 18 because there were three who had missing data and we couldn't tell, or seven or eight percent, with fever associated with neutropenia or febrile neutropenia.

To look at infectious events again, we pooled a series of preferred terms related to infection. They are in order of incidence from left to right in the second row, et cetera. The per patient incidence was 43 percent for any -- for patients having any of these findings. There were 149 events. The same strategy was used for hemorrhagic events. These are, once again, in order of incidence, the highest being at the top. Some of these are far more serious than others, obviously. There was a 12 percent patient incidence, 31 events.

Transfusions and growth factor use, in the ISS-A group, 229 patients once again, 16 percent of patients received red cell transfusions, 15 percent platelet, 12 percent G-CSF or GM-CSF. The median duration of use of the growth factors was 16 days. Epoetin alpha was given in seven percent of the patients, and the median duration of use was 52 days.

A symptom complex primarily consisting of constitutional signs and symptoms, gastrointestinal problems, pharyngitis, rhinitis, also myalgias, arthralgias and in many cases rash was noted in

association with the infusion but not directly on the day of infusion but rather in the period of seven days after the infusion.

After the dosimetric dose, 55 percent of patients during the days zero to seven, dosimetric dose was given on day zero, 55 percent of the patients had one or more of the findings that I just discussed on the previous slide and 46 percent after the therapeutic dose. This is not actually correct. It's the seven days after the therapeutic dose that this incidence is taken from with 222 events reported.

Gastrointestinal toxicities. Even the early imaging studies demonstrated that there was uptake of the radiolabeled in the Waldeyer's ring and in the GI tract presumably due to binding to normal CD20 cells, and they were both acute, which are the peri-infusional toxicities I've been describing, and delayed gastrointestinal toxicities throughout the GI tract that were reported. I should note that acute toxicities were also observed with the unlabeled antibody, and of course this would be restricted to Arm B of the 002 study.

Once again, the same strategy is used for gastrointestinal toxicities. Four preferred terms related to upper GI and six related to lower GI toxicities are listed. The incidence was 38 percent for any of these and 24 percent for lower GI. Number of events are shown to the right.

Because of the known effect of iodide, radiolabeled iodine on the thyroid gland, we looked at the possibility of hypothyroidism and most particularly elevated TSH as an indication. Because of the limited number of data points and later kinds of collection, we looked here at as many patients as we could, the group of 620, which represents the ISS-A and ISS-B groups. There were 362 values, TSH values, after treatment, 34 patients who showed elevated TSH. The median time to TSH elevation was slightly less than a year, the confidence intervals of these data and the range are shown below.

This is a time-to-event curve. The x axis, which is I think very hard to tell from the back, is in months, up to 96 months. Let me focus your attention on 60 months, which is here. To the y

axis we have the cumulative percent of elevated TSH. The upper confidence interval and the lower confidence interval are shown by the dotted lines. We have cumulative incidence between 25 and 30 percent at that time point that I picked out at 60 months.

HAMA was evaluated, both site and central assay were used for this data. Once again, the data is taken from both combined ISS-A and ISS-B group. There were 604 patients who were HAMA-negative at baseline, there were 16 patients who were positive. At least one had -- at least one follow-up assessment was available at 515, and 51 patients were HAMA-positive. The median time to HAMA was late for an antibody response, 96 days. I point this out to you because I will show you the data for the 003 group, which is essentially a group in much better condition with respect to not having received chemotherapy. But the HAMA response was late in this group. The range is shown below.

This is the same curve. On the x axis we're looking at months from the dosimetric dose, up to 24 months. And on the y axis is the percent

cumulative incidence. These patients were all censored at the last available values, and I should point out that as we move along in terms of time, the numbers of available data drop very rapidly, and so the data is less reliable. The dotted line show the upper and lower confidence limits.

This is the HAMA evaluation in the 003 study, which, as I said, are untreated patients. There were 77 patients who were looked at at baseline, there were 73 who were negative, three who were positive and one with no data. After treatment, 70 percent of these patients were HAMA zero positive. The median time to zero positivity was 27 days. This is the time-to-event curve for that. Years to HAMA, up to five years on the x axis, present positive HAMA on the y, upper and lower confidence intervals.

Myelodysplastic disease or acute leukemia. We're showing this in a somewhat different way. These studies are arrayed in order of their time of initiation so that at the top the 000 is the oldest study and they progressively move down. I think one was turned around here, but with that exception these

studies are, in terms of time that they started, with the expanded access study at the bottom as the latest.

The incidence figures are shown here, and they progressively move down as one would anticipate as the possibilities of experience in the median years for experience increase. The median years to the myelodysplastic disease are shown in the final column.

Next slide. This is, once again, a graph of the incidence. The years are shown up to 8.5 years. The cumulative reported incidence are shown on the graph with the upper and the lower confidence intervals.

I'd like to summarize now the efficacy and the safety. Efficacy. The primary efficacy trial was conducted, and this is the 004 study, was conducted in 61 chemo-refractory patients who demonstrated a significantly higher proportion of patients with a longer duration of response following TTR as compared to the last qualifying chemotherapy. The overall response rate in this group, 46 percent; the complete response rate, 20 percent and the median response duration, and you can compare this to other licensed

preparations, was 11.7 months.

The second major efficacy trial was the 012 in 30 of the Rituximab-refractory patients. The overall response rate was 60 percent; complete response, 30 percent and the median duration at or around two years. Finally, supportive studies showed overall response rates from 48 to 63 percent and median duration of responses from one to three years and complete responses, 27 to 33 percent.

Safety. Hematologic toxicity Grades III or IV were seen in two-thirds of patients. The median duration of the Toxicity was 30 days. There was prolonged B cell lymphopenia. We found an incidence of 43 percent of infectious events, 12 percent incidence of hemorrhagic events. I've shown you how I derived those. There was a symptom complex noted of infusional toxicities comprised of constitutional findings, gastrointestinal problems, myalgia, rash, et cetera, in about 50 percent of patients. There was clinical and serologic immune responses, a 20 percent cumulative incidence of HAMA at 18 months in the heavily pre-treated patients and a 70 percent

cumulative incidence of HAMA in the chemotherapy-naive patients, once again at 18 months. And clinical sequelae to the possible serologic response, anaphylactoid reactions of serum sickness were infrequently observed.

Hypothyroidism, there was observed a 30 percent cumulative rate of TSH elevation at five years and a projected observed 45 percent cumulative rate at seven years. Once again, at these late points the data is thin. Leukemias and myelodysplasia were observed with increasing cumulative frequency, with 23 percent in the study with the longest follow-up, that's five out of the 22 patients. And across all studies the incidence is three percent with a median time of 2.1 years to the development of these problems. And that's it.

CHAIRPERSON PRZEPIORKA: Thank you, Dr. Litwin. Do we have questions for the FDA? Dr. Blayney.

DR. BLAYNEY: Thank you. First of all, I'd like to compliment you, Dr. Litwin, you and your team on the clarity of the briefing document

presentation. I enjoyed reading it. I'd also like to say that in the protocol -- the document contains several protocol amendments which took over three or four -- almost four years, and to me this speaks that this was not an easy clinical investigation to carry out, and that period of time probably was necessary to get it right, as we've heard today.

My real question and the question upon which the issue is joined is what procedures did you and your team undertake to review this MIRROR review of the data? I think many of the questions earlier have alluded to the fact that looking at responses to previous therapies before a patient was enrolled in a test of a new treatment is a difficult thing to do. And we've heard investigators talk about that. Did you have any way -- do we have assurances from you and your crew that this was independently verified, audited or monitored in some way?

DR. LITWIN: Yes. We appreciated your concern with this problem, which we were very concerned with at the time, and worked with the Sponsor to make sure that every piece of data,

including clinical information that might bear on whether the -- what the state of the patient was was collected. We had no independent monitoring of the collection of this data with the exception of what material came in was able to be reviewed. Dr. Mills, do you want to comment any further on this.

DR. MILLS: In terms of the MIRROR Panel, we did send an independent review charter, and then had those looked at in terms of our interpretations and understanding of those from the case report forms that were submitted. We've also looked at the quality of that data and the follow-up onto it, in terms of the long-term responder group also. And, admittedly, some of the early in terms of the prior chemotherapy certainly was performed more in a clinical practice setting than was indeed a clinical trial setting. But overall we felt that the interpretations were adequate for us to be able to assess them.

DR. LITWIN: I would point out that the Dr. Mills was a co-reviewer and actually reviewed most of the efficacy.

DR. BLAYNEY: So am I to understand that

you saw case report forms that were extracted from the clinical data and did some tests of that extraction or the case report forms?

DR. MILLS: We actually looked at the clinical assessments of those, and from our standpoint, both for radiographic assessment as well as for oncologic evaluation, because there was an oncologist as well as a radiologist interpreting these independently for us. Dr. Shastri accompanied me in terms of the oncology review, especially focused on the long-term responders to assess those. We looked also at the radiographic evaluations and did require a number of the long-term responders to be reevaluated by the MIRROR Panel to be able to get a full and complete assessment.

DR. BLAYNEY: Thank you.

CHAIRPERSON PRZEPIORKA: Other questions? Dr. Krook.

DR. KROOK: As I reviewed what you put together, which I again congratulate you, there were -- on Page 32, there were a fair amount of protocol violations identified. Some of these, having been on

numerous auditing teams, we would disqualify the patient. And my question is does that -- as you looked at this, you or Dr. Mills, did that have any bearing on the situation. Some of these had informed consents signed after the drug was given, as I read this. And then there was some iodine that wasn't given or is this just what you kind of accept?

DR. LITWIN: There were a lot of protocol violations, many too many, and the sponsorship actually shifted somewhere throughout the year of 2000, so I think that was possibly part of the problem in this. Those protocol violations that we think that we were most concerned with included patients who didn't have any measurable lesions, which there were a small but unfortunate number, and patients in whom the initial radiographic studies were not complete as they should have been. But there were also, and this is study-specific, a large number of violations that concerned the use of the lugols solution and the proper administration of the doses. And we remain concerned with whether the dosing was given as accurate as it should be under these appropriate

circumstances. And that was a serious problem, it was present in many of the studies, particularly 012 and 002, and I think it's got to be weighed in with the balance of a group of studies that suffered from many serious problems, at least in the initial periods.

DR. KROOK: Did it improve as time went on? I mean you listed 000, 001. Did it appear that some of these improved as time went on, as additional studies were done?

DR. LITWIN: I'd say it's fair to say that the later studies, 002 particularly, were done better, but the expanded access trial, which is of course a different type of trial, we felt had many serious problems, as I think I've illustrated on that slide showing ISS-B in which many of the patients came from the expanded access trial and in which we felt that the amount of monitoring was not adequate.

CHAIRPERSON PRZEPIORKA: I have a question, Dr. Litwin. I expect that the package insert would have the instructions that were similar if not identical to what was used in the protocol. And as this goes out to community hospitals and other

individuals who are not participating in the protocol or taking part in the educational sessions that were involved in the protocol, do you believe that the protocol -- the way the protocol was written would be adequate to hand over to a nuclear medicine physician anywhere else in the country and have this treatment be administered safely?

DR. LITWIN: Dr. Mills?

DR. MILLS: From the standpoint this is a challenging protocol and that the dosimetry model for administering the dose I think can be accomplished by nuclear medicine physicians but not without adequate training and full knowledge and understanding of how to assess this dose in this dose statement that comes from the dosimetry. They are going to need, they being the general community if this would be approved, would need extensive training and follow-up to assure that they could perform this dosimetry calculation to determine the dose appropriately. This has been an issue even in the clinical trials that they were not -- the clinical sites that had been participating were not always able to accomplish the protocol

reproducibility.

CHAIRPERSON PRZEPIORKA: Mr. Ohye.

MR. OHYE: Is this a subject we're going to ask the Sponsor to address?

DR. LITWIN: Oh, sorry I said that.

DR. JACOBS: We have submitted December 10 the training materials that we would be using for not only the clinical trials but postmarketing training at the sites, monitoring and assuring that the dosing is correct and collecting all residual activities. So we will be working with the FDA even in the postmarketing to assure that this is address in training materials and our ability to make sure that the procedures that we have are adequate to monitor those sites, re-train if needed and to perform it in the correct manner.

CHAIRPERSON PRZEPIORKA: I think we're actually thinking about the non-protocol sites. What do you provide to non-protocol sites to make sure that they administer this drug appropriately?

DR. JACOBS: We also have submitted exactly the same -- similar training for those sites that would be non-protocol sites. I was referring to

those as well. So there would be a procedure of oversight for training and assuring that the dosimetry calculations are being correctly performed when even a non-protocol site started initiating and using Bexxar.

CHAIRPERSON PRZEPIORKA: And how many non-protocol sites were using the validation of those training materials?

DR. JACOBS: When you say non-protocols, we're talking about more post-commercialization as far as that. So non-protocol sites are you talking about as far as EAP? The EAP, we had about 60 sites on the EAP before it was closed down. Last year it was 80 sites.

CHAIRPERSON PRZEPIORKA: Other questions? If not, we will move on to the questions to the Committee from the FDA. Dr. Keegan or Dr. Siegel, do you have an introduction?

DR. KEEGAN: Not a specific introduction other than to note that we've ordered the questions to ask first about the indication for which the Sponsor is requesting a standard or conventional approval, and the next two questions deal with the indication for

which the Sponsor has accelerated approval. And if you have any questions about those as you go along, please bring them up.

CHAIRPERSON PRZEPIORKA: So there are four questions that we need to address, and the way we'll do this is I will read through the questions in detail and ask for discussion from the Committee. Once we've exhausted the discussion or the discussants, we will take a vote with the exception of any essay questions that Dr. Siegel and Dr. Keegan have put in there, in which case we will not vote and they will simply have to pay attention to us.

(Laughter.)

So the data is again summarized on the first page of the questions. The second page starts the first question, Rituximab refractory follicular lymphoma, the Zevalin therapeutic regimen was evaluated by ODAC on September 11, 2001. The Committee recommended standard approval for Zevalin for the treatment of patients with Rituxan-refractory follicular lymphoma based on an overall response rate of 59 percent and median duration of response of 6.8

months in a single-arm trial, supported by preliminary survival data from a randomized control trial conducted in chemotherapy refractory Rituximab-naive patients.

The supportive study in Rituximab-naive patients showed no evidence of impairment of survival and 143 patients equally allocated to the Zevalin therapeutic regimen versus Rituximab at the approved dose and schedule. At the time of the original submission of the BLA, several of the trials listed above were ongoing. In response to FDA's request for additional safety and efficacy information, the final study report for CP97-012 was submitted on September 7, 2001 and an amended final study reports for CP97-012 was submitted on July 11, 2002. This is the only study that assesses the activity of the TTR in patients whose disease is refractory to only transiently responsive to Rituximab.

The Sponsor has requested an indication for the treatment of patients with follicular lymphoma, a subset of the patients enrolled. In this subpopulation, the overall response rate was 63

percent and the median duration of response, 2.1 years. TTR activity was similar for the overall survival population which included patients with low-grade non-follicular and low-grade transformed lymphoma.

So the question is do the results, that is overall response rate of 63 percent and median duration of 2.1 years and the 30 patients enrolled in the Phase 2 study, CP97-012, supported by the results observed in the other patients enrolled in the study and the activity in studies conducted in Rituxan-naive patients with chemotherapy-refractory disease, constitute substantial evidence of clinical benefit? And we'll start the discussion with Dr. Krook.

DR. KROOK: I would believe after reviewing this and listening that it does constitute substantial evidence of clinical benefit. One of the questions which I have is whether one could define, I think by the regulations, adequate well-controlled trial. I think it's an adequate trial. I have a little bit of a problem saying that it's well controlled based on what I heard, what I read and

otherwise. But I would answer this question yes.

CHAIRPERSON PRZEPIORKA: Any other comments or discussion? Dr. Kelsen.

DR. KELSEN: Actually, it's more a question. If Zevalin is an improved indication -- sorry, is an improved agent for this indication and through no fault of the Sponsors because these things happen over time, we have a drug, an experimental drug being proposed for the same indication but it hasn't been compared to the drug which is already licensed for that indication, it seems like an unusual circumstance, I'm just wondering about a precedent in the Agency's approach to this problem.

DR. SIEGEL: Well, thank you for asking that question, it's a very important one and one that it's also important to make clear. In this particular indication, Zevalin has a standard approval, as was recommended by ODAC, not an accelerated approval. The legal standards for approval in that setting do not at all involve comparative efficacy of safety to already approved regimens. So for hypertension, for diabetes, whatever, there's lots of approved therapies. A new

one comes along it has to be safe and effective, it doesn't have to be as good or better.

So for this indication, the standard is safe and effective. We cite in the background the Zevalin data, as I think they are relevant. The Committee did think in the past it was appropriate for approval. And I would say this, that although the legal standard isn't written that way, certainly in areas of treatment of acute myocardial infarction/, cancer or other settings where we know we have a drug with an impact on mortality, there largely has been a de facto standard that you'd better be as good if not better. So a new drug that has a lesser -- one series of drug with a mortality effect or serious irreversible morbidity effect, although the law doesn't require that the general advice of advisory committees and the general approach to those settings has largely been one to show -- to raise the bar to being as good but not necessarily and not in fact often addressed by head-to-head studies.

Now, the answer to your question vis-a-vis the indication we're going to come to shortly, which

is for -- where most of the data are, which is chemotherapy-refractory but not Rituxan-refractory patients, there the approval, also as recommended by this Committee for Zevalin, is an accelerated approval. An accelerated approval requires a demonstration of meaningful therapeutic benefit beyond existing therapy. I think it's -- as you point out, however, where drugs are developed sequentially, a new drug recognizing that standard and recognizing that another drug may be -- is there as an existing therapy, can address that in trial design. The Agency is quite aware that in a setting such as this and others that we have seen that one cannot -- it becomes very difficult to accomplish that if drugs are developed over the same time course, for one, for example, to either have a head-to-head trial or a trial in patient refractory to an earlier treatment if they're really developed over the same time frame. And all I can say in that regard is that there are substantial discussions within the Agency as to how best to interpret our regulations and laws regarding what is an appropriate way to meet the legal

requirements.

The interpretation in oncology to this point in time has been the same one that we gave to -- that we told Corixa in our communication of March of this year, which is that they needed to demonstrate how they met this standard of meaningful therapeutic benefit beyond existing therapy in order to be eligible for the accelerated approval, and that we hadn't seen that in their application, and we indicated, as has been covered amply in the press and indicated by the Company too, that we would expect additional clinical trials to be necessary. The Company has come back to us with data about prolonged and durable complete responses that have been presented that we'll be getting to in future questions.

So that's a very lengthy answer and to summarize it in two sentences, for this particular indication in which there is not being sought an accelerated approval, there's not a legal standard that requires a head-to-head comparison or any advantage beyond existing therapy, simply that the

drug be safe and effective. For the next indication, we're going to -- there is a standard. We are discussing how to interpret that internally and would seek from this Committee discussion of the data, the meaning and the implications of the data, and that will figure into our internal deliberations of how to address that standard. Okay? Does that sort of get at the question?

DR. KELSEN: I think I've got the answer.

(Laughter.)

DR. SIEGEL: I bet that's the last question anyone's going to ask me, right?

CHAIRPERSON PRZEPIORKA: Mr. Ohye?

MR. OHYE: Some of us were here when Zevalin was approved, and Dr. Pelusi reminded me that it was in this room. And with reference to this first indication, I think we've seen data that's comparable if not superior to what we saw at the time when Zevalin was approved. And with respect to a duration response, we're seeing definitely more data. Thank you.

CHAIRPERSON PRZEPIORKA: Dr. Brawley.

DR. BRAWLEY: At the risk of getting in even more trouble, I am -- the word "substantial" is key in the first question. I actually do believe that the Company has demonstrated that this is an active agent. I am very much concerned about the quality of the data that they have presented, the protocol violations. In some sense, I wonder is it fair to put us in the predicament of this drug which many of us believe to be active but the data has not been presented as cleanly as I would like to show that it's clearly active. And so I would hope behind me here is the dream team of lymphoma, and I would hope that whatever happens today Corixa works with that dream team to better develop this drug and to better answer the questions that we have here. Even though we're going to have to answer them today, I would hope they would address them in the future. And I'm certain that five, six years ago when many of these trials were being run the dream team wasn't consulting for them.

CHAIRPERSON PRZEPIORKA: Thank you, Dr. Brawley. Other questions or comments? Dr. Blayney.

DR. BLAYNEY: Yes. I think the answer to this question is yes, but I think the question that hasn't been answered is about standard radiation therapy. Chemotherapy-refractory patients do, in some measure, respond and respond for a long time with standard radiation therapy, and that question wasn't answered with this or with the previous agent. I think the other thing, it's clearly not fair to compare Zevalin with this agent because lymphoma is, as has been pointed out, a heterogenous disease, and if you pick your patients, you can get a lot of different response rates. So I think we need to bear that in mind. Thank you.

CHAIRPERSON PRZEPIORKA: Dr. Carpenter.

DR. CARPENTER: Unless I don't understand the presentation, very few of these people had disease which was not Stage III or more, which would not be appropriately managed with radiotherapy. So I think that comparison's probably not the one we need to be focusing on here.

DR. BLAYNEY: I think if somebody relapses in an isolated area, palliative radiation therapy --

DR. CARPENTER: Yes, but that's not who was in these studies.

DR. BRIDGES: I don't know if the question related to toxicity. Are you concerned about the issue of toxicity and combining people that have palliative radiation or even upfront curative for Stage I and II and then have progressed. They may ultimately go through chemo, they ultimately go through this treatment. Were those two issues that you were sort of addressing there?

DR. BLAYNEY: I was more concerned about a regulatory and comparative issue. I mean somebody who gets a response to systemic therapy and then relapses in an isolated area, perhaps as a low-grade lymphoma, can respond quite a long time. I think the other issue is that some place needs to be addressed is about dosimetry and about dose-limiting toxicity to isolated body parts, which you may be thinking about and I think needs some attention once, if the label is actually drawn about where and when normal tissue tolerance for this agent on the top of previous radiation, radiated fields needs to be looked at or at

least addressed by the clinician who's using the drug.

CHAIRPERSON PRZEPIORKA: Dr. Kelsen?

DR. KELSEN: Well, since you're talking about toxicity, the one toxicity that disturbs me the most as a solid tumor guy is myelodysplasia or acute leukemia, so could I just ask a non-comparative but comparative factual question? With the product that's already available, Zevalin, do you see the same incidence of MDS and acute leukemia? Is that something we should be worried about or is there an understanding they haven't done a heat-to-head comparison? Is there something that would leap out at you that one is more likely to cause this devastating toxicity than another? I don't know the answer to the question. Maybe the Sponsor's experts could address it for us.

DR. KEEGAN: Actually, in terms of Zevalin data, I can tell you that when we looked back at the data that were available last year with the population involved for a substantially shorter period of time, the rate was about 1.7 percent, 1.4 percent, versus the three to seven percent depending upon which group

you look in for these trials. But in the absence of a head-to-head comparison, I think it's a little bit difficult. But I would like to emphasize that implicit in the question that's asked, is the sense of is there net clinical benefit? Do the risks associated with this therapy -- do the benefits conferred by this therapy outweigh the risks? And that was also why the Zevalin data was summarized to show you the kinds of information that were available in comparative data on time to progression and survival that were available for Zevalin that helped address that sense of net clinical benefit. And so you're being asked do you have that same satisfaction with the data that are presented here?

DR. KELSEN: Yes. I asked that question specifically because if I remember the little bit of data we saw, again not comparing it, but just listing them, I clearly got an impression there wasn't a big difference. But I don't remember seeing that particular piece of information, and that seems to me to be the most dangerous toxicity.

DR. FISHER: Dr. Kelsen, could we make a

comment? You seemed to invite us up to make a comment. Rich Fisher again. The comment I would make is, just as a lymphoma person, is two things. One, the follow-up is significantly shorter on the Zevalin data, and so that affects the incidence. I don't think -- there are cases on both that are not grossly dissimilar but I don't think you can make detailed comparison. And, secondly, the patients are much more heavily pre-treated on some of these, which would increase the incidence. That being said, I don't think we can make more statements than that for you.

DR. KEEGAN: Yes. I would just amend Dr. Fisher's remarks. I think, actually, in looking across the Zevalin data, the amount of prior chemotherapy, the median amount prior to chemotherapy was actually quite similar in their safety database.

CHAIRPERSON PRZEPIORKA: And from the point of view of a hematologist, the curve that was placed up there looks very similar to the curves of any lymphoma getting chemotherapy and radiation, and we have to remember that this drug is radiation just like any other radiation. There's nothing magic about

it. Dr. Blayney.

DR. BLAYNEY: In the old days when radiation was used to treat lymphoma, the incidence of second leukemia was pretty small, background type with radiation only. It's the combination with which these are likely to be used that's leukemogenic.

CHAIRPERSON PRZEPIORKA: Dr. Carpenter.

DR. CARPENTER: I just think when the Zevalin data were presented to us the median follow-up was on the order of two and a half years. And as has been pointed out by several people who have commented on this, the peak time to see the leukemia and myelodysplasia is on the order of five to six years. There's adequate follow-up with this drug to begin to see what you're going to get. I don't think without longer follow-up on the Zevalin that you can safely make a comparison.

CHAIRPERSON PRZEPIORKA: Dr. George?

DR. GEORGE: I don't want to be a wet blanket here but the -- I'm still concerned with the substantial evidence of clinical benefit issue. I'm impressed by the long-term remissions that were

observed on this and other studies, but I was trying to -- and I have difficulty separating my approach to this on this Committee advising the FDA as opposed to what I would say if I were reading this in the literature. I would say that's very interesting, I would like to see a lot more additional study of this before I could draw a firm conclusion. So I don't know how I'm going to come down on this right now, but I just have to say we're talking -- we have to remember we're talking about 30 or 40 patients here and to be approving something that would be used, I suppose, in a much wider population.

CHAIRPERSON PRZEPIORKA: Dr. Martino?

DR. MARTINO: The question forces us to look at this particular piece of the data. I think what our job is is to make an overall decision, ultimately, and in answering this question, one cannot help but also be influenced by everything else that has been presented. It really is not an item in isolation. It's simply the way the question is worded that forces that point.

CHAIRPERSON PRZEPIORKA: Mr. Ohye.

MR. OHYE: I was just trying to address Dr. George's comment and that I think we're dealing here -- we also have to think in terms of an even playing field, and if you think back to what happened on September -- I beg your pardon, if you think what happened in September, happened to be the 11th, when we reviewed Zevalin, we didn't have a large body of data, and more particularly we didn't have any long-term data as compared here.

CHAIRPERSON PRZEPIORKA: Dr. Brawley? Dr. Krook?

DR. KROOK: I have to agree that the issue is substantial. It is a relatively small study but it took a long time to get this together, and it's probably never going to be done again. And I look at the duration, I look at the people or the patients who are treated who have this, and I'm impressed by the duration and what's occurred. I mean usually we wind up going with arm number five or number six of some chemotherapy, and to me this looks better than what I can do at arm four or five.

CHAIRPERSON PRZEPIORKA: Dr. Siegel?

DR. SIEGEL: I just wanted to clarify a couple of issues regarding regulatory standards. The question was not intended to force you to look at these data in isolation. We recognize that data in closely related indications are supportive of each other and are a guidance on evidence of effectiveness as well as a related guidance on evidence of effectiveness in oncology indications, it's very clear about that. So this question -- and, specifically, that's why it refers also to the Rituxan-naive patients. It's asking -- the direct evidence of data are the patients who are Rituxan-refractory. We're asking about that indication, but we certainly recognize that the other data for Rituxan-naive patients are relevant from both a safety and efficacy point of view and wouldn't want to imply otherwise.

The notion of substantial evidence of -- actually, it's of efficacy, safety and efficacy, comes from our legal standard, and it can be interpreted how you see fit. In part, that's why we put the Zevalin data here as there was certainly a feeling at that meeting that a database, albeit somewhat different in

size and in nature and in patient populations and we certainly agree with other comments that you can't make a head-to-head comparison but just wanting to ensure that a Committee was reminded about nature of other decisions on a related question.

Finally, there's one other point. Oh, adequate and well-controlled trial, yes. There was a comment on this being a well-controlled trial. An open labeled trial in most people's minds is not a controlled -- with this one arm, it's not a controlled trial. Oddly enough, our regulations as well as our guidance document do refer to several different types of control groups in a trial and recognize that historical controls actually can be considered a controlled trial.

Now, I'm not going to sit here as an advocate of single arm trials or historically controlled trials. We believe in cancer trials, however, that when you're looking at tumor response rates that in fact in most cancers there's a reasonably strongly presumption that an untreated group would not have a substantial response rate, a

spontaneous response rate, and someone can actually make determinations about response rates from those trials, and that's why we do approve drugs, whether for accelerated approval or not. They need to be adequate and well-controlled trials, just as a matter of explanation. that is why we are able to approve drugs on the basis of trials that I think many in an academic community, many of my European colleagues would look at that and say, "Not a controlled trial." They may still approve the drug, but they would say that's not a controlled trial. So it's somewhat of a semantic thing, but it is very clear in our regulations, and the guidance about them that single arm trials can be considered controls with historical control groups and their guidance makes clear that implicit historical controls in cases such as this can be used.

CHAIRPERSON PRZEPIORKA: Dr. Taylor?

DR. TAYLOR: I guess I'm a little bit concerned. I don't disagree that we have to have it on an even playing field, but we're looking at more data, so we have longer data, and then those followed

the longest we had a 23 percent of incidence of MDS or acute leukemia. So we have more information, and we shouldn't ignore that. And you can say, well, it's a small number of patients, and I don't disagree. But each of the columns for the longer they were followed they had more. And then we're willing to accept a response rate on a small group of patients. I think you have to accept that we have longer data and not ignore that longer data.

CHAIRPERSON PRZEPIORKA: Hearing no other comments, I'll call the question and start the vote. So for Rituximab-refractory follicular lymphoma, do the results overall response, 63 percent, median response duration, 2.1 years, and 30 patients enrolled in the Phase II study supported by results observed in other patients enrolled in this study and the activity and studies conducted in Rituxan-naive patients with chemotherapy-refractory disease constitute substantial evidence of clinical benefit? Dr. Martino.

DR. MARTINO: Yes.

DR. PELUSI: Yes.

DR. BRAWLEY: I believe there's

substantial evidence of clinical benefit, but I do not believe the evidence demonstrates that, so, no.

DR. TAYLOR: No.

DR. BRIDGES: Yes.

DR. LITWIN: Yes.

CHAIRPERSON PRZEPIORKA: Yes.

DR. KELSEN: Yes.

DR. REAMAN: Yes.

DR. CARPENTER: Yes.

DR. KROOK: Yes.

DR. GEORGE: No.

DR. BLAYNEY: Yes.

CHAIRPERSON PRZEPIORKA: The final tally is ten yes, three no.

The second question follows very quickly thereafter. Chemotherapy-refractory low-grade and follicular lymphoma with or without transformation. Number two, are the overall response rates and durations of responses observed across the five clinical trials conducted by the Sponsor, in light of the toxicity profile observed, likely to predict clinical benefit in patients of chemotherapy-

refractory low-grade and follicular lymphoma with or without transformation? We'll start with comments on this question. Dr. Krook?

DR. KROOK: It's somewhat similar to before is that if one looks at the response rates which were shown as we go further in line with cytotoxic chemotherapy, one has to believe that this is at least as good, if not better, than anything I can do with an extra, or anybody can do with an extra line of cytotoxic chemotherapy.

The second issue is the toxicity issue, which in my belief is that at least the patients which were looked at were heavily pre-treated and have been through a lot, and we heard this from our patient advocates. And that the toxicity to accept because you have taken something for lymphoma or taking a pill such as thyroid, I think that's a very small thing in light of things. So I believe that the answer would be that there is a clinical benefit in people like this, with and without transformation.

CHAIRPERSON PRZEPIORKA: Dr. Martino.

DR. MARTINO: I am particularly persuaded

by the fact that these are trials where patients have had several chemotherapies beforehand, and in spite of that we are seeing a reasonable number of responses and in spite of that we're seeing patients for whom that response lasts a reasonable length of meaningful time with relatively mild toxicity compared to most of the things that we give these patients. So I actually find the data in total to be something which I think will add considerably to what we can offer patients with probably less toxicity and less of a price tag in terms of toxicity than is our usual behavior.

CHAIRPERSON PRZEPIORKA: And I just wanted to echo the two previous speakers in how amazing this data is to get a 20 percent response rate, complete response rate in patients who are so heavily pre-treated with minimal toxicity. However, I also am concerned about the hematologic toxicity as well as the potential for leukemia in these patients. That is clearly not something I would jump to as first-line therapy in patients with stage III or stage IV disease but definitely for patients for refractory disease or refractory relapse diseases, it's clearly much better

than anything we can do currently. Dr. Pelusi?

DR. PELUSI: I have to agree, but I think it's great that we would at least have another option. And, again, I think one of our biggest roles is giving the informed consent saying, we really know that this data does exist in terms of the risk for long-term issues, but I think that patients are becoming very savvy and they need to be able to have the choices put on the table for them.

CHAIRPERSON PRZEPIORKA: Dr. Krook?

DR. KROOK: I would like to make it's more of a comment than anything else to my colleagues who've been before us, particularly the patient advocates with lymphoma. One of the things which I've learned being on this Committee, occasionally we have people which I respect who have come up here and said, "Hey, I've been in duration for a long time," looking at it as not a curative treatment. Again, it's another tool and the armamentaria is, as she says, if you look at the curves and we have long durations but we still have a lot of people who in the first year or two fail to respond and something else had to be done.

So this isn't the end as we see these people come. That's just a comment.

CHAIRPERSON PRZEPIORKA: Dr. George.

DR. GEORGE: I feel differently about this. This is for an accelerated approval. One thing I had to comment on, though, was the study design. When I first looked at this, it was interesting that the patients that were on this study I was trying to characterize in my own mind what they were, what kind of patients. They were heavily pre-treated, obviously, but one interesting quirk in the design was they had to be less than six months from their last qualifying chemotherapy, I mean their duration of remission or response.

And the interesting thing about that is in the way the analysis was first presented, although it really wasn't emphasized in the final analysis, was to compare the lengths of remission to the first -- I mean to the new treatment to the previous one. Well, it's almost impossible for that first treatment to be longer because it was sort of artificially short. I mean it was required to be short or the next one would

have to had to be really short, had to be less than 30 days, less than that. And the median remission in the first week was three months at best.

So you're talking -- it is true that that was a very bad group and so it's good to see these long-term remissions, but in the kind of analysis that was looked at, there was a little quirk there that would make it very difficult for you to -- it's not a balanced playing field, so to speak.

But in this case, I have a question, I guess. Is it relevant to discuss the follow-up studies or the things that would be required at this point or should we do it some other --

CHAIRPERSON PRZEPIORKA: I think that may be part of Question 4.

DR. SIEGEL: I think we're asking that in Question 4, yes.

DR. GEORGE: Oh, that's coming.

DR. SIEGEL: Yes. I would like to interject here that I couldn't agree more with your comment about that particular analysis. It's troubled me all along. It was developed and agreed to a number

of years ago, but to have the outcome in one side of a statistical analysis be determined by the entry criteria, you could have gotten a response rate of zero simply by not enrolling anybody who had responded, and you won't have any durable responders. And that's why we presented the data in terms of looking at the subsets of those who had had -- who are non-responders to the prior therapy and showing that nearly half of those had responded and those who were responders and showing that nearly half of that small group had responded and had some pretty durable responses. I think you can get meaningful information, but the statistical analysis is biased and somewhat problematic because of the design.

CHAIRPERSON PRZEPIORKA: Other comments? Then I will call the question. Number 2 for chemotherapy-refractory low-grade and follicular lymphoma with or without transformation. Are the overall response rates and durations of responses observed across the five clinical trials conducted by the Sponsor, in light of the toxicity profile observed, likely to predict clinical benefit in

patients with chemotherapy-refractory low-grade and follicular lymphoma with or without transformation? Dr. Blayney?

DR. BLAYNEY: Yes.

DR. GEORGE: Yes.

DR. KROOK: Yes.

DR. CARPENTER: Yes.

DR. REAMAN: Yes.

DR. KELSEN: Yes.

CHAIRPERSON PRZEPIORKA: Yes.

DR. LITWIN: Yes.

DR. BRIDGES: Yes.

DR. TAYLOR: Yes.

DR. BRAWLEY: Yes.

DR. PELUSI: Yes.

DR. MARTINO: Yes.

CHAIRPERSON PRZEPIORKA: Even without a calculator the tally is 13 yes, zero no. Okay. Thank you.

On to the third question. The issue of long-term responders. The Sponsor has retrospectively defined and identified a subpopulation of patients

with long-term responses. The Sponsor defined these according to the following criteria: Achieved a CR, CCR or PR to the treatment, and the time to progression from study entry was less than one year -- rather, was at least one year. These criteria were not prospectively discussed or agreed upon with the FDA, and the Sponsor has provided no clear rationale or justification for these criteria based on literature review or other sources. The 76 patients meeting these criteria constitute two-thirds of all patients who have responded to the treatment. The FDA further segregated this subset into 78 patients who received the dose and schedule for which marketing approval is being sought and eight patients who received a different dose and schedule. The efficacy results are summarized in the table above Question 3.

The question is does the findings of a subpopulation of patients with long-term responses demonstrate that the treatment provides meaningful therapeutic benefit to patients over existing treatments; that is, improved patient response over available therapy? Dr. George, do you have any

comments?

DR. GEORGE: I know how I'm going to vote on this and so I have to be careful. I was waiting for other discussions, but I think the answer is clearly no in this case. I won't elaborate.

CHAIRPERSON PRZEPIORKA: Any other discussion? Dr. Carpenter? No?

DR. CARPENTER: I think you're just going to have to look at what else is out there for people that have had a median of four prior treatments. And the choices are simply -- the available choices are simply not very good. Is this an ideal drug, I think the answer is it's almost certainly not, it's got some problems. But does it provide a clear advantage to available other therapies? In this population, many of whom are not appropriate for things like high-dose therapy, I think it probably does.

CHAIRPERSON PRZEPIORKA: Dr. Kelsen.

DR. KELSEN: Could I ask a clarification from the FDA? It seems to me like this addresses the issue of Zevalin directly. As I would read this would be Zevalin has received accelerated approval, is

available commercially. Is there clear and compelling evidence that this drug is superior to Zevalin? Is that the correct way to read your question?

DR. SIEGEL: Well, first to say there would be no intent for the words, "clear" and "compelling," to be in there, okay? There's nothing in our regulation or standards that would suggest that meaningful therapeutic benefit is clear and compelling -- that there's a standard of clear and compelling to be met in making that determination.

The answer is, in part, yes, but I think we were just discussing the fact that this question is somewhat less than optimally worded.

DR. KELSEN: Could you reword it?

DR. SIEGEL: Yes. Well, I can tell you what we need from you, okay? Because I think that there are complex issues here. Partially, we're looking at long-term responders, and I think it would be fair to say that it would be impossible, at least for this Committee, to make a determination as to whether Zevalin does or does not have similar amount of long-term responders because they didn't have as

much long-term data available at the time of presentation.

I think that raises some interesting issues as to whether documentation of long-term response is a benefit if there are other therapies for which you don't know whether that exists. And I think that one can make a strong case on either side of that question.

I think that it is also true that in exploring the question of how to deal with available therapies particularly in light of the issue you raised earlier where there aren't head-to-head comparisons, we communicated to this Company back in March an approach that was consistent with what oncology companies have been told over the last several years by the Division of Oncology, which is that to the extent that there is a drug with treatment with indications for refractory patients, the next drug to come along should either study patients refractory to that or demonstrate benefits that that drug hadn't shown if that's an existing therapy. And I think as we have further explored approaches to

accelerated approval throughout the Agency, we've discovered that there's different nuances to the way that is looked at. And so the fact of the matter is that there's a lot of discussion going on internally with how we deal with the accelerated approval, regulation, the underlying fast track law.

And I think that -- so I say that to get to then not to reword the question but rather to tell you what would help us the most. And that would be not to ask you to try to interpret a legal standard that has a lot of subtleties that need to be fully explored and can't be and haven't been fully explored to you, but rather to use -- what would help us the most would be to hear from you based on your expertise in dealing with this disease as to what are -- what is the clinical meaning of these long-term responders? Is this something that is out of the norm of what one has seen with chemotherapy and other therapies? Is this something that as is purported to be by the Sponsor, these whatever percent they are going out for a number of years, something that's telling us something important about this drug, what is it

telling us, what is our expectation? And we will, I think, to the extent we can get your expert opinion on those matters, we will take that information and do our best to apply appropriate regulatory standards. All right?

CHAIRPERSON PRZEPIORKA: I will just comment then that it has been stated and pounded into young oncologists' heads never to do analysis of survival of responders versus non-responders. I can tell you from someone who's been trying to figure out how to come up with criteria for response that are meaningful, it's sometimes important to look at that information to see whether or not a response by one definition gives you really long-term survival as opposed to a response by a second definition. But I don't know that that actually gives you any information about clinical meaning.

And so in this situation I think we already have a response definition and they've achieved their goal using the standard response definition. And the fact that their responses are longer than others may and or may not actually have

any substantial meaning. We may get into the situation where we do a study and there are five percent responders that are complete responses and last for ten years. So is that clinically meaningful? What happened to the other 95 percent who got no response whatsoever? So I personally would not start walking down that slippery slope whatsoever.

On the other hand, Dr. Blayney also pointed out that patients with lymphoma who get radiation are known to have good, long responses, and this is radiation. So this is a nice way to give radiation to someone who doesn't have all their disease in one field but can get the benefits from high-dose radiation that we would not be able to give to this population with any kind of chemotherapy at this era. Dr. George?

DR. GEORGE: My response to this question when I said it was no was precisely because of the last part of the question which has to do with does it provide meaningful therapeutic benefit to patients over existing treatments or, for example, improved patient response over available therapy? That's what

I think we don't know, and I guess I'm just a diehard in favoring controls compared to trials to answer that kind of question. And I won't make go so far as to claim it's the only way to get that answer, but it's pretty darn close, and it's by the far the best way. And so if you just stopped the question and said, does it provide benefit to patients, I'd say yes.

CHAIRPERSON PRZEPIORKA: Dr. Krook.

DR. KROOK: Probably speak as the gentlemen or the physician who's been on ODAC the longest since I'm about three years off. But I'm also, as a lot of people in the room are, we all treat -- a lot of clinicians treat lymphoma here, and my problem with the question, and as I listen to the discussion, I may come to know, I think there are other available treatments. I mean I've been through this where we're trying to approve a drug for third-line pancreas cancer. I mean the nature of that disease is different than what we're dealing with. I have, as my colleagues in the room, you may find somebody who can do fairly long with something fairly simple and the problem it becomes is to individualize

the therapy, and what I think this offers us is, as somebody said, it's really radial therapy with a monoclonal antibody, and that's what's different about this.

You know, we've got people who have probably responded who have 13 different previous chemotherapies. Look at the list up here. We have alphabet soup as we used to say in oncology. So I think there's other available therapy that may do equally well in an individual patient as I see them from day to day in this group. Now, if you talk about people who've transformed, that may be a little different than the person who still had follicular lymphoma.

CHAIRPERSON PRZEPIORKA: Dr. Martino?

DR. MARTINO: I think this data does have a suggestion that there are some people for whom this is good long-term therapy. The question deals with the issue of comparing to other things, which leads you to simply making leaps of faith. There have been no comparison data presented, so one can either guess or pretend one knows things one doesn't know.

CHAIRPERSON PRZEPIORKA: Dr. Blayney?

DR. BLAYNEY: I don't see how this helps you with the label. There are some people who are going to respond, either the label or approval. There are some people who, for whatever reason, have been retrospectively identified who respond for a long time.

On the subject of long-term responders, I'm very concerned about the myelodysplastic acute non-lymphocytic leukemia aspect of this treatment. You've shown between two and three percent per year incidence of this. Very few people have been treated at full dose who are out six years where it looks like the peak is. So that if you do a back-of-the-envelope calculation, you're talking about 12 to 18 percent at six years developing a myelodysplastic syndrome which will be fatal because they had received a treatment that radiates the bone marrow in totality, one out of seven. And I think that ought to give oncologists pause when they use this treatment and not move it to first line. I realize that's a little bit off the subject, but you do raise long-term responders, and

that's something that I think is quite concerning.

CHAIRPERSON PRZEPIORKA: Seeing no other hands, I will call the question.

DR. SIEGEL: Yes. I would -- I think it's quite clear from the discussion, it was actually clear before the discussion, that this question is asking for interpretation of -- I mean the reason your answer, well, how does it help us, the question mirrors regulatory decision that exists as reflected in the fast track language from 1997 as well as the accelerated approval regulation that requires us to make certain determinations. However, I think that because of issues, as I said, that extend beyond oncology and how we interpret that, it's probably neither necessary nor helpful to have a vote. The comments to date about what these response data and what these durable data mean clinically are very useful. If they're further, I would encourage that, but I would like to take the prerogative of not asking for a vote on this question.

CHAIRPERSON PRZEPIORKA: Okay. So Dr. Siegel has withdrawn this question, and we'll move on

to Number 4.

DR. BRAWLEY: Given that, can I make one --

CHAIRPERSON PRZEPIORKA: Dr. Brawley, yes.

DR. BRAWLEY: Very briefly.

DR. SIEGEL: Please.

DR. BRAWLEY: Okay. I believe that there is meaningful therapeutic benefit with this drug. I do not believe it has been proven that there is benefit over existing treatments.

CHAIRPERSON PRZEPIORKA: Dr. Reaman.

DR. REAMAN: Can we ask Dr. Siegel to amend the question rather than withdraw the question?

DR. SIEGEL: Sure. If you'd like to. I hear a pretty clear consensus here that people are cautious about how to interpret response data and to translate that to benefit, that they feel that this drug is benefitting some patients and that there is not adequate data of appropriate design to compare this to existing therapies. And I think sounds like there's consensus on those issues, and that's useful advice to us. I don't feel a need for a question with

a vote. However, if you would like it amended in a certain way, that's fine. I'm seeing heads nod. I think I heard the message, and I -- okay. Then I'm not sure exactly what to ask for a vote on. We could leave it as written or we could change it to something else, but the important thing here is to get the advice.

CHAIRPERSON PRZEPIORKA: Okay. Moving on then to Number 4, please comment on the types of information that should be obtained in additional studies to further characterize the safety and effectiveness of the regimen. Specifically comment on the following: The Sponsor has proposed a trial of Rituximab versus the therapy in patients with lymphoma who have received at least one and no more than two prior chemotherapy regimens. The primary objectives of this data is demonstration of a longer time to progression, alternative therapy or death in the treated patients. Survival is a secondary objective.

Also, please comment on the need to conduct studies to further assess delayed toxicities, including MDS, secondary malignancies, hypothyroidism

and HAMA. Does anyone have comments on either of these? And I noticed they didn't include quality of life, but if anybody wants to address that, please feel free. Dr. Pelusi?

DR. PELUSI: Well, I guess I will address that. I do think we need to look at quality of life studies, and I think we need to really look at the impact on families, and many times we look at quality of life based on the patient, but, you know, this is a time and a place where it may behoove us to really look at the impact on the main caregiver, because during this phase that is going to be important to let other family members know what could be expected down the road with this drug.

CHAIRPERSON PRZEPIORKA: Dr. Kelsen.

DR. KELSEN: I noted during the discussion that the Sponsor plans to compare this agent to Zevalin head to head, and I would support that very strongly.

CHAIRPERSON PRZEPIORKA: Dr. Carpenter?

DR. CARPENTER: I think sort of broader studies of where you're going to get this information

is probably -- it's an early disease, it's not going to be complicated by nearly the issues of all the prior therapy because it's early, and that's going to be -- it's going to get substantial follow-up, and there's going to be a comparator without the radiation, which gets at the issue at hand. To me that's the ideal place to get some of these longer-term issues solved and just encourage the longer, careful follow-up of that group of patients in that study, because that's already ongoing, those data are being collected, that if it's focused on that, that's the ideal place to answer this kind of question.

CHAIRPERSON PRZEPIORKA: Dr. George.

DR. GEORGE: I'm a little confused. I don't -- are there two studies being proposed, the Rituximab and the Zevalin study?

DR. CARPENTER: Yes.

DR. GEORGE: Who should I be asking, I don't know. But Zevalin was talked about briefly so that there would be these two, at least.

DR. KEEGAN: Yes.

DR. GEORGE: One is ongoing.

DR. KEEGAN: Dr. George, I think maybe the Sponsor will have to describe this. We've not seen a detailed proposal, the Bexxar-Zevalin study, only a concept issue. So we don't -- I couldn't describe it for you; perhaps they will.

DR. JACOBS: Actually, there are three studies: The SWOG study which is already ongoing, the randomized trial comparing Bexxar to Rituxan, which has been submitted to FDA, and we've actually, over the last six months to a year, have been negotiating on the final protocol. In April of this year, we also discussed doing a randomized trial of Bexxar to Zevalin, and we've had discussions with our experts, and we'll be submitting that protocol so the FDA -- we've had these preliminary discussions, but that protocol will be coming in January. We were going to submit it prior to this meeting, but there were other additional changes that were coming from the Rituxan versus Bexxar that were appropriate to just standardize it and make those changes in the protocol prior to sending it in.

CHAIRPERSON PRZEPIORKA: And I wanted to

add a comment that in this proposed study of Rituxan versus Bexxar for patients who have received at least one and could be no more than one, chemotherapeutic regimen that the eligibility criteria reflect the potential serious toxicities long-term for those patients and not include those individuals for whom a much less toxic therapy would be appropriate. Other comments from the Committee? Dr. George?

DR. GEORGE: Just a little follow-up on that, I guess. With this concern of myoelastic disease and secondary malignancies, I think the study is going to have to be long enough. I mean it is going to have to be one of these certainly five plus years of follow-up. So that's an issue, but I don't see how you can do it short term. I mean you've got long-term studies going on.

CHAIRPERSON PRZEPIORKA: And I would agree with Dr. George. I've had some serious concerns reading through the documents that the current incidence of AML or MDS was based on physician-reported cases whereas there may be some patients who are out there not seeing their physicians, their

physicians don't know about them, and so I'm in agreement with Dr. George, there has to be a very close follow-up long term for all patients on those studies. Dr. Martino?

DR. MARTINO: Is there no interest -- a question to the Company really -- is there no interest in looking at this agent prior to chemotherapy? I mean one of the things that impresses me about this drug is that it -- granted that there are some long-term issues, but it appears to me that this is easier than a lot of other things that we do. So I'm just curious as to have we no interest in really looking at this as a first relapse, so to speak?

CHAIRPERSON PRZEPIORKA: Actually, it's more specifically to Dr. Bridges. Would you consider using something like this in patients with stage III or IV lymphoma?

DR. BRIDGES: I think that could clearly be an area of use. The studies there we've looked at watchful waiting is a choice and we've shown that watchful versus aggressive therapy with the regimens that exist today don't offer a survival advantage. I

think it would be a good population of patients to consider an initial trial.

DR. KEEGAN: Could I ask for some additional discussion on two points. Dr. Przepiorka, you mentioned that you thought that patients who were entered with minimal pre-treatment should be patients who are higher risk. Could there be some comment on how that patient population might be characterized? Would it be IPI or something else?

CHAIRPERSON PRZEPIORKA: Well, I think we had mentioned -- I think that the scope -- the answer to that question is, will take more time than the Committee has, but the thing that comes to light, to the first, top of my mind is the patient who comes back with localized disease and this would be their first relapse. I'd be concerned regarding long-term toxicities in that population, somebody who has localized disease and no symptoms.

DR. KEEGAN: And the other question is, I just wanted to raise the issue, and the reason we presented the data from 003 in the previously untreated patients was the sterlingly high incidence

of an immune response to this Murine antibody and first-line for which we actually have no information on whether that might prevent readministration of any Murine antibody in the future. We certainly would expect that the presence of an immune response to a Murine antibody might alter the biodistribution and therefore make it unsafe to administer Murine antibodies. Is there a concern about use of this upfront for that reason in terms of just blocking -- preventing patients from taking other Murine products in the future?

CHAIRPERSON PRZEPIORKA: Dr. Blayney?

DR. BLAYNEY: In the upfront setting, you have a reasonably, as has been demonstrated, immune intact person who's capable of mounting an antibody, and I don't know what the long-term sequelae in terms of other diseases that we may not even have thought about that tissues in the body that might be innocent bystanders to immune epitopes expressed and respond on the mouse antibodies. So I think there's opportunity to look at other long-term sequelae in that setting as well.

CHAIRPERSON PRZEPIORKA: Dr. Keegan, back to you, does the FDA have any evidence from any study that HAMAs interfere with humanized antibody therapy?

DR. KEEGAN: I was going to say not with humanized or chimeric antibody therapies. We do have data with imaging agents where Murine antibodies were used as the imaging agent and readministration in that setting, and I'm going to let Dr. Mills describe that.

DR. MILLS: The concern that I would have for you is if we generate a HAMA in these subjects, you're going to alter the biodistribution of any Murine antibody in the future that's going to be administered to these subjects. Knowing that Bexxar is indeed a Murine antibody that would raise for it. You also should understand, though, that Zevalin, the radiolabel for the therapeutic and the diagnostic is also a Murine antibody. So the presence of a HAMA would be a relative contra-indication that we would want to consider in a clinical trial if we generate it with early administration of Bexxar. So, again, the concern is for every time in the diagnostics studies where we've studied extensively the presence of HAMA,

all of the Murine antibodies were altered in the biodistribution on the follow-up administration 100 percent.

DR. KEEGAN: Specifically, what happened was that the antibody was generally delivered directly to the reticular endothelial system, so it was rapidly cleared frequently from the blood and dumped in the liver and spleen rather than going to the usual sites. So we do have precedent with imaging agents that would suggest that HAMA will likely prevent the ability to reuse this product in the future, at least in a significant proportion of patients. There may be some patients where that might not happen. The data are not extensive. And a follow-on to that comment, then I would presume that the Committee might find it useful to study specifically retreatment in a carefully controlled setting.

DR. MILLS: And we could assess that presence of an altered biodistribution by using the diagnostic label, not the therapeutic label to see if indeed the findings we've seen on diagnostic studies previously will occur again in the presence of these

1 therapeutics.
2 CHAIRPERSON PRZEPIORKA: That's actually a
3 very important study because if in fact that is true,
4 then we as oncologists are not used to ordering HAMAs
5 routinely for our patients. But if in fact it does
6 alter diagnostic studies using other Murine
7 antibodies, we would certainly like to know about
8 that.
9 DR. SIEGEL: In that regard, it's worth
10 noting, because we've also observed this, it doesn't
11 change the overall risk/benefit but it's something one
12 needs to know about is that a number of laboratory
13 tests, including a number of endocrinological tests,
14 involve use of Murine antibodies in vitro to assess
15 the presence of materials in the serum and the
16 presence of HAMA in the serum. We'll invalidate those
17 -- there's ways around that and it doesn't figure into
18 the overall risk/benefit, but it is worth knowing that
19 so you don't misinterpret certain studies.
20 CHAIRPERSON PRZEPIORKA: Additionally, I
21 think one thing that might be added to this list is
22 fertility, although Dr. Press has told us about his

patients who have demonstrated their fertility after therapy. I'm thinking the denominator may not be very large and we're just hearing about a few in the numerator. And as we look at upfront protocols for this type of therapy, we should have hard data on that so that patients can make the correct option.

DR. MILLS: Just one other point to make with that is that there were some comments earlier about the amount, the centigrade that were administered to any of the target organs. Do not be reassured by comparing those numbers to external beam radiation therapy centigrade. There is no known relationship, and so while we identified the number and we feel it's reproducible, the relationship to any safety tolerance that's been established with external beam is purely speculation.

CHAIRPERSON PRZEPIORKA: Ms. Krivacic?

MS. KRIVACIC: I think the other issue that I would like to see from a patient perspective is the issue of administering concomitant meds as well, such as your growth factors, and if this has an impact in terms of any kind of adverse events, because I

think with the Zevalin trial that was something that was brought up and there was some discussion about that if there was indeed some interaction. So that would be something I'd like to see.

CHAIRPERSON PRZEPIORKA: Other comments from the Committee? Mr. Ohye.

MR. OHYE: I have one general comment, if I may, at the end of this meeting. I know there was some criticism about the length of time it took to get Bexxar approved, but as I look at the regulatory history as sort of dispassionate, old broken-down regulatory guy, I think kudos are in order for both the Agency and Corixa for taking a very difficult and challenging approval process and getting your arms around this, taking data that are 12 years old, sending people in the field to audit data, examining subpopulations very carefully to make sure that you didn't miss anything. And I think kudos are in order to Corixa for coming on board and recognizing that there was an important drug here, and congratulations for bringing this through.

CHAIRPERSON PRZEPIORKA: Any other

comments from the Committee? Hearing none, I call this meeting adjourned. Thank you and good night to everyone.

(Whereupon, at 6:02 p.m., the Advisory Committee meeting was adjourned.)