

FOOD AND DRUG ADMINISTRATION
SIXTY-EIGHTH MEETING
OF THE
ONCOLOGIC DRUGS ADVISORY COMMITTEE

8:00 a.m.
Tuesday, September 11, 2001

Versailles Ballroom
Holiday Inn - Bethesda
8120 Wisconsin Avenue
Bethesda, Maryland

ATTENDEES

COMMITTEE MEMBERS:

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ATTENDEES (Continued)

COMMITTEE MEMBERS: (Continued)

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ATTENDEES (Continued)

COMMITTEE MEMBERS: (Continued)

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VOTING PATIENT REPRESENTATIVE:

SUSAN KRIVACIC
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NON-VOTING INDUSTRY REPRESENTATIVE:

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ATTENDEES (Continued)

NON-VOTING GUEST SPEAKER:

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MARJORIE SHAPIRO, PH.D.

JAY SIEGEL, M.D.

IDEC PHARMACEUTICALS REPRESENTATIVES:

LEO GORDON, M.D.

SANDRA HORNING, M.D.

RICHARD LANDIN, PH.D.

BRYAN LEIGH, M.D.

PRATIK MULTANI, M.D.

LESLIE L. SHELLY, PH.D.

THOMAS WITZIG, M.D.

CHRISTINE A. WHITE, M.D.

ALSO PRESENT:

ELEANOR METZ

C O N T E N T S

BLA 125019, ZEVALIN (ibritumomab tiuxetan)
IDEC PHARMACEUTICALS CORPORATION

AGENDA ITEM	PAGE
CONFLICT OF INTEREST STATEMENT By Dr. Templeton-Somers	9
OPEN PUBLIC HEARING: By Eleanor Metz	11
INTRODUCTION By Dr. Marjorie Shapiro	14
IDEC PHARMACEUTICALS PRESENTATION Introduction By Dr. Leslie Shelly	17
Scientific & Medical Summary of Zevalin By Dr. Christine White	21
Questions from the Committee	50
MEASURING NORMAL TISSUE EFFECTS OF RADIONUCLIDE THERAPY By Dr. Ruby Meredith	82
FDA PRESENTATION By Dr. Philippe Bishop	101
Questions from the Committee	119
COMMITTEE DISCUSSION AND VOTE	177

P R O C E E D I N G S

(8:00 a.m.)

1
2
3 DR. NERENSTONE: Good morning. If the
4 committee will take their seats, we'll get started.

5 This morning we're going to be talking about
6 Zevalin's application, BLA 125019. I'd like to thank
7 everyone for coming.

8 I'd like to start by introducing the committee,
9 and we'll start with Mr. Ohye.

10 MR. OHYE: I'm George Ohye, nominee for
11 industry representative.

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

14 DR. BRIDGES: Don Bridges, radiation
15 oncologist, Maryland Regional Cancer Care, Rockville,
16 Maryland.

17 DR. REDMAN: Bruce Redman, University of
18 Michigan Cancer Center.

19 DR. TAYLOR: Sarah Taylor, medical oncologist,
20 University of Kansas.

21 DR. PELUSI: Jody Pelusi, oncology nurse
22 practitioner, Phoenix Indian Medical Center, and consumer
23 representative.

24 MS. KRIVACIC: Susan Krivacic, patient rep,
25 Austin, Texas.

1 DR. GEORGE: Stephen George, biostatistics,
2 Duke University.

3 DR. BLAYNEY: Douglas Blayney, medical
4 oncologist, Wilshire Oncology Medical Group, Pasadena,
5 California.

6 DR. NERENSTONE: Stacy Nerenstone, medical
7 oncology, Hartford, Connecticut.

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

10 DR. LIPPMAN: Scott Lippman, M.D. Anderson
11 Cancer Center, Houston.

12 DR. LEVINE: Alexandra Levine, hematologic
13 oncologist, University of Southern California, L.A.

14 DR. PRZEPIORKA: Donna Przepiorka, cell and
15 gene therapy, Baylor, Houston.

16 DR. KELSEN: David Kelsen, medical oncologist,
17 Sloan-Kettering.

18 DR. CARPENTER: John Carpenter, medical
19 oncologist, University of Alabama in Birmingham.

20 DR. MILLS: George Mills, acting branch chief
21 for the oncology section in CBER.

22 DR. BISHOP: Philippe Bishop, CBER, medical
23 oncologist.

24 DR. KEEGAN: Patricia Keegan, Deputy Director,
25 Clinical Trials, CBER.

1 DR. TEMPLETON-SOMERS: Thank you all for
2 coming. I realize that space is a little tight. If people
3 from the public can find some seats. I think there are a
4 couple in the front row or in the last two rows over on the
5 side. You're welcome to go ahead.

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

10 Based on the submitted agenda and information
11 provided by the participants, the agency has determined
12 that all reported interests in firms regulated by the
13 Center for Drug Evaluation and Research present no
14 potential for a conflict of interest at this meeting with
15 the following exceptions.

16 In accordance with 18 U.S.C., section 208(b),
17 full waivers have been granted to David Kelsen, M.D.;
18 Douglas Blayney, M.D.; Susan Krivacic; George Sledge, M.D.;
19 Scott Lippman, M.D.; and Alexandra Levine, M.D.

20 Further, in accordance with 21 U.S.C.
21 355(n)(4), Dr. Douglas Blayney, Susan Krivacic, and Dr.
22 Sarah Taylor have been granted waivers that permit them to
23 vote on matters concerning Zevalin.

24 A copy of these waiver statements may be
25 obtained by submitting a written request to the agency's

1 Freedom of Information Office, room 12A-30 of the Parklawn
2 Building.

3 In addition, Dr. Kathy Albain and Dr. Sarah
4 Taylor have interests that do not constitute financial
5 interests in the particular matter within the meaning of 18
6 U.S.C., section 208, but which could create the appearance
7 of a conflict. The agency has determined, notwithstanding
8 these interests, that the interest of the government in
9 their participation outweighs the concern that the
10 integrity of the agency's programs and operations may be
11 questioned. Therefore, Dr. Albain and Dr. Taylor may
12 participate in the committee's discussions and vote
13 concerning Zevalin.

14 With respect to FDA's invited guest speaker,
15 Dr. Ruby Meredith has reported interests that we believe
16 should be made public to allow the participants to
17 objectively evaluate her comments. Dr. Meredith is a co-
18 investigator of clinical studies and a projected principal
19 investigator at her institution for proposed clinical
20 studies.

21 We would like to note for the record that
22 George Ohye is participating in this meeting as an industry
23 representative, acting on behalf of regulated industry. As
24 such, he has not been screened for any conflicts of
25 interest.

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

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

11 Thank you.

12 DR. NERENSTONE: We're now going to turn to the
13 open public hearing part of the meeting. Eleanor Metz.

14 MS. METZ: Good morning. I'm sorry for the
15 delay.

16 Distinguished panel, I am here representing
17 myself and I'm impatiently and anxiously waiting for
18 Zevalin to be approved by the FDA. I've been told by my
19 wonderfully supportive oncologist at John Hopkins, Dr.
20 Richard Ambinder, that this drug would again be one of the
21 best choices of therapy for me as my follicular mixed non-
22 Hodgkin's lymphoma is relapsing again. I implore you to
23 expeditiously approve this drug for people like me.

24 So, how do I know about this drug? I was
25 fortunate to be part of the phase III trial of, at that

1 time known as, Y2B8, Zevalin, on April 26, 1999, as a
2 patient at Johns Hopkins. And for the records, I was
3 patient 23. Trust me, I had a great deal of trepidation,
4 but under the excellent care provided by Dr. Ian Flinn, who
5 I believe is in the audience today, research nurse Amy
6 Goodrich, and a whole bunch of other people at Hopkins,
7 Zevalin turned out to be a very good choice for me.

8 I've been a patient at Hopkins for 11 and a
9 half years and have gone through many types of chemotherapy
10 as my cancer has reoccurred. And it's true that I needed
11 some transfusions shortly after Zevalin was administered,
12 but through it all, I was able to work, lead a normal life.
13 It's been two-plus years, and I work. Until very recently
14 there's been little growth internally.

15 As I said, two-plus quality years. During this
16 time, I've become a grandmother, and since my children were
17 9 and 17 when I was originally diagnosed, I didn't think
18 I'd get to see that day. This drug Zevalin, along with the
19 care at Hopkins, my own determination, the will of God, et
20 cetera has gotten me this extra time.

21 My drug therapies are very limited. As a
22 matter of fact, before I went on Zevalin, I was going to
23 have to go on a very hard chemotherapy called ESHAP. Well,
24 let me share a short story. I promise you it will be
25 short.

1 I was visiting my son one day, my son the
2 lawyer I say with a smile.

3 (Laughter.)

4 MS. METZ: When his friend, the doctor, -- I
5 was telling him about my upcoming chemotherapy. He saw my
6 son a few days later and he said I should ask about Y2B8.
7 Initially I wasn't considered a candidate, but then I heard
8 that there was the phase III trial and Dr. Ambinder felt I
9 should give it a try and work with Dr. Flinn. And it just
10 felt right. It turned out to be right for me. This drug
11 has been wonderful for me.

12 In my professional life, I work with gifted and
13 talented students in a local school system, and I hope the
14 skills that I'm giving these students will help them go
15 into the field of developing these incredible drugs.

16 We cancer patients make very difficult choices.
17 We're dealing with this horrible disease, and I know I'm
18 not telling you anything you don't know. But I hope I'm
19 giving you the personal touch with the human face. I, like
20 so many others, including those that don't live near
21 centers that have these wonderful trials, need the
22 opportunity to do these researched options.

23 I implore you to approve this so that I and
24 others, with the guidance of our oncologists, get a chance.
25 My chance with Zevalin was successful. Two-plus years is

1 very good for me. My daughter is soon to graduate from
2 College Park. I want to see my grandson grow up, and I
3 want to continue to serve and enjoy my family, my education
4 community, and my religious community. Basically I want to
5 live. So, I hope the results from this drug give you the
6 courage and the wisdom to approve this so that I and others
7 can benefit from it.

8 Thank you.

9 DR. NERENSTONE: Thank you very much.

10 DR. TEMPLETON-SOMERS: We received a number of
11 e-mails from the public also in support of Zevalin and
12 other drugs, and those letters are available for the public
13 to view out at the desk in the books. And all of the
14 committee members have been supplied copies of those
15 letters ahead of time. But in the interest of time, I
16 think we're going to leave them to being read privately as
17 opposed to out loud. Thank you.

18 DR. NERENSTONE: We're going to now turn to the
19 drug application. Dr. Shapiro of the FDA will do the
20 introduction.

21 DR. SHAPIRO: Good morning. I'm Dr. Marjorie
22 Shapiro, one of the product reviewers and the chair of the
23 Zevalin BLA committee.

24 This morning the agency and IDEC
25 Pharmaceuticals will present an analysis of the data

1 | obtained from the clinical trials involving Zevalin. First
2 | I will introduce the BLA Review committee and then briefly
3 | describe the product. After the presentations by IDEC and
4 | our guest speaker, Dr. Philippe Bishop will finish the FDA
5 | presentation.

6 | Besides myself, the other members of the review
7 | committee are Philippe Bishop, George Mills, Satish Misra,
8 | Dave Green, Mary Andrich, Leon Epps, Deborah Trout, Kevin
9 | O'Brien, and Michael Noska.

10 | The 2B8 antibody, or ibritumomab, is a murine
11 | IgG1 kappa anti-CD20 monoclonal antibody. It is the murine
12 | parent of the chimeric molecule, rituximab. Ibritumomab is
13 | manufactured by standard procedures and subsequently
14 | conjugated with a chelator/linker, MX-DTPA, or tiuxetan.
15 | Ibritumomab tiuxetan conjugate is packaged into kits for
16 | radiolabeling with indium, and another kit is used for
17 | radiolabeling with yttrium 7 to 9 days later.

18 | This is a schematic diagram of the antibody
19 | conjugate prior to radiolabeling.

20 | The kit components include the ibritumomab
21 | tiuxetan, the 50 millimolar sodium acetate solution,
22 | formulation buffer, and a reaction vial. Even though the
23 | kit components for radiolabeling with indium or yttrium are
24 | identical, there will be separate kits for radiolabeling
25 | with the different isotopes.

1 If the committee recommends approval of this
2 product, you should be aware that there are some
3 outstanding manufacturing issues that need to be resolved.
4 To prepare radiolabeled Zevalin, the nuclear pharmacy will
5 place one order with the distributor for IDEC. This
6 distributor will coordinate the shipping of the indium kit,
7 the yttrium kit, and the yttrium. The nuclear pharmacy
8 will place a separate order for the indium directly from an
9 approved source. Both radiolabeled forms of Zevalin will
10 be prepared on site at the nuclear pharmacy.

11 The agency considers all components, including
12 rituximab, indium Zevalin, and the yttrium Zevalin, to be
13 part of the total Zevalin therapy. The step 1 components,
14 rituximab and the indium Zevalin, and the step 2
15 components, rituximab and yttrium Zevalin, are administered
16 7 to 9 days apart.

17 The proposed indication for Zevalin is for the
18 treatment of patients with relapsed or refractory low-
19 grade, follicular, or CD20 positive transformed B-cell non-
20 Hodgkin's lymphoma and rituximab-refractory follicular non-
21 Hodgkin's lymphoma.

22 Thank you.

23 DR. NERENSTONE: Obviously the FDA will
24 continue their presentation. Now we'll turn to the sponsor
25 for IDEC Pharmaceuticals' presentation.

1 DR. SHELLY: Good morning, Dr. Nerenstone,
2 members of the Oncologic Drugs Advisory Committee, and FDA
3 staff. I am Leslie Shelly, Associate Director of
4 Regulatory Affairs at IDEC Pharmaceuticals.

5 Today I would like to provide an overview of a
6 novel agent, ibritumomab tiuxetan, or Zevalin, which
7 represents a new class of therapies,
8 radioimmunotherapeutics.

9 Specifically IDEC is requesting approval of
10 Zevalin for the treatment of patients with relapsed or
11 refractory low-grade, follicular, or CD20 positive
12 transformed B-cell non-Hodgkin's lymphoma and treatment of
13 patients with rituximab-refractory follicular non-Hodgkin's
14 lymphoma.

15 Non-Hodgkin's lymphoma is predominantly of B-
16 cell origin and expresses the CD20 antigen. Collectively
17 non-Hodgkin's lymphoma ranks fifth in cancer incidence and
18 mortality, with an incidence in the United States of
19 approximately 55,000 per year and a prevalence of
20 approximately 300,000 cases. Of these, 65 percent are low-
21 grade or follicular. With progressive disease, there's an
22 increased incidence of transformation from indolent non-
23 Hodgkin's lymphoma to a more aggressive histology.

24 The median age at diagnosis is 60 years.

25 The median survival for low-grade or follicular

1 is 6.2 years. For transformed patients, the estimated
2 median survival is 7 to 22 months.

3 Relapsed or refractory indolent non-Hodgkin's
4 lymphoma is an incurable disease. Although there are other
5 treatment options available for physicians, there's only
6 one approved agent, rituximab. Given that the disease is
7 incurable and that there are limited treatment options for
8 these patients, there's a need for new and innovative
9 therapies.

10 The Zevalin regimen consists of the following.
11 On day 1, patients receive an initial infusion of rituximab
12 at 250 milligrams per meter squared to optimize
13 biodistribution of subsequently administered radiolabeled
14 antibody. This is followed by indium-111 Zevalin for
15 imaging. Biodistribution of the indium-labeled antibody is
16 assessed by obtaining images at 2 to 24 hours, 48 to 72,
17 with an optional third image at 90 to 120 hours.

18 Approximately 1 week later, patients receive a
19 second dose of rituximab followed by a single therapeutic
20 dose of yttrium-90 Zevalin. The standard dose of yttrium-
21 90 Zevalin is 0.4 millicuries per kilogram body weight.
22 This is reduced to 0.3 millicuries per kilogram body weight
23 for patients with mild thrombocytopenia. The maximum dose
24 for any patient is 32 millicuries.

25 Radiolabeling of Zevalin with either indium-111

1 or yttrium-90 will occur at the nuclear pharmacy. A single
2 point distribution system will be established for
3 distributing the Zevalin kits and the yttrium-90 isotope
4 for use with the kits. This will ensure that control is
5 exercised over the yttrium-90 isotope for use with Zevalin.

6 Clinical development of Zevalin was initiated
7 in 1993. Seven clinical trials have been conducted, six
8 completed, with one, 106-98, still ongoing. The total body
9 of clinical experience is 489 patients with an integrated
10 safety database of 349 patients and an integrated dosimetry
11 database of 179.

12 IDEC conducted two key trials that evaluated
13 the safety and efficacy of Zevalin based on the following
14 agreements with FDA. 106-04 is a phase III randomized
15 trial against the standard of rituximab in patients with
16 relapsed or refractory low-grade, follicular, or CD20
17 positive non-Hodgkin's lymphoma. The primary endpoint was
18 overall response rate. The trial was designed with an 80
19 percent power to detect a difference in overall response
20 rate between the arms. The secondary endpoint, time to
21 progression, was to be clinically equivalent to the
22 control.

23 The second key trial, 106-06, was a phase III
24 trial in rituximab-refractory patients.

25 The product received fast track designation on

1 June 5, 2000. A biologics license application was
2 submitted to FDA on November 1, 2000.

3 The data we will present today demonstrate that
4 Zevalin has significant clinical activity with acceptable
5 toxicity. In a patient population that has an incurable
6 disease requiring treatment, there's a need for other
7 agents to treat non-Hodgkin's lymphoma. We believe that
8 Zevalin represents a clinically meaningful advance in
9 therapy for these patients.

10 We'd like to express our gratitude to FDA for
11 providing guidance through the development of this product
12 and working with us in a collaborative manner.

13 We're pleased to have in attendance individuals
14 who have been instrumental in the development of Zevalin.
15 These include a number of our investigators who are
16 available to answer any questions.

17 These clinical scientists, as well as our
18 clinicians and biostatisticians, are available today and
19 have played important roles in the development of Zevalin.

20 Dr. Christine White, Vice President of Medical
21 Affairs at IDEC Pharmaceuticals and a medical oncologist
22 and hematologist, will provide further background on the
23 product and review the safety and efficacy data that we
24 feel support our indication. During the question and
25 answer period, Dr. Pratik Multani, a medical oncologist and

1 hematologist, and Dr. Bryan Leigh, a radiation oncologist,
2 will join Dr. White. Now I'd like to introduce Dr.
3 Christine White.

4 DR. WHITE: Dr. Nerenstone, advisory committee
5 members, FDA representatives, ladies and gentlemen, it is
6 my pleasure to come before you today to summarize the
7 clinical development of ibritumomab tiuxetan, or Zevalin,
8 radioimmunotherapy for non-Hodgkin's lymphoma.

9 My presentation today will be organized as
10 follows. First, I will address some background information
11 with regard to non-Hodgkin's lymphoma treatment
12 alternatives, radioimmunotherapy, and Zevalin. I will then
13 briefly discuss the phase I and II conclusions and our
14 conclusions from our imaging and dosimetry trial. Since
15 this data is extensively outlined in your briefing
16 document, I will only briefly touch upon conclusions here.
17 I will then, in more detail, summarize the efficacy results
18 of the phase III randomized trial and the phase III
19 rituximab-refractory trial, adding some additional
20 information with regard to the efficacy in the transformed
21 patients and the non-follicular low-grade patients. I'll
22 then turn to integrated safety and give detailed
23 information on our randomized trial safety, as well as the
24 integrated safety summary of 349 patients treated with
25 ibritumomab tiuxetan. Finally, I will summarize our

1 conclusions.

2 Initially patients with low-grade or follicular
3 non-Hodgkin's lymphoma are often sensitive to therapy.
4 However, response rates and response durations decrease
5 with relapses and successive courses of therapy. In 1986,
6 Dr. Gallagher published the results of a study at St.
7 Bartholomew's in London looking at response rates and
8 response durations with successive courses of alkylator
9 therapies. You will see on this slide that response rates
10 diminished from 70 percent initially to 39 percent by the
11 fifth therapeutic intervention, and response durations
12 dropped from over 1.5 years to a matter of months by the
13 fourth therapeutic intervention.

14 This slide also illustrates that these patients
15 require multiple successive therapies.

16 Treatment of relapsed or refractory low-grade,
17 follicular, or transformed non-Hodgkin's lymphoma typically
18 involves multiple cycles of therapy per course of therapy.
19 In this slide are summarized the results from the
20 literature of single agent trials and multiple chemotherapy
21 agent trials in relapsed or refractory low-grade,
22 follicular, or in some cases transformed disease. And you
23 will see that response rates range from 10 percent to 66
24 percent with the more aggressive therapies.

25 Toxicities of commonly used regimens can be

1 formidable. Up to 59 percent of patients can develop grade
2 4 neutropenia, and this, of course, is recurrent with
3 recurrent cycles of therapy. Up to 39 percent grade 4
4 thrombocytopenia, up to 40 percent of patients can develop
5 grade 3 and 4 infections, and treatment related deaths,
6 unfortunately, can be substantial with 16 percent, 17
7 percent, and even 23 percent of the patients dying of acute
8 toxicity in these studies. In addition, some agents have
9 grade 3 or 4 neurotoxicity in up to 10 percent of patients
10 or renal or hepatic toxicity, both reversible and
11 nonreversible, in up to 21 percent of patients.

12 There's no cure for relapsed or refractory low-
13 grade, follicular, or transformed non-Hodgkin's lymphoma,
14 and no regimen has been shown to be superior with regard to
15 survival. Patients need additional treatment options. In
16 the absence of cure or survival benefit, treatments that
17 induce remission and prolong time off therapy are valuable.

18 The rationale for developing radioimmunotherapy
19 in non-Hodgkin's lymphoma stems from the inherent
20 sensitivity of non-Hodgkin's lymphoma to radiation.
21 External beam radiation can be curative in limited stage
22 non-Hodgkin's lymphoma, but cannot be applied to advanced
23 stage disease because of toxicity. Antibodies that are
24 radiolabeled can target radiation to the tumor cells.
25 Radioimmunotherapy can kill both bound tumor cells and

1 neighboring tumor cells in the same mass, overcoming the
2 problem of access in poorly vascularized tumors or bulky
3 tumors.

4 Critical factors for successful therapy with
5 radioimmunotherapy include target antigen, antibody
6 selectivity, choice of isotope, and stability of antibody-
7 isotope linkage.

8 Zevalin, or ibritumomab tiuxetan, is the murine
9 monoclonal antibody, ibritumomab, which is the murine
10 parent of the rituximab engineered chimeric antibody. It
11 binds the same epitope on CD20 and is covalently bound to
12 tiuxetan, which stably retains 90 yttrium upon chelation.
13 The CD20 antigen is expressed only on B lineage cells. It
14 is important for cell cycle differentiation and initiation.
15 And very importantly for immunotherapy, it does not shed
16 into the blood, does not down-regulate upon binding, and
17 does not modulate.

18 We have chosen 90 yttrium as the isotope to use
19 in radioimmunotherapy for the following reasons. It has a
20 half-life of 64 hours. The high beta energy of 2.3 MeV and
21 path length of 5 millimeters make it advantageous in
22 treating bulky tumors and poorly vascularized tumors.
23 Because it is a pure beta emitter, patients can be treated
24 as an outpatient in all cases without having to be
25 restricted, shielded, or have any particular restrictions

1 on their behavior or environmental impact.

2 I will now turn to the phase I/II study
3 conclusions.

4 From our phase I study and our phase I/II
5 study, we were able to conclude that unlabeled,
6 pretreatment rituximab improved Zevalin biodistribution.
7 The maximum tolerated dose was determined to be 0.4
8 millicuries per kilogram, 0.3 millicuries per kilogram in
9 patients with mild thrombocytopenia. In all cases the
10 maximum dose was 32 millicuries.

11 Toxicity was primarily hematologic and
12 reversible and correlated with millicurie per kilogram
13 dose.

14 Clinical variables, including baseline platelet
15 count, a surrogate for bone marrow damage from prior
16 chemotherapy and prior external beam radioimmunotherapy, as
17 well as percent bone marrow involvement, a surrogate for
18 specific targeting of Zevalin to the disease in the marrow,
19 were more predictive of toxicity than was dosimetry.

20 Clinical parameters proved adequate for dosing.

21 The overall response rate was 82 percent in
22 low-grade non-Hodgkin's lymphoma in our phase I/II study,
23 and 42 percent in intermediate-grade predominantly diffuse
24 large cell non-Hodgkin's lymphoma.

25 The median time to progression in the patients

1 who received the 0.4 millicurie per kilogram dose was 15.4
2 months. These are the responders. And the median time to
3 progression in those patients who received 0.4 millicurie
4 per kilogram and achieved a complete response has not been
5 reached yet with a range of 28.3 to 37.2-plus months.

6 Turning to imaging and dosimetry, this is a
7 representative scan from a patient who was imaged with
8 indium-labeled Zevalin. At 4 hours, there is Zevalin still
9 in the blood pool, as evidenced by appearance of the iliac
10 vessels and the cardiac shadow.

11 By 66 hours, this large periaortic and
12 retroperitoneal mass, seen very well here on CT-scan, is
13 specifically targeted by the Zevalin radioimmunotherapy and
14 appears very bright. You can also see the liver shadow.

15 At 139 hours, there is retention of the Zevalin
16 radioimmunotherapy in the large mass.

17 On SPECT scan, you can see that the targeting
18 to the mass is very intense, much more so than the
19 targeting to the liver, which is the major organ of
20 metabolism.

21 Tumors imaged in all low-grade follicular and
22 transformed patients. Radiation absorbed doses to normal
23 organs was acceptable in all patients. There was minimal
24 urinary excretion, 7 percent over 7 days time, which is 3.5
25 physical half-lives of the isotope. There was no

1 correlation between hematologic toxicity and dosimetry
2 parameters or pharmacokinetic parameters.

3 This bar graph shows the median 90 yttrium
4 radiation absorbed doses to tumor and to normal organs.
5 You will see that the median dose here to tumor is
6 approximately 1,500 centigray with a range up to 24,000
7 centigray. The spleen, which is often involved with
8 lymphoma, receives 1,000 centigray. The testes and the
9 lungs were 950 centigray median and 220 centigray median,
10 and we feel that this may be overestimated as our methods
11 for dosimetry did not include the proper attenuation
12 correction factors for these superficial organs. So, that
13 is an absolute maximum. Median dose to liver was 520
14 centigray; to bone marrow, 143 centigray; and to kidneys,
15 13 centigray; total body, 58 centigray. This is the
16 acceptable maximum dose to bone marrow, 300 centigray,
17 defined in the protocol, and 2,000 to normal organs. And
18 you can see that the normal organs received far less than
19 the acceptable limits.

20 I will now turn to the efficacy results from
21 our phase III randomized and our phase III rituximab-
22 refractory trials.

23 There were approximately 200 patients in these
24 two trials, the phase III randomized and the rituximab-
25 refractory trials, and these patients were a representative

1 population with regard to the greater population of
2 patients with low-grade, follicular, or transformed non-
3 Hodgkin's lymphoma. In this table, you can see that
4 patients on the Zevalin arm of the phase III trial, the
5 rituximab arm of the phase III trial, and on the rituximab-
6 refractory trial were similar with regard to age, gender
7 ratio, histologic classification, stage, and marrow
8 involvement to the referenced group of 433 patients first
9 defined in 1982 at the time of the definition of the
10 International Workshop Histologic Classification, and also
11 to 1,850 patients described in seven comparison studies in
12 the literature.

13 Our phase III randomized study was conducted at
14 these 27 institutions.

15 The study design was as follows. It was
16 stratified by histology, IWF A, which was actually non-
17 follicular low-grade, follicular, which was the second
18 category, or transformed. And the patients received either
19 the Zevalin regimen as previously described, that is, two
20 doses of rituximab 250 milligrams per meter squared, the
21 first followed by 5 millicuries of indium-labeled Zevalin,
22 the second followed by 0.4 millicurie per kilogram of 90
23 yttrium Zevalin with a maximum of 32 millicuries. Or if on
24 the control arm, the patients received rituximab, 375
25 milligrams per meter squared weekly times 4.

1 The primary endpoint prospectively defined was
2 overall response rate. The study was designed with an 80
3 percent power to detect a difference of 25 percent in
4 overall response rate with an alpha of 0.05. Overall
5 response rate was determined by an independent lymphoma
6 expert confirmation of response panel comprised of
7 radiologists and oncologists expert in lymphoma who were
8 blinded to what treatment the patient received and to the
9 investigator-assessed response.

10 Secondary endpoints included duration of
11 response, time to progression, time to next therapy,
12 complete response, clinical complete response, partial
13 response, and quality of life.

14 Patients were enrolled in the trial if they had
15 bidimensionally measurable disease initially greater than 3
16 centimeters. Later the trial was amended to be greater
17 than 2 centimeters. Less than 25 percent marrow
18 involvement by biopsy, looking at the cellular space. A
19 WHO performance status of 2 or less, and adequate
20 hematologic function, including an absolute neutrophil
21 count of 1,500 or greater, and a platelet count of 150,000
22 or greater.

23 Patients were excluded if they had prior
24 myeloablative therapy or radioimmunotherapy, prior
25 radiation to more than 25 percent of the active marrow,

1 prior anti-CD20 therapy, total bilirubin or creatinine
2 greater than 2, or a lymphocyte count circulating greater
3 than 5,000.

4 The two arms of the study were well balanced.
5 There was no statistically significant difference in these
6 prognostic factors, and in particular, I will point to
7 number of prior regimens, response to last therapy, marrow
8 involvement, splenomegaly, bulky disease, and
9 chemoresistance.

10 Patients were 60 years of age median in the
11 Zevalin arm, 57 on the rituximab arm. But the age of the
12 patients extended up to 80.

13 Most of these patients had follicular
14 histology: 75 percent on the Zevalin arm; 83 percent on
15 the rituximab arm. Smaller numbers of patients with non-
16 follicular, low-grade, or transformed histologies were
17 entered.

18 The median number of prior therapies was 2,
19 with a range to 6.

20 43 percent of patients on the Zevalin arm and
21 36 percent on the rituximab arm had bone marrow
22 involvement.

23 10 percent on Zevalin arm and 4 percent on the
24 rituximab arm had splenomegaly.

25 18 percent on the Zevalin arm and 13 percent on

1 the rituximab arm had extranodal disease, and about 45
2 percent of these patients had bulky disease greater than 5
3 centimeter lesions. 8 percent had lesions at least 10
4 centimeters or more.

5 Nearly half of these patients were resistant to
6 their most recent chemotherapy and up to 64 percent were
7 resistant to any prior chemotherapy. Resistance is defined
8 for this protocol as no response or time to progression of
9 less than 6 months.

10 This bar graph shows the response assessment by
11 protocol-defined response criteria on the phase III
12 randomized trial. There was a 73 percent response rate on
13 the Zevalin arm, 47 percent on the rituximab arm, and this
14 difference was statistically significant with a p of 0.002.
15 There were 18 percent complete responders and 3 percent
16 clinical complete responders on the Zevalin arm, 11 percent
17 and 4 percent on the rituximab arm.

18 This table shows response by histology. Again,
19 the majority of patients were follicular histology, and
20 there was a 76 percent response rate on the Zevalin arm, as
21 compared to a 47 percent response rate on the rituximab
22 arm, with a p of 0.002 with regard to this statistically
23 significant difference. There was no statistically
24 significant difference in the non-follicular, low-grade, or
25 transformed groups. The IWF A or non-follicular, low-grade

1 group included small lymphocytic lymphoma patients,
2 MALTomas, lymphoplasmacytic, and monocytoid B.

3 This table shows response rate in patients
4 resistant to their most recent chemotherapy. The response
5 was 64 percent on the Zevalin arm, 36 percent on the
6 rituximab arm, with a statistically significant difference
7 and a p of 0.045. Again, resistance to last chemotherapy
8 was defined as no response or a time to progression of less
9 than 6 months.

10 Looking at patients with regard to tumor bulk
11 less than 5 centimeters or greater than 5 centimeters, in
12 this larger tumor bulk category there was a 67 percent
13 response rate on the Zevalin arm and a 45 percent response
14 rate on the rituximab arm.

15 At the time that these protocols were
16 developed, there was no standardized criteria for response
17 for non-Hodgkin's lymphoma. For that reason, IDEC worked
18 with the FDA to develop protocol-defined response criteria.
19 Subsequently, however, the National Cancer Institute has
20 convened an international workshop to establish NHL
21 response criteria that would be standardized
22 internationally. These have been published and are now
23 being used, rapidly adopted to evaluate trials and to
24 compare.

25 The LEXCOR measured response rate, using the

1 international workshop response criteria, was 80 percent
2 for the Zevalin arm and 56 percent for the rituximab arm.
3 This difference was statistically significant with a p of
4 0.002. The complete response rate was 30 percent for the
5 Zevalin arm and 16 percent for the rituximab arm, and this
6 difference was statistically significant as well, with a p
7 of 0.040. There were 4 percent unconfirmed complete
8 responders on both arms.

9 This table summarizes duration of response,
10 time to progression in all patients, and time to
11 progression in responders. There was no statistically
12 significant differences in each of these variables between
13 arms. The duration of response on the Zevalin arm was
14 estimated by Kaplan-Meier methods at 14.2 months; on the
15 rituximab arm, 12.1 months. Time to progression in the
16 responders was 15.4 months by Kaplan-Meier estimation on
17 the Zevalin arm and 13.8 months by Kaplan-Meier estimation
18 on the rituximab arm. At the time of this analysis, 32
19 percent of the patients had ongoing responses on the
20 Zevalin arm and 19 percent on the rituximab arm, with a
21 median observation time of 22 months.

22 This is a slide that demonstrates duration of
23 response by histology. Again, looking at the follicular
24 histology where the majority of patients were, the duration
25 of response estimated by Kaplan-Meier methods is 18.5

1 months on the Zevalin arm as compared to 12.1 months on the
2 rituximab arm. This difference is not statistically
3 significant.

4 This is a Kaplan-Meier curve of time to
5 progression in all patients, again not statistically
6 significant.

7 This is the same group of all patients, and
8 this is a Kaplan-Meier curve of time to next therapy, and
9 there is a trend towards greater time to next therapy in
10 the Zevalin arm as compared to the rituximab arm, with a p
11 of 0.084.

12 In follicular patients, this is a Kaplan-Meier
13 curve of time to progression. Again, there is a trend
14 towards a greater time to progression in the Zevalin arm as
15 compared to the rituximab arm, with a p of 0.062.

16 For follicular patients, this is time to next
17 therapy by Kaplan-Meier analysis. Again, a trend towards
18 longer time to next therapy in the Zevalin arm as compared
19 to the rituximab arm, with a p of 0.058.

20 Looking only at patients who achieved a
21 complete response or a clinical complete response, there is
22 a trend towards longer time to progression in the Zevalin
23 arm as compared to the rituximab arm, though this is not
24 statistically significant in this small group. No median
25 has been reached yet for the Zevalin patients.

1 To summarize the phase III randomized trial
2 efficacy results, efficacy objectives were met. The
3 primary objective of overall response rate was
4 significantly higher, as determined by an independent
5 blinded lymphoma expert confirmation of response panel, as
6 compared to the control arm.

7 Secondary objectives were also met, including a
8 comparable overall time to progression. In addition,
9 although this trial was not powered to show differences in
10 TTP, a trend towards longer TTP in the follicular patients
11 and in the complete response and clinical complete response
12 patients was demonstrated. There was also a trend towards
13 longer time to next therapy in all patients, and the median
14 time to progression responders has been 15.4 months by
15 Kaplan-Meier estimation.

16 I will now turn to the phase III rituximab-
17 refractory trial results. This trial was conducted at
18 these 17 institutions.

19 Study design was as follows. 28 patients
20 received the same regimen I described before: rituximab
21 250 milligrams per meter squared on two occasions, 1 week
22 apart; the first being followed by indium-labeled Zevalin,
23 5 millicuries, the second being followed by 90 yttrium-
24 labeled Zevalin, 0.4 millicurie per kilogram with a maximum
25 of 32 millicuries. By protocol design, 29 patients did not

1 receive indium-labeled Zevalin imaging or dosimetry.

2 The primary efficacy endpoint was a target
3 overall response rate in 35 percent of rituximab-refractory
4 follicular patients. Rituximab-refractory was defined as
5 no response or a time to progression of less than 6 months
6 to rituximab. The response was again evaluated by the
7 independent lymphoma expert confirmation of response panel,
8 again blinded to the treatment received and also to the
9 assessed response by the investigator.

10 Secondary endpoints were duration of response,
11 time to progression, time to next therapy, CR, CCR, PR, and
12 a comparison of overall response rate and duration of
13 response to the prior rituximab and to the last
14 chemotherapy, as is demonstrated on this line graph.

15 Median age was 54 years with a range to 73
16 years.

17 This was a more heavily pretreated, more
18 advanced disease population. There was a median of four
19 prior chemotherapy regimens with a range to nine.

20 32 percent of patients had bone marrow
21 involvement.

22 18 percent had two or more extranodal disease
23 sites.

24 12 percent had splenomegaly.

25 Three-quarters of these patients had bulky

1 disease, defined as greater than 5 centimeters. 44 percent
2 had tumor lesions greater than 7 centimeters, and 19
3 percent had tumor lesions of 10 centimeters or more.

4 Two-thirds of these patients were resistant to
5 last prior chemotherapy, again defined as no response or
6 time to progression of less than 6 months.

7 The response assessment by the LEXCOR, lymphoma
8 expert confirmation of response, panel using the protocol-
9 defined response criteria, included an overall response
10 rate of 59 percent, with a complete response of 4 percent.
11 By international workshop NHL response criteria, the
12 overall response was 74 percent, with a complete response
13 rate of 15 percent.

14 Duration of response was estimated by Kaplan-
15 Meier methods at 7.7 months; time to progression in all
16 patients, 6.8 months; and time to progression in
17 responders, 9.1 months.

18 Analysis was performed to compare Zevalin to
19 the prior therapy, both rituximab and prior chemotherapy.
20 The methodology was as follows.

21 The analysis favored one therapy if the patient
22 responded to one therapy but not to the other, or if the
23 patient responded to both but the duration of response was
24 at least 3 months longer. This analysis was actually done
25 for 3 months and 1 month. Both are in your briefing

1 document, but I will present the 3-month more conservative
2 analysis.

3 It was neutral if the patient did not respond
4 to either or responded to both, but the duration of
5 response was 3 months greater.

6 Here are the results of that analysis. The
7 analysis favored Zevalin in 48 percent of patients, favored
8 prior therapy in 9 percent of patients, that is, in the
9 comparison to rituximab, and was neutral in 43 percent of
10 patients. This difference was statistically significant
11 with a p by sign rank of less than 0.001 and by sign of
12 0.011.

13 When comparing Zevalin to the last
14 chemotherapy, the analysis favored Zevalin in 30 percent of
15 patients, favored prior therapy in 30 percent of patients,
16 and was neutral in 41 percent of patients. This difference
17 was not statistically significant, which was a better than
18 expected result in that the chemotherapy was the patient's
19 third regimen and the Zevalin was the patient's fifth
20 regimen on median.

21 To summarize the rituximab-refractory trial
22 results, the efficacy objectives were again met. There was
23 a significant overall response rate in the heavily
24 pretreated, bulky disease, rituximab-refractory patient
25 population.

1 Secondary endpoints were also met. There was a
2 statistically improved efficacy demonstrated with Zevalin
3 therapy as compared to the prior rituximab therapy, and
4 there was no difference between Zevalin therapy and the
5 prior chemotherapy, a better than expected result in that
6 the chemotherapy was the third regimen and the Zevalin the
7 fifth on median. The median time to progression in
8 responders in this patient population of advanced disease,
9 heavily pretreated, and bulky disease was 9.1 months.

10 I would now like to give some more details with
11 regard to efficacy in the transformed and non-follicular
12 low-grade groups.

13 Across our phase I/II, phase II, and phase III
14 Zevalin trials, there were 15 patients with transformed
15 histologies. Of those 15 patients, 6 responded for an
16 overall response rate of 40 percent; 2 achieved complete
17 responses for an overall complete response rate of 13
18 percent. Time to progression ranges from 0.8 to 37.2-plus
19 months, and 3 patients, or 20 percent of this small group,
20 are still in ongoing remission at 11-plus, 22-plus, and 37-
21 plus months.

22 With regard to the non-follicular low-grade
23 histology patients -- again, these are including small
24 lymphocytic lymphomas, lymphoplasmacytic, MALTomas, and
25 monocytoid B -- there were 16 patients in our phase I/II,

1 phase II, and phase III Zevalin trials. 9 responded for an
2 overall response rate in this small group of 56 percent
3 with a complete response in 1 patient, or 6 percent. Time
4 to progression has been 6.1 months to 12.6-plus months,
5 with 2 patients, or 14 percent, in ongoing remission in
6 excess of a year.

7 I will now summarize our integrated safety.

8 Adverse events are primarily hematologic with
9 Zevalin. Nonhematologic adverse events are primarily grade
10 1 and 2. Zevalin is not associated with hair loss, severe
11 mucositis, persistent nausea and vomiting, and other
12 symptoms common with chemotherapy. There's a low incidence
13 of serious infection and a low incidence of human anti-
14 mouse antibody or human anti-chimeric antibody.

15 This bar graph demonstrates the most frequent
16 nonhematologic adverse events in a population of 349
17 patients treated with Zevalin. Grade 1 is in yellow, grade
18 2 in light blue, grade 3 in orange, and grade 4 in green.
19 You can see on this graph that nonhematologic adverse
20 events were primarily grade 1 and 2. They included
21 fatigue, nausea, chills, fever, headache, and throat
22 irritation previously described with rituximab infusion.

23 There was no difference in adverse events
24 between patients who were less than 65 years of age and
25 greater than 65 years of age.

1 This bar graph looks at only the phase III
2 randomized trial patients and, in particular, displays the
3 most frequent nonhematologic adverse events in the Zevalin
4 arm in yellow and in the rituximab control arm in orange.
5 This center vertical line divides grade 1 and 2, which is
6 on the left, and grade 3 and 4, which is on the right.
7 Initially you can see that there are very few grade 3 and 4
8 nonhematologic adverse events.

9 With regard to grade 1 and 2 events, there were
10 more events of nausea, vomiting, abdominal pain, cough, and
11 dizziness and dyspnea, particularly in anemia patients, on
12 the Zevalin arm. There were more events of pruritus and
13 angioedema on the rituximab arm.

14 This graph depicts whole blood counts over
15 time. In yellow is hemoglobin. This is the median
16 hemoglobin for 349 patients. The yellow dotted horizontal
17 line is a hemoglobin of 10. This red line is the platelet
18 count for 349 patients, the median, and this red horizontal
19 line is a platelet count of 50,000. The green line is the
20 absolute neutrophil count median, and the green dotted
21 horizontal line is an absolute neutrophil count of 1,000.

22 This is a scatter plot showing all blood counts
23 on all 349 patients. There's a gathering of the data in
24 what appears to be vertical lines because most blood counts
25 were taken on weekdays and not weekends.

1 You can see that with regard to absolute
2 neutrophil count, there's a trend downward with a nadir at
3 week 9 and subsequent recovery. 5 percent of patients
4 recovered to an absolute neutrophil count over 1,000
5 following the week 13 period. After week 13, patients who
6 had recovered were not obligated to have blood counts
7 drawn, so many of the recovered patients disappear on this
8 graph following this line. There were 4 patients who did
9 not recover. They included 2 patients who died, one of
10 lymphoma and one of an event that I will discuss in a few
11 minutes, and 2 patients who remain neutropenic and
12 asymptomatic.

13 This is a scattergram of all platelet counts on
14 349 patients over time. Again, you see there's a trend
15 downward with a nadir at week 7 and then recovery. Again,
16 those patients who have recovered don't have their platelet
17 counts taken, for the most part, after the 91st day here,
18 or 13th week. 3 percent recovered their platelet counts to
19 50,000 after week 13, and again the 4 patients, 2 who died
20 and 2 who have not recovered their counts. Patients who
21 went on to subsequent therapy had blood counts no longer
22 displayed in this graph after subsequent therapy.

23 This is the method that we used at the request
24 of the FDA to determine duration of hematologic toxicity.
25 This arrow here that I'm pointing to is the first date of

1 grade 3 or 4 hematologic toxicity, and this arrow here is
2 the last date of grade 3 or 4 hematologic toxicity. We
3 determined duration by going to the blood count prior to
4 the first date in grade 3 or 4 and looking at the blood
5 count following the last blood count in grade 3 or 4, and
6 this was the duration of hematologic toxicity. This is 1
7 week in this interval and another week in this interval for
8 most patients.

9 The median nadir absolute neutrophil count for
10 the entire population was 800 in ANC. 28 percent of
11 patients had an absolute neutrophil count grade 3 nadir,
12 and 30 percent had a grade 4 nadir. Using the method that
13 I just described, the median days within grade 3 or 4 only
14 for those patients who had a grade 3 or 4 nadir was 22.

15 The median platelet nadir was 41,000. 52
16 percent of patients had grade 3 platelet nadirs. 10
17 percent had grade 4 platelet nadirs, and the median days
18 within grade 3 or 4 for patients who had grade 3 or 4
19 platelet nadirs, using the method I just described, was 24.

20 Median hemoglobin was 10.5, 14 percent grade 3
21 and 3 percent grade 4 nadirs, with median number of days,
22 using the same method, of 14.

23 There was no difference in hematologic toxicity
24 for patients less than 65 years of age or patients greater
25 than 65 years of age.

1 We also conducted a phase II study that looked
2 at dose reduction in patients who were mildly
3 thrombocytopenic at baseline, in other words, those
4 patients with poorer bone marrow reserve, more damage from
5 prior chemotherapy, or radiation. In these patients,
6 similar to slightly worse hematologic toxicity occurred
7 even though the patients received a 25 percent less dose.

8 Grade 3 and 4 hematologic toxicity correlated
9 with the percent bone marrow involvement. This was not
10 surprising because the more bone marrow involvement, the
11 more targeting of the Zevalin to the marrow. It also
12 correlated with the number of prior therapies and whether
13 the patient had purine analogs in the past.

14 Despite myelosuppression, the clinical
15 consequences of myelosuppression were not great. This
16 trial allowed growth factors to be used and transfusions to
17 be given at the physician's discretion. Only 18 percent of
18 patients were given growth factors. 13 percent were given
19 G-CSF and 8 percent were administered erythropoietin. 20
20 percent received a red blood cell transfusion and 22
21 percent received a platelet transfusion. However, there
22 were only 2 percent of patients who experienced grade 3 to
23 5 bleeding events.

24 The incidence of infection is displayed in this
25 table. Looking at any grade infection, in the integrated

1 safety experience of 349 patients, there were 29 percent
2 who had any grade infection. Only 5 percent of these were
3 grade 3 or 4. Only 7 percent of patients were hospitalized
4 with infection.

5 Looking at the phase III randomized trial, 43
6 percent of the patients in the Zevalin arm and 20 percent
7 in the rituximab arm had any grade of infection. The
8 excess infections in the Zevalin arm were predominantly
9 urinary tract infections and upper respiratory infections.
10 Only 7 percent of patients on the Zevalin arm had a grade 3
11 or 4 infection, and 7 percent were hospitalized with
12 infection. None of the patients on the rituximab arm had a
13 grade 3 or 4 infection, and only 1 percent was hospitalized
14 with infection. This was during the 13-week treatment
15 period defined as 12 weeks following the Zevalin
16 administration.

17 In the follow-up period, which was defined as
18 from 13 weeks up to 4 years or when the patient went off
19 study for progression of disease, there were 10 percent any
20 grade infections in both arms. On the Zevalin arm, 4
21 percent of patients had a grade 3/4 infection which
22 required hospitalization; on the rituximab arm, 1 percent
23 which required hospitalization.

24 Median B-cells recovered to normal by month 6.
25 Median T-cells remained normal. Median IgG and IgA

1 remained normal. Median IgM, which began at very low
2 normal at baseline, had a transient decline but recovered
3 by month 6. The development of human anti-mouse antibody
4 occurred in 1.4 percent of patients after treatment, and
5 the development of human anti-chimeric antibody in 0.5
6 percent of patients.

7 5 patients have developed myelodysplasia or
8 acute myelogenous leukemia out of 349, for a raw total of
9 1.4 percent. Myelodysplasia or acute myelogenous leukemia
10 developed from 4 years to 14 years post-diagnosis in these
11 5 patients and from 8 months to 34 months post-Zevalin in
12 these 5 patients, although this 1 patient who was diagnosed
13 at 8 months in retrospect had blasts in the peripheral
14 blood at week 4 after Zevalin.

15 All of these patients had extensive alkylator
16 therapy in the past from 11 months to 18 months to 28 to 21
17 months of alkylator therapy, and this patient who could not
18 have alkylator therapy quantitated had had prior
19 chlorambucil, CHOP, ProMace-CytaBOM, and FAMP.

20 Chromosomal abnormalities were found in the 4
21 patients where they were looked for. In 3 of these
22 patients, they were chromosomal abnormalities that have
23 been described with chemotherapy-associated myelodysplasia
24 and AML.

25 This table displays the annualized rate for

1 time to development of myelodysplasia or AML. The Kaplan-
2 Meier estimate from date of diagnosis was 0.6 percent and
3 from date of first infusion of Zevalin, actually rituximab
4 in the Zevalin regimen, was 1.1 percent. The number of
5 events per person-years was 0.3 percent from date of
6 diagnosis and 1.2 percent from date of first infusion. The
7 literature quotes in 1,100 patients a 4 to 8 percent
8 incidence in patients who have not had high-dose therapy
9 with stem cell or bone marrow transplant rescue and a 1 to
10 1.5 percent per year for a 2- to 9-year incidence.

11 There have been 70 deaths among the 349
12 patients to date. 56 deaths have occurred secondary to
13 progression of non-Hodgkin's lymphoma. 2 patients died in
14 neutropenic sepsis following additional chemotherapy. The
15 5 patients who developed myelodysplasia or AML have died.

16 There have been two treatment related deaths.
17 These were both traumatic intracranial hemorrhages in
18 patients at platelet nadir. In one case the patient was
19 also on therapeutic Coumadin for a history of chronic DVT
20 and was taking self-prescribed ibuprofen.

21 There were 5 deaths that were due to unrelated
22 or pre-existing illnesses. These included the following:
23 pneumonia at 16 months post Zevalin, occurring when the
24 patient was receiving CHOP chemotherapy plus rituximab; a
25 patient who died of COPD after CVP therapy 29 months

1 following Zevalin; a patient who died of respiratory
2 failure, 2.7 months following Zevalin. This patient had
3 preexisting idiopathic pulmonary fibrosis and had been on
4 escalating doses of azathioprine. A patient who had a
5 history of coronary artery disease, a coronary artery
6 bypass graft times 3, hypertension, CHF, and COPD died of a
7 cardiac arrest at 2.4 months following Zevalin. And a
8 patient who was oxygen dependent when they came onto study
9 and on 10 liters the day that they received the Zevalin
10 therapy died at week 1.

11 The question has been asked as to whether
12 patients can receive subsequent chemotherapy in the event
13 of relapse following Zevalin. 139 of our patients have
14 received subsequent chemotherapy following relapse.
15 Response assessment was available for 40 patients. The
16 others were still undergoing chemotherapy. Of those 40
17 patients, 50 percent responded to various types of
18 subsequent therapy, and please note that some patients have
19 been treated with single agent purine analogs and also with
20 other aggressive therapies like ESHAP, DHAP, ICE, ProMACE-
21 CytaBOM, CHOP-Bleo, and fludarabine-containing
22 combinations, as well as transplantation and CHOP. When we
23 look on the two arms for the Zevalin-treated patients and
24 the rituximab-treated patients, there is only a small
25 number of patients who have gone on to chemotherapy where

1 response assessment is available, but there are similar
2 rates of response in those two groups of patients.

3 10 patients have received transplants following
4 Zevalin. Nine were autologous and one was allogeneic. 6
5 of the patients who had autologous transplants had their
6 stem cells collected after Zevalin. 2 additional patients
7 have had stem cells collected but have not yet undergone
8 their transplants.

9 In conclusion, Zevalin represents a new class
10 of targeted therapy. It is well-tolerated outpatient
11 therapy and it is completed in 8 days. Adverse events are
12 primarily hematologic, and their severity is related to the
13 baseline platelet count, which is a surrogate for prior
14 damage from prior chemotherapy and external beam radiation,
15 and to the percent bone marrow involvement, which is a
16 surrogate for specific targeting.

17 Nonhematologic adverse events have been
18 predominantly grade 1 and 2. There has been a low
19 incidence of serious infection, and treatment-related
20 mortality has been less than 1 percent.

21 The incidence of human anti-mouse and human
22 anti-chimeric antibody is less than 2 percent.

23 There have been rare cases of myelodysplasia
24 but within the expected rate for this patient population.

25 Clinical benefit has been established. The

1 overall response rate is statistically higher than the
2 rituximab control in the randomized phase III study. There
3 have been trends towards longer time to progression in the
4 follicular patients and in the patients who achieved
5 complete response, as well as longer time to next therapy
6 in all patients.

7 Significant activity has been demonstrated in a
8 heavily pretreated, bulky disease, rituximab-refractory
9 population.

10 The median time to progression in the
11 responders, both in the phase I/II trial and in the
12 randomized phase III trial, has been 15.4 months.

13 I hope that the data that I've shown you today
14 has convinced you that Zevalin therapy represents a
15 clinically meaningful advance for patients with relapsed or
16 refractory, low-grade, follicular, or CD20 positive
17 transformed non-Hodgkin's lymphoma, as well as patients
18 with rituximab-refractory non-Hodgkin's lymphoma. I thank
19 you for your attention.

20 DR. NERENSTONE: Thank you very much.

21 We're going to open it now for questions from
22 the committee to the sponsor. Dr. Sausville.

23 DR. SAUSVILLE: Could you clarify how you would
24 see the indium portion of the regimen as playing into the
25 use in the field, so to speak, and how one outcome or

1 another with the indium would contribute to subsequent use
2 of the yttrium-labeled product?

3 DR. WHITE: Yes. In our phase I/II and even in
4 our phase III randomized trial, at the recommendation of
5 the FDA, we included dosimetry. We believe that dosimetry
6 is absolutely mandatory in the phase I/II and phase II
7 development of a radioimmunotherapy. We included the
8 dosimetry in order to summarize the radiation absorbed
9 doses to normal organs.

10 Indium-labeled Zevalin was used as a gamma
11 emitter in order to be able to produce the images and to
12 obtain that dosimetry. Since we discovered and were able
13 to confirm the clinical parameters were sufficient for
14 dosing and the dosimetry estimated radiation absorbed doses
15 to normal organs were acceptable in all patients, it is no
16 longer necessary to do complex dosimetry.

17 However, we now do indium-labeled Zevalin
18 imaging, and an image is obtained at two or three time
19 points, as was described in the presentation. That image
20 is examined to look for any evidence of contraindication
21 for proceeding to therapy. The types of areas that one
22 might look for there would be total urinary obstruction or
23 altered biodistribution, something like that.

24 DR. SAUSVILLE: Right. So, I guess then you
25 would have criteria written in to how it would be used

1 | potentially that would have fairly precise definitions of
2 | those sorts of criteria?

3 | DR. WHITE: Yes, we do, and we have included
4 | them in our protocols and would also include them, of
5 | course, in a package insert. If you're interested, we can
6 | show those criteria.

7 | DR. SAUSVILLE: In your experience, have you
8 | seen, shall we say, that all tumors tend to label or image
9 | as well as others? Is there a range of, shall we say,
10 | imaging that might suggest that this could be a variable in
11 | response?

12 | DR. WHITE: Let me answer that first, and then
13 | we'll get into the imaging criteria.

14 | First of all, let me say that we did tumor
15 | dosimetry in selected patients with selected tumors. It's
16 | more difficult to do tumor dosimetry logistically because
17 | the entire perimeter of the tumor is not always visible.
18 | Tumors in all patients with low-grade, follicular, or
19 | transformed lymphoma image. However, we know, from doing
20 | tumor dosimetry, that larger tumors have a tendency to get
21 | a trend towards a lower dose than smaller tumors do. The
22 | homogeneity appears approximately the same.

23 | Joining me here at this microphone is Dr. Bryan
24 | Leigh, who's a radiation oncologist and worked with our
25 | dosimetry, and he's going to present the imaging

1 requirement and might be able to comment a little bit
2 further with regard to the intensity of targeting with
3 regard to the indium-labeled Zevalin.

4 Before you start, I just wanted also to
5 introduce Dr. Pratik Multani, who's a medical oncologist
6 and was our safety officer for the past two years, who will
7 join me with regard to safety questions.

8 Bryan.

9 DR. LEIGH: Thank you.

10 Let me just review what we see as the purpose
11 of imaging. It's a visual evaluation of the Zevalin
12 biodistribution, and that should be differentiate from
13 complex dosimetry where you actually calculate the
14 radiation absorbed dose to an organ. So, it's similar to
15 an Oncoscint scan or a bone scan where you're looking at
16 the image and making a decision based on the visual
17 interpretation.

18 We've been asked by the FDA to include this as
19 a safety measure that may detect unexpected areas of high
20 radioactivity uptake that may indicate that the patient
21 should not proceed to the yttrium-labeled Zevalin.

22 As you've seen, the indium is given
23 approximately 1 week before the yttrium-labeled Zevalin and
24 following an infusion of rituximab. The first image is
25 obtained between 2 and 24 hours after the indium, the

1 second one between 48 and 72 hours after the indium, and
2 then an optional third image to resolve any ambiguities.

3 In a second I'll show you what is expected to
4 be seen on the images, and we'll make this available
5 through our medical information department. The
6 radioactivity is typically seen in the blood pool on the
7 first image, less so on the second image, moderately high
8 to high uptake in the normal liver and the spleen, and low
9 uptake in the lungs, kidneys, urinary bladder, and bowel.

10 There's an example of this on the next slide.
11 Here you can see what a typical patient's indium scan would
12 look like. There are anterior and posterior scans at three
13 time points. The first time point you can see the activity
14 in the blood pool, as evidenced by the blood vessels and
15 the cardiac shadow. Later you see targeting of the
16 activity to an abdominal mass and to inguinal lymph nodes
17 as well as posterior cervical lymph nodes and even more
18 targeting on the later image.

19 Working with the FDA, we've identified some
20 potential items that could be discovered on the indium
21 scan. Potential things that might indicate that the
22 patient should not proceed to treatment might be if the
23 blood pool is not visualized on the first image, with rapid
24 clearance to the liver, spleen, and marrow by the
25 reticuloendothelial system, that may indicate that the

1 patient has an unknown HAMA causing rapid clearance. A
2 second item is if there was increased uptake in the kidneys
3 or the bladder, it may identify urinary tract obstruction,
4 and also high uptake in the lungs or kidney, more intense
5 in the liver on the second image might indicate that
6 there's disease in the lungs or kidneys that we were not
7 aware of.

8 I'd just like to end by pointing out that we
9 have observed any of these altered biodistributions to
10 date, but they still remain a possibility and we would like
11 to include the imaging as a safety measure.

12 DR. WHITE: These are the criteria that are in
13 our trials and would be included in the labeling.

14 DR. SAUSVILLE: So, there would be quantitative
15 limits of how much could be taken up by these other sites
16 then.

17 DR. LEIGH: No, there would not be quantitative
18 limits.

19 DR. WHITE: This is a visual --

20 DR. SAUSVILLE: This is what I'm a little
21 unclear about. In other words, you're saying a little bit
22 of this, a little bit of that. How would we use this in
23 practice I guess?

24 DR. WHITE: In actuality in our experience now
25 with 489 patients and 200 patients where we have dosimetry,

1 again we found acceptable radiation absorbed doses to
2 normal organs in all cases. But we have only treated those
3 489 patients that have been submitted in the BLA. Of
4 course, with a broader experience sometimes you can pick up
5 something there at a very low incidence or very rare
6 frequency. The imaging is only being included as an extra
7 safety step for the nuclear medicine physician to take a
8 look and make sure there's no dramatic altered
9 biodistribution or dramatic complete urinary obstruction.

10 We would be prepared to further collect data on
11 imaging as time went on to see how useful it is as we get
12 into a broader, larger patient population.

13 DR. SAUSVILLE: Again, my comment is I think it
14 was a really good thing to do in the initial studies and
15 the dosimetry was useful. It's just that I think one would
16 have to carefully consider what level of complexity it adds
17 to its actual use potentially in a widespread way in
18 contrast to what we learn.

19 Turning to another question that occurred to
20 me, the patient population that you studied in your phase
21 III's had not had prior bone marrow transplantation, as I
22 understand it, with any type of preparative regimen.

23 DR. WHITE: That is correct.

24 DR. SAUSVILLE: So, do you foresee that
25 population as needing to be either studied in greater

1 detail or perhaps have some level of stratification in
2 subsequent studies? How do you propose to deal with that
3 substantial fraction of the population?

4 DR. WHITE: Absolutely. Our proposal would be
5 that the labeling of this product at commercialization
6 would prohibit the use in patients who have had prior bone
7 marrow transplant. However, we are interested in further
8 studying patients with prior bone marrow transplant or stem
9 cell rescue with high-dose therapy as to whether those
10 patients can receive potentially a lower dose or what the
11 proper approach to those patients is. Actually Dr. Julie
12 Vose in Nebraska is just beginning an investigator-
13 initiated trial which will examine exactly this question.
14 I think she just has entered her first patient or two.

15 DR. NERENSTONE: Dr. Blayney.

16 DR. BLAYNEY: Thank you. I have three
17 questions.

18 Why do you think the incidence of HAMA, human
19 anti-mouse antibody, is so low in your patients?

20 DR. WHITE: Our speculation is as follows.
21 When we had our very first phase I study in 1993, that
22 study differed -- and by the way, the safety from that
23 study was not integrated in the 349 patients because the
24 study used ibritumomab rather than rituximab as the
25 pretreatment cold antibody. It also dose escalated the

1 | myeloablative ranges and had some other differences as
2 | well.

3 | In that study, we had about a 12 percent HAMA
4 | rate. When we started using rituximab as the pretreatment
5 | cold antibody, our expectation was that we would deplete B-
6 | cells effectively and that there might be a lower HAMA rate
7 | because of that B-cell depletion.

8 | In actuality since that time with all of those
9 | patients that we have described, there has been a less than
10 | 2 percent HAMA rate. So, we believe that it may very well
11 | be due to the prior rituximab. Of course, lymphoma
12 | patients develop HAMA at a lower rate than do solid tumor
13 | patients, but other trials using murine antibodies in
14 | lymphoma patients with other agents have described up to a
15 | 66 percent HAMA rate. So, I think it is the rituximab
16 | given prior to the Zevalin radiolabeled antibody.

17 | DR. BLAYNEY: What guidance do you propose to
18 | give to physicians who may want to treat patients who have
19 | had previous external beam radiation therapy to bulk
20 | disease or who may ask about retreating patients who have
21 | previously received your labeled monoclonal?

22 | DR. WHITE: Let me take those separately.

23 | With regard to patients who have had previous
24 | external beam radiation therapy, our only guideline which
25 | would be in the package insert would be not to include

1 patients who have had radiation therapy to more than 25
2 percent of their active marrow. Now, I must tell you
3 realistically that was the one thing in our trials that
4 didn't seem to become a problem with regard to excluding
5 patients. I've only heard of a couple of patients who were
6 excluded on that basis.

7 With regard to soft tissue radiation therapy,
8 we will include in the package insert an actual table of
9 the mean, median, and also range of radiation absorbed
10 doses by millicurie administered so that a patient who had
11 received external beam could have his radiation oncologist
12 be aware of that information. We have not found a problem
13 with regard to prior external beam radiation therapy or,
14 for that matter, patients who have had subsequent external
15 beam radiation therapy. The agency asked us specifically
16 to look for any adverse events that occurred with
17 subsequent external beam radiation therapy and a specific
18 CRF form was designed for that purpose, and we have seen no
19 problems up to this time.

20 The second part of your question was with
21 regard to retreatment. We do not advocate retreatment at
22 this time, and again in a package insert it would
23 specifically say that this is for single course therapy
24 only. Retreatment is another area that needs to be
25 studied, and actually the National Cancer Institute, under

1 a clinical trials agreement that they have with us, has
2 moved ahead and approved Dr. Witzig and Dr. Wiseman at Mayo
3 Clinic to look at a retreatment trial. That is not a
4 retreatment trial at relapse but rather a retreatment trial
5 that would look at a second dose of therapy approximately
6 12 weeks or so out when the patient was hematologically
7 recovered and would be a dose escalation trial. But we
8 feel that there needs to be considerably more study before
9 we would have enough information to understand retreatment.
10 It would be excluded.

11 DR. BLAYNEY: Finally, could you expand a
12 little bit on the coordination? It strikes me if you're
13 obtaining a radioactive isotope from one vendor and a
14 monoclonal antibody from IDEC, getting these to places that
15 may not be as experienced as your investigative sites
16 represents a challenge for stability as well as preparation
17 in the radiopharmacy lab.

18 DR. WHITE: Right. It's actually less complex
19 than it seems. Most hospitals in the United States have a
20 relationship with a commercial radiopharmacy. That's the
21 radiopharmacy that brings them their technicium and their
22 indium and their gallium for their regular use every single
23 day. For all of those hospitals who have a relationship
24 with a commercial radiopharmacy, it would be the commercial
25 radiopharmacy probably who would call up and order. They

1 | would call one phone number. Once they called that phone
2 | number, a kit would be shipped -- this is a cold kit --
3 | from IDEC to the radiopharmacy and from our supplier of
4 | yttrium, at a different location, the yttrium would be
5 | shipped just like any other isotope by a radioisotope
6 | manufacturer to the same address to arrive on the
7 | appropriate day.

8 | For the indium component, however, since most
9 | of these radiopharmacies and hospitals have already
10 | relationships with the two suppliers of indium that are
11 | approved for supplying indium -- that would be approved and
12 | were in our clinical trials for supplying indium -- they
13 | would make a separate phone call to order the indium in the
14 | same way that they do for other indium needs.

15 | Then at the radiopharmacy would be the
16 | compounding of the product, which is about a 5-minute
17 | process. We have had experience now -- in fact, maybe we
18 | can bring up that radioincorporation slide -- with 533, I
19 | believe, radioincorporations at many hospital and
20 | radiopharmacy sites, I think 40 or 50 in this group, and 98
21 | percent of the doses, 523 out of 533, at these 40 sites
22 | exceeded the 95 percent release specification of the ITLC,
23 | which is a routine type of QC study at a radiopharmacy.
24 | The mean radiochemical purity is 98 percent with a standard
25 | deviation, and the median radiochemical purity was 98.6

1 | percent. So, in actuality this will be easier and less
2 | complex than it seems.

3 | DR. BLAYNEY: What about the stability after
4 | the isotope is mixed with the chelator?

5 | DR. WHITE: Yes. It is stable for 8 hours
6 | after it is radioincorporated, and that is, of course,
7 | within the time frame that it would be used. The
8 | radiopharmacy, if it was off-site -- it could be on-site,
9 | it could be off-site -- it would compound that morning and
10 | then, on its usual run or a special run, drive it up to the
11 | hospital or outpatient nuclear medicine department that it
12 | was being used at. And then it would be infused after the
13 | rituximab was completed, and the rituximab could be
14 | completed either at the oncologist's office and then the
15 | patient come to the nuclear medicine department for the
16 | Zevalin component, or if there were provisions and the
17 | usual approach was at the hospital, then that could be done
18 | there.

19 | DR. BLAYNEY: Thank you.

20 | DR. NERENSTONE: Dr. Pelusi.

21 | DR. PELUSI: My questions were along the same
22 | lines as Dr. Blayney's in terms of this coordination. So,
23 | you just mentioned then that the patient could come into
24 | the oncologist's office, then go to the nuclear medicine
25 | department, and then return back to the oncologist's

1 office. Is that how you see that occurring?

2 DR. WHITE: Yes. Since the oncologist really
3 has experience administering rituximab and has all the
4 provisions for administering rituximab, the patient would
5 go to the oncologist's office. They would have the
6 rituximab infusion. Then they could either be hep-locked
7 or the line could be taken out, and they would go across
8 the street or down the street, or whatever, to the nuclear
9 pharmacy where they would receive the indium-labeled
10 Zevalin on the first day and seventh, eighth, or ninth day
11 the yttrium-labeled Zevalin in the same way. Of course, we
12 would expect that the oncologist would be the one following
13 the patient after administration of the agent.

14 DR. PELUSI: I was just again looking at the
15 safety issues in terms of some of the smaller community
16 hospitals when many people from the oncologist's office are
17 not necessarily in the closest proximity to some of the
18 hospitals in terms of timing as well. That could be an
19 issue.

20 DR. WHITE: Yes. The majority of our patients
21 had treatment with the radiolabeled Zevalin within 4 hours
22 of the completion of the infusion of the rituximab. We had
23 a small experience at a greater time interval, but at least
24 4 hours are reasonable.

25 DR. NERENSTONE: Dr. Przepiorka.

1 DR. PRZEPIORKA: Thank you.

2 Can you tell us a little about the short-term
3 or, if you have information, the long-term effects of the
4 radiation dose to the testes?

5 DR. WHITE: Yes, I can. First of all, let me
6 start by saying that our experts, both Dr. Stabin and Dr.
7 Sparks at Oak Ridge Institute of Science and Education, who
8 did our dosimetry, as well as Dr. Wiseman, who is both an
9 oncologist and nuclear medicine physician and professor at
10 Mayo Clinic, tell us that the methods that we use
11 overestimate the dose to the testes because they assume
12 that the organ that you're estimating is in the center of
13 the body, and they assume that there has been attenuation
14 by the tissues on top of the organ. Well, of course, that
15 is not the case with the testes. I think that we may, as
16 time goes on, do some more complex dosimetry to better get
17 at that dose.

18 That dose, of course, is a significant dose,
19 although low-dose biologic radiation from an isotope is not
20 the same as external beam. Still, with that dose, one
21 might ask the question as to whether there would be an
22 effect on sperm or on hormone levels. A lot of lymphoma
23 patients who have had chemotherapy beforehand will be
24 oligospermic to begin with and may have lower levels of
25 androgens.

1 However, what we proposed to do is, in some of
2 our just planned and newly begun investigator-initiated IND
3 trials, to look at baseline both sperm counts and androgen
4 levels and look again after Zevalin to see if there's any
5 biological effect and if it's important to have any
6 therapeutic intervention in these patients.

7 DR. PRZEPIORKA: You have given us the dose of
8 the drug in millicuries per kilogram. Can you give us an
9 idea of how much antibody that is in mgs per kg?

10 DR. WHITE: Yes, I can. It's less than 2
11 milligrams of antibody.

12 DR. PRZEPIORKA: Your predose of Rituxan was
13 based on some studies you had done in the phase I/II, if I
14 read that correctly, where you found that with 100
15 milligrams per meter squared, you got 92 percent targeting
16 to the tumor. Then in your briefing document you said, so
17 we decided to use a dose of 250 milligrams per meter
18 squared, but in treatment you actually used 500 per meter
19 squared because they get two doses of a humanized antibody
20 very close together.

21 Do you have any dosimetry to determine whether
22 or not that huge dose of Rituxan you give before the
23 therapeutic dose reduces your targeting?

24 DR. WHITE: Yes. Let me answer that question
25 and maybe we can pull up the pretreatment antibody slide.

1 First of all, what we compared in our very
2 first phase I study was no pretreatment antibody. This was
3 done by Dr. Susan Knox at Stanford with 1 milligram per
4 kilogram, or approximately 70 milligrams, of cold
5 ibritumomab, and that was compared to 2.5 milligrams per
6 kilogram, or approximately 175 milligrams, of cold
7 ibritumomab. In that study, dosimetry and imaging did
8 improve with increasing pretreatment antibody dose.

9 Now, as I had said a little earlier, we wanted
10 to move to trying the rituximab rather than the ibritumomab
11 prior to the radiolabeled Zevalin. So, we began with a
12 similar dose of rituximab, about 170 milligrams, but this
13 time we were dosing in milligrams per meter squared just
14 because that is the convention for rituximab. So, 100
15 milligrams per meter squared. Then we escalated further to
16 250 milligrams per meter squared or 425 milligrams. Here
17 we saw no difference. So, in other words, there was an
18 improvement as we went up, but here there was a plateau, no
19 difference in dosimetry or imaging.

20 So, we needed to choose one of these doses in
21 order to improve biodistribution and minimize HAMA, and we
22 decided to choose the higher dose for a greater
23 contribution to therapeutic effect. But this was not just
24 a single dose. These were before each Zevalin dose in
25 every case, in this case, in this case, and in this case.

1 | So, this is what we had explored.

2 | Did that answer your question?

3 | DR. PRZEPIORKA: Directly. Thank you.

4 | You had indicated that there were several
5 | patients who had blood stem cells collected after Zevalin.
6 | Can you tell us a little bit about whether or not they were
7 | transplanted and whether or not they engrafted or whether
8 | or not they were actually able to collect stem cells after
9 | Zevalin?

10 | DR. WHITE: Yes. We know of 8 patients who
11 | have had stem cells collected after Zevalin to date, and 6
12 | have already been transplanted and all engrafted well. 2
13 | are waiting for the right time to undergo transplant. We
14 | have not heard of a single instance -- and we have inquired
15 | -- of a failure to be able to harvest stem cells. As I
16 | said, in those 6 patients who had stem cells harvested
17 | after Zevalin and 3 who had already had stem cells banked
18 | before they ever had Zevalin, all 9 of those patients
19 | engrafted well.

20 | DR. PRZEPIORKA: Finally, you included in your
21 | patients under the definition of refractory those who had
22 | no response to prior therapy, as well as those who failed
23 | within 6 months. Now, that is a common way to describe a
24 | refractory patient for standard chemotherapy, but it may
25 | not hold to be true with Zevalin. Are the response rates

1 | in those two groups the same?

2 | DR. WHITE: I actually have a slide on that
3 | too. That would be in the 106-06 trial, responders versus
4 | nonresponders. It was about a duration of response of
5 | about 4 months because we used a TTP of less than 6 months
6 | as our parameter, and we divided it down and took a look at
7 | that, rituximab nonresponders versus the ones who were the
8 | short responders with a TTP of less than 6 months. And
9 | there were comparable response rates, a slightly smaller
10 | number here, 51 percent versus 67 percent. In the
11 | rituximab responders group, though, there were 17 percent
12 | CRs and there were none in the rituximab nonresponders.
13 | So, there may be an effect there.

14 | DR. NERENSTONE: Dr. Levine.

15 | DR. LEVINE: Going to the transformed patients,
16 | you've got a total of 15 patients with transformed lymphoma
17 | and that's one of the indications you're interested in. On
18 | your randomized trial, the Rituxan group, 3 out of 4, which
19 | is interesting, 75 percent response rate on the Rituxan,
20 | not different than the Zevalin. Can you discuss that in
21 | terms of your request for indication here?

22 | DR. WHITE: Yes. Moving forward, when we
23 | planned that trial, we expected to have larger numbers of
24 | transformed patients. We did have transformed patients on
25 | our dose-reduced trial as well and just a couple in our

1 phase I/II trial, and you saw the total experience of those
2 15 patients with a 40 percent response rate and a 13.3
3 percent complete response rate. It is a small population
4 of patients, without question.

5 These patients, though, are very, very needy
6 patients. By one series, the median survival is 7 months,
7 so they transform and die rapidly. Some are chemotherapy
8 resistant. So, it may be that when a physician weighs the
9 potential risk and benefit of a treatment, as physicians
10 always do, that they may find in that type of a patient who
11 was critically in need of therapy that timing was critical,
12 that they may want to choose a therapy that had a higher
13 chance of a response and that that outweighed the toxicity.
14 So, we wouldn't want to preclude these patients, although
15 we certainly acknowledge that the body of evidence is
16 considerably smaller.

17 As far as the rituximab response, we were, of
18 course, pleased to see that the rituximab response was
19 good, but it was just 4 patients.

20 DR. LEVINE: Were any of those transformed
21 patients any of the patients who subsequently had bone
22 marrow stem cells or peripheral blood stem cells harvested,
23 or were any of those individuals those who had subsequent
24 chemo? And how did they tolerate that?

25 DR. WHITE: None were in the transplant group,

1 but I do not have at my fingertips what subsequent
2 chemotherapy they specifically had. We could maybe try to
3 take a look at that, and see if we can come up with
4 something by the end.

5 DR. LEVINE: Another question. Was there any
6 difference in the prevalence of HAMA in those who had
7 Rituxan prior in your trial with the Rituxan-refractory
8 patients? Any difference in the patients who received the
9 product after having had Rituxan earlier?

10 DR. WHITE: I see your question.

11 DR. LEVINE: Assuming that people will have
12 multiple such products over time.

13 DR. WHITE: Yes. Again, the patients who had
14 prior Rituxan, if they had developed an antibody to prior
15 Rituxan, it would have been a HACA, and that rate is known
16 to be less than 1 percent.

17 But across all trials, each time we
18 resummarized the HAMA rate, when we had some trials open
19 and some trials completed, sometimes not, ever since we
20 switched to rituximab, it has always been less than 2
21 percent, and I do not believe there was any preponderance
22 on any one trial.

23 DR. LEVINE: I'm sorry. One more. It was a
24 similar kind of question as to the real Rituxan resistance.
25 You also defined chemotherapy resistance as resistance or a

1 response less than 6 months. If you look at the patients
2 who really were resistant to chemo and their subsequent
3 response to Zevalin, do you have those data?

4 DR. WHITE: I'm sorry. I do not have those
5 data.

6 DR. LEVINE: Thank you.

7 DR. NERENSTONE: Dr. Sledge.

8 DR. SLEDGE: Three questions. First, can you
9 show us survival curves in the randomized trial?

10 DR. WHITE: Yes, I can. Can we bring up
11 survival curves?

12 Thankfully, there have not been that many
13 deaths yet on the randomized trial, but we do have survival
14 curves. You have to temper your examination of these
15 survival curves, which you can see are exactly the same, by
16 the fact that over half of the patients on the rituximab
17 arm who did not respond to rituximab went on to receive
18 Zevalin on another trial.

19 DR. SLEDGE: Thank you.

20 Second, do you have any data on crossover
21 response to rituximab for a patient who has had prior
22 Zevalin?

23 DR. WHITE: I am aware of a couple of patients
24 who have had prior Zevalin and have gone on to rituximab
25 who have responded and also a couple who have not. I don't

1 have any definitive, quantitative data on that.

2 We did collect information on the first
3 subsequent therapy, but not all subsequent therapies. And
4 the numbers of patients who had rituximab as their first
5 subsequent therapy was low.

6 DR. SLEDGE: Third, actually a question for
7 some of your investigators here. This committee always
8 wrestles with the issue of clinical benefit, and typically
9 we've not thought of response per se as being a clinical
10 benefit but rather a survival endpoint or some symptomatic
11 benefit. What's the clinical benefit here, if I may ask
12 some of your investigators?

13 DR. WHITE: Yes. Let me open and then I would
14 like to call some of our investigators to the --

15 DR. SLEDGE: Actually I'd like to hear from the
16 investigators.

17 DR. WHITE: Okay. Thank you. I'm sorry. Dr.
18 Witzig is here. Dr. Witzig from Mayo Clinic has experience
19 with more than 100 and now with the open label trial
20 approaching 150 patients, and I think maybe he can speak to
21 net clinical benefit, maybe followed by Dr. Leo Gordon who
22 also has a very large patient experience.

23 DR. WITZIG: I think the big clinical benefit
24 is it's a single-dose therapy, and these patients were all
25 heavily pretreated and many of them have had many

1 chemotherapy recipes. Now they come in and get a one-day
2 treatment with virtually no side effects like nausea,
3 vomiting, hair loss, and the next day they go back to work
4 and go back to their usual activities. So, from a quality
5 of life standpoint and patient acceptance standpoint, it's
6 been remarkable.

7 In addition, we're seeing a lot of complete
8 remissions, much more than Rituxan, 30 percent versus 16
9 percent. As you've seen on some of those curves, those CR
10 patients are really doing quite well for a number of years
11 and not requiring any further treatment.

12 So, I see it as a major advance in the
13 treatment of lymphoma. It offers these people something
14 new and it's very well-tolerated and a very high patient
15 acceptance rate with a high CR rate.

16 DR. WHITE: Thank you.

17 And Dr. Leo Gordon, who is Cancer Center
18 Director and Chief of the Department of Hematology and
19 Oncology at Northwestern University.

20 DR. GORDON: Thank you. I can pretty much echo
21 Dr. Witzig's comments. I think these are patients who are
22 progressing on prior therapy, symptomatic, and when you're
23 seeing a 30-some percent complete remission rate and an
24 overall response rate of 70 to 80 percent, those are
25 symptoms that are disappearing. These are people who are

1 requiring therapy and with really 2 weeks of treatment with
2 remission that lasts for a long time. There is significant
3 clinical benefit from the investigator and from the
4 clinical oncologist standpoint with what I think is fairly
5 acceptable minimal hematologic toxicity. So, I think
6 there's a significant benefit.

7 DR. WHITE: Thank you.

8 Maybe Dr. Sandra Horning, who is the Chair of
9 the Lymphoma Section of the Eastern Cooperative Oncology
10 Group, could also approach the microphone.

11 DR. HORNING: Well, I would really echo the
12 comments that have been made previously and just encourage
13 you to think about the patients with these disorders and
14 primarily the low-grade lymphoma patients for whom, it is
15 true, we have not defined curative therapy, but the
16 opportunity to have a series of therapeutic options that
17 are effective that can be used sequentially over time,
18 particularly those that offer good quality of life are very
19 meaningful.

20 In fact, there are data from our own
21 institution that indicate that in the 1990s and up to the
22 present that patients with follicular lymphoma are actually
23 living longer without a defined curative therapy, and I
24 think it's a tribute to the entre of monoclonal antibodies.
25 I think that Zevalin adds to this armamentarium.

1 DR. SLEDGE: Thank you.

2 DR. NERENSTONE: Dr. Albain.

3 DR. ALBAIN: I've been in the question queue
4 for a while and my question was the same as Dr. Sledge's
5 regarding clinical benefit.

6 So, just to follow up, are you seeking
7 conventional approval or accelerated approval for this
8 application?

9 DR. WHITE: Maybe our regulatory staff member,
10 either Leslie Shelly or Alice Wei, can address the
11 regulatory approval.

12 DR. SHELLY: We will be seeking conventional
13 approval.

14 DR. ALBAIN: So, with that in mind, do you have
15 any hard quality of life data or other supportive data to
16 go along with what we've heard from the three investigators
17 regarding translation of this very remarkable response rate
18 into other measures of clinical benefit?

19 DR. WHITE: If we can bring up a quality of
20 life slide.

21 We attempted to have a quality of life
22 secondary or tertiary endpoint and collected FACT-G quality
23 of life instrument data. Unfortunately, compliance was not
24 100 percent. Only 45 patients out of the 73 on the Zevalin
25 arm and 36 out of the 70 on the rituximab arm actually

1 completed baseline and follow-up questionnaires so that we
2 could compile this data.

3 The baseline level on FACT-G was lower for the
4 Zevalin arm than the rituximab arm. In both cases, there
5 was an improvement in FACT-G. The improvement was
6 statistically significant for the Zevalin arm, not for the
7 rituximab arm, but we did not emphasize this data as we
8 felt, along with our discussions with the agency, that
9 these incomplete samples were not adequate to truly focus
10 on this data as a quality of life endpoint.

11 DR. NERENSTONE: Dr. George.

12 DR. GEORGE: I have a couple of design and
13 results questions. On the TTP endpoint, I believe it was
14 stated that this was a secondary endpoint looking at
15 equivalence. The problem I see, was this defined ahead of
16 time? What did you mean by equivalence?

17 DR. WHITE: Yes, it was prospectively defined.
18 At the time that this phase III protocol was designed, in
19 collaboration and in agreement with the FDA, we chose
20 overall response rate as an adequate and appropriate
21 primary endpoint. At that time we knew that the target
22 population of 150 patients would not permit a comparison of
23 TTP, so TTP in all and TTP in responders was a secondary
24 endpoint. And it was specifically stated in the
25 statistical section of the protocol that the trial was not

1 | powered to compare TTP, but instead that we sought clinical
2 | equivalence, not statistical equivalence, and that was
3 | defined in the protocol prospectively as a median plus or
4 | minus 1.5 months. So, it was felt at that time that the
5 | overall response rate was an appropriate endpoint.

6 | DR. GEORGE: I was just doing some back-of-the-
7 | envelope calculations. You haven't ruled out a decrement
8 | in this, of course. You haven't ruled out a decrement in
9 | the time to progression by the usual kind of standards.

10 | The other question I have concerns the
11 | refractory trial. There also you had a target overall
12 | response rate of 35 percent.

13 | DR. WHITE: Yes, and that was just chosen
14 | clinically. Just in discussion with our 17 investigators
15 | who were involved in that trial, we said in a rituximab-
16 | refractory population, what type of a response rate would
17 | you like to see as a clinically meaningful, important
18 | response rate in the rituximab-refractory population, and a
19 | target of 35 percent came from that discussion.

20 | DR. GEORGE: So, it was historical just by
21 | survey.

22 | DR. WHITE: Yes, in terms of known response
23 | rates in this relapsed and refractory disease.

24 | DR. NERENSTONE: Ms. Krivacic.

25 | MS. KRIVACIC: Can you talk about the AEs, or

1 | adverse events, that you possibly saw during some of the
2 | growth factors that were given to the patients for
3 | supportive care?

4 | DR. WHITE: I'll ask Dr. Multani to address
5 | that question.

6 | DR. MULTANI: 18 percent of patients received
7 | some sort of growth factor after Zevalin therapy. 13
8 | percent of patients received a neutrophil growth factor,
9 | G-CSF, and 8 percent of patients received erythropoietin.
10 | Some patients received both. We didn't have adverse events
11 | that were attributable to the growth factors themselves,
12 | however.

13 | DR. NERENSTONE: I have a brief question. I'm
14 | a little bit concerned about the thrombocytopenia that
15 | we're going to be seeing. I think the community
16 | oncologists are very comfortable with neutropenia and we
17 | have lots of antibiotics and we know what to do with that.
18 | The mean nadir platelet counts of 41,000 in your
19 | nonhematologically impaired patients and down to 24,000 or
20 | significant numbers for a prolonged duration would make
21 | some of us in the community concerned.

22 | In addition, your two fatalities were
23 | intracranial hemorrhage.

24 | Are you going to have any recommendations about
25 | concomitant Coumadin therapy in these patients?

1 DR. WHITE: Yes. In fact, after the events of
2 intracranial hemorrhage, after the first one, we notified
3 the physicians of that event, and when the patient had the
4 traumatic intracranial hemorrhage who was on Coumadin and
5 unfortunately also on self-prescribed ibuprofen, we did
6 amend all of our trials to exclude patients who were on
7 Coumadin. And we would propose that in the labeling we
8 could either exclude or at least certainly caution
9 physicians that, if at all possible, patients should be
10 taken off of Coumadin at least at the time when the nadir
11 is expected.

12 The nadir, by the way, is pretty reliable in
13 terms of the timing down and timing up, so it can be
14 anticipated.

15 DR. NERENSTONE: Dr. Taylor.

16 DR. TAYLOR: Along those lines, though, did you
17 give prophylactic antibiotics during this time? You have a
18 very high percentage of grade 3 and 4 neutropenia.

19 DR. WHITE: Prophylactic antibiotics was at the
20 discretion of the physician, and there were 10 percent of
21 patients who were given prophylactic antibiotics.

22 DR. NERENSTONE: Dr. Blayney.

23 DR. BLAYNEY: It strikes me that one other way
24 to accomplish what you have set out here is, because you
25 got some response rate with your humanized antibody,

1 rituximab, and you're shrinking bulk tumors with radiation,
2 if I say to you why can't I get the same response with
3 rituximab/external beam radiation and not have my patient
4 pay the price of a 20 percent chance of platelet
5 transfusion and 20 percent chance of red cell transfusion
6 and the nuisance of growth factors, et cetera.

7 DR. WHITE: I might ask one of our
8 investigators to also address this. But with rituximab, of
9 course, there is a 48 percent response rate and a 6 percent
10 complete response rate. External beam radiation to a
11 single mass or more than one mass would be expected to
12 further shrink that. But it would not cause 30 percent of
13 the patients to enter complete remission most likely.

14 Maybe Dr. Witzig or one of the other
15 investigators might want to address that specific question.

16 DR. WITZIG: Well, I think almost 80 to 90
17 percent of our patients had stage 3 to 4 disease and a lot
18 of them had marrow involvement. So, giving them external
19 beam radiation would not have controlled the entire
20 disease.

21 In addition, one of the remarkable things we've
22 noticed is even in patients with large abdominal masses,
23 you can deliver a high-dose radiation this way with
24 virtually minimal toxicity to adjacent bowel or bladder,
25 other normal organs, which in my experience would not be

1 possible with traditional external beam radiation therapy.

2 DR. BLAYNEY: Thank you.

3 DR. WHITE: Any other investigator that wants
4 to address that.

5 (No response.)

6 DR. NERENSTONE: Well, thank you very much.
7 Not seeing any further questions from the committee, we
8 will break. If people can be back for our next
9 presentation at 10:15. Thank you.

10 (Recess.)

11 DR. NERENSTONE: If the committee could please
12 take their seats.

13 DR. TEMPLETON-SOMERS: Excuse me. I think most
14 of you already know that there's been a terrorist attack in
15 New York and in the Washington, D.C. area. It sounds like
16 several different locations and many, many people are
17 injured or killed. All flights are grounded. So, nobody
18 is going anywhere for a little while. The beltway is
19 closed. Government is closed. Those of you that the FDA
20 has paid for your travel in will obviously pay for your
21 hotel as long as we need to and any other travel problems.

22 I'm not sure what else there is to say. We'll
23 finish the Zevalin session since we are part way through,
24 and then we'll re-evaluate the situation at noon and see if
25 everybody is here for the Gliadel session. Thank you.

1 DR. NERENSTONE: I'd like to continue with Dr.
2 Meredith who is going to be talking about normal tissue
3 effects of radionuclide therapy.

4 DR. MEREDITH: Thank you.

5 We don't know as much about the tolerance of
6 normal organs to radionuclide therapy as we do to external
7 beam. This has just not been as well studied. So, in my
8 presentation today, I'm going to make a comparison as to
9 where it is today.

10 Before I give you some numbers that actually
11 compare the two, I'd like to give you some qualifiers as to
12 how these numbers were derived. The external beam data
13 that I would enumerate is a tolerance dose 5/5 or 50/5.
14 This means a 5 percent or a 50 percent risk of severe, late
15 complications by 5 years. In comparison to the
16 radionuclides, I've listed virtually any toxicity that's
17 been noted, whether it was acute, very transient or whether
18 late.

19 The numbers of patients for external beam is
20 obviously much larger in most reports than that for
21 radionuclides. Many of these are derived from studies with
22 less than 50 patients. In the external beam data, most of
23 this is derived from patients who had possibly surgery but
24 no other modalities, for the most part. And for the
25 radionuclides, most of these have failed numerous other

1 | therapies, including multiple chemotherapy regimens.

2 | For external beam data, this is highly
3 | fractionated at 2 gray per day 5 days per week, whereas
4 | most of the radionuclide data is a single dose. And we
5 | know that a single dose of external beam is more toxic than
6 | fractionated in most instances.

7 | It's high energy external beam data versus the
8 | radionuclides is a lower energy. External beam is also a
9 | high-dose rate compared to a low-dose rate and usually an
10 | exponentially decreasing dose rate with radionuclides.

11 | For the external beam, I will restrict this to
12 | whole organ toxicity, although we know in most organs that
13 | partial organ irradiation is much better tolerated and at
14 | higher doses than whole organ toxicity. For the most part,
15 | whole organ toxicity is applicable to radionuclide therapy.

16 | To give you some numbers, bone marrow toxicity
17 | has been the dose-limiting toxicity in most radionuclide
18 | studies. You can see from radionuclide information that
19 | very little dose to the bone marrow, from some of our
20 | studies using lutetium-177 labeled antibody, results in
21 | some toxicity. With I-131 labeled antibodies that have a
22 | circulation time of about 2 days, the MTD has been about
23 | 185 centigray. All these numbers are listed in centigray,
24 | and these numbers are for non-marrow targeting therapy and
25 | for diseases that did not have significant marrow

1 involvement.

2 For thyroid, we know that there's a great
3 difference between the TD5/5 and the 5/50 for external
4 beam. We don't have real good information on the
5 radionuclides. Part of this is that the TSH can increase
6 especially after I-131 therapy, and patients are placed on
7 Synthroid. So, we don't really know how many of these may
8 become hypothyroid if they weren't treated.

9 The kidney is one of the more radiosensitive
10 organs and you can see there's not a lot of difference
11 between the dose for a TD5/5 and a TD5/50 for external beam
12 radiation. Again, this is for severe complications,
13 whereas for the radionuclides, I've listed studies where
14 any toxicity has been noted. This is 2 patients who
15 received greater than 2,170 or 1 patient that received
16 somewhere up to 3,100. In this case it was less than 5
17 percent of the patients in these studies and there was some
18 increased creatinine. We don't have long-term follow-up.

19 In terms of bladder, it's more radioresistant
20 than many other organs, and for radionuclides some
21 hemorrhagic cystitis has been seen somewhere between 4,000
22 centigray and a much higher dose. There will be more
23 information on this shortcoming in the literature from
24 studies of holmium.

25 The lungs are relatively radiosensitive. I

1 listed here a total body radiation single-dose tolerance,
2 which you can see is about half that of fractionated
3 radiation. When this has been looked at as a dose-limiting
4 organ for myeloablative studies of radiolabeled antibodies,
5 we see that the place where we're seeing toxicity is about
6 the same actually as with external beam, and these are
7 instances where no chemotherapy was given at the time of
8 the radioimmunotherapy, although most of the patients had
9 had prior chemotherapy.

10 For the brain, we don't have a lot of good
11 information from radionuclides in terms of whole brain. In
12 fact, in many instances where treatment has been given
13 either to a cavity after a tumor was resected or into the
14 tumor itself, the dose to the normal brain is felt to be
15 quite low and complications have generally been some
16 instances of edema and rarely headache or seizure. In each
17 case you can see that when radionuclide is given into a
18 tumor resection cavity, relatively high doses can be
19 tolerated and very high doses have been tolerated without
20 significant toxicity when the radionuclide is injected
21 directly into a tumor.

22 I've listed here that the meninges are probably
23 more resistant than normal brain because for external beam
24 you really can't separate the two and so I could not find a
25 separate number for meninges.

1 Our information from radionuclides here
2 generally comes from intrathecal administration, and this
3 is usually after external beam radiation. Complications
4 have been few with relatively high doses. This has mainly
5 been transient aseptic meningitis.

6 As much as 160 millicuries of I-131 labeled
7 antibody can be given as a single dose, and cumulative
8 doses of over 300 millicuries. From some of these, the
9 surface dose was calculated to be close to 6,000 centigray.

10 We really don't have radionuclide reports for
11 spinal cord.

12 For stomach and intestine, these have about the
13 same toxicity from external beam and with radionuclide
14 therapy. Here I've listed some nausea. In most cases
15 there are a few reports of nausea at less than 2,700 and
16 generally it's mild until you get about the level of 6,000,
17 which you can see is greater than the normal toxicity from
18 external beam. There are some cases of grade 4 diarrhea,
19 and in those cases patients got a relatively high dose, in
20 fact much greater than tolerated by external beam.

21 In terms of bowel serosa, again for external
22 beam you can't separate it from the mucosal surfaces, but
23 there is data to suggest that the serosa itself is more
24 tolerant than the mucosal surfaces. For radionuclide
25 therapies, we know that there is more toxicity with P-32

1 | than has been tolerated by targeted therapy with
2 | radiolabeled antibodies. This may be because you have a
3 | more uniform dose with the P-32 and this is more targeted
4 | to tumor areas. In fact, we know that 8,000 at tumor
5 | deposits can be tolerated with rare complications,
6 | including adhesions or some GI complaints.

7 | Liver is one of the dose-limiting toxicities in
8 | myeloablative studies. And again sometimes at relatively
9 | low doses, mild nausea has been noted, but in general, in
10 | terms of dose-limiting toxicity, this has been around the
11 | dose of 2,400 by yttrium-90 radioimmunotherapy and higher
12 | doses, at least for some patients, with I-131 therapy.
13 | When the radionuclide has been combined with other
14 | regimens, including chemotherapy and total body radiation,
15 | as preparation for myeloablative therapy, you can see that
16 | the tolerance is a little less, although if you add the
17 | external beam plus the radionuclide therapy, it turns out
18 | to be about the same as a radionuclide alone.

19 | Pancreas. I did not find something in the
20 | literature for the TD5/5 or 5/50, but from general practice
21 | I can tell you that the TD5/5 is greater than 4,500, and if
22 | you get up to about 6,000 even to small areas of the
23 | pancreas, you get in trouble. We don't have much
24 | information from radionuclides in terms of the whole
25 | pancreas, but very high doses have been given to small

1 areas of the pancreas when this is injected into the tumor
2 itself, a P-32 regimen giving more than 1 million centigray
3 to small areas. This has been well-tolerated and dose
4 fractionation of this has been tolerated.

5 I'm going to quickly go through a few other
6 aspects here in terms of how accurate are these
7 radionuclide dose estimates and can we compare doses
8 between studies.

9 First off, radionuclide dosimetry is generally
10 much less accurate than external beam. I'll go into how
11 accurate are tracer studies, that the calculated dose is
12 not necessarily the dose that correlates well with the
13 biologic effect, and how accurate are comparisons between
14 radionuclide dose estimates.

15 In general, radionuclide dosimetry is just less
16 precise than external beam. I believe Dr. White gave an
17 explanation this morning. As an example, I just said if
18 you had a parenchymal lung tumor, there would probably be
19 no attenuation correction for radionuclide dosimetry,
20 whereas for external beam, you would take into
21 consideration that there is less attenuation in the lung
22 tissue itself and more dense tissue at the chest wall.

23 Also, with external beam radiation, as soon as
24 you turn on the machine, you get full, immediate dose to
25 all organs, whereas with radionuclide therapy, in general

1 | there is a buildup of organs and then an exponential
2 | decrease.

3 | You would think that tracer studies where a
4 | small amount of a radiolabeled agent is given and dosimetry
5 | and imaging performed would be the best indicator for the
6 | later therapeutic dose. And we have a few studies in which
7 | tracer studies were done and then dosimetry was repeated
8 | with the therapeutic study, which gives us a basis for a
9 | direct comparison in individual patients. I've listed some
10 | examples here. One is from our own institution where we
11 | used I-131 LYM-1 for non-Hodgkin's lymphoma, and the
12 | variance between the tracer dose and that for the
13 | therapeutic was between .9 and 1.38. This was using the
14 | tracer 7 days before the therapeutic administration.

15 | The University of Washington, which has done
16 | myeloablative studies using I-131 labeled antibodies for
17 | non-Hodgkin's lymphoma and leukemia, have found a
18 | correlation here between .67 and 1.15. This is the example
19 | I gave for their effective biological clearance from lung.
20 | They have done this for multiple organs, and they're on the
21 | same ball park.

22 | Another example is from an indium-labeled
23 | antibody used for CEA positive tumors, and the reported
24 | data was a concordance between .6 and .99 for most normal
25 | organs.

1 In a study conducted in breast cancer patients
2 at M.D. Anderson using I-131 labeled CC49 and the patients
3 received interferon after the tracer dose, it was noted
4 that there was a mean increase in the whole body residence
5 time and this was felt to be an interferon effect.

6 However, I would like to notice that the percentage
7 difference here between the tracer and the therapeutic is
8 in the same ball park as the others, and in this case they
9 can predict that the whole body residence time will be
10 increased; whereas on the other tracer studies, it's not
11 predictable on an individual basis whether your dose
12 estimate will be an under-estimate or an overestimate.

13 I'd like to say here that calculated dose, that
14 is, the number given for radiation exposure is not the same
15 as the biologic dose because we know that there are a lot
16 of physiologic and biologic interactive factors. For
17 radionuclides, among these include a very heterogeneous
18 distribution at the cellular level at least, even if it
19 looks relatively homogeneous on imaging. There are dose
20 rate effects. There's an effective range of radiation,
21 such as some radionuclides may have a range of four or five
22 times penetration in tissue as others. Radiation biologic
23 effectiveness or relative biologic effectiveness varies and
24 there are other characteristics that need to be taken into
25 account.

1 Among biologic factors that affect tolerance,
2 we know that some things are important, and there may be
3 different degrees of impact from the various factors. But
4 some of these can include age, prior therapies, the time
5 since prior therapy, the disease status, is the patient
6 anemic, do they have marrow replacement from disease, from
7 fibrosis, other factors. There are genetic and physiologic
8 factors or conditions that are important. Such as, hypoxia
9 can decrease radiation effectiveness. There are also
10 genetic and physiologic factors that can affect repair from
11 radiation damage.

12 Some of the factors that are felt to be
13 important have been analyzed at least briefly, and
14 adjustments for biologic factors have been found to improve
15 correlations between radiation doses and effects. One of
16 these studies looked at prior chemotherapy and the time
17 since prior chemotherapy, and found that in general if it
18 was less than 3 months from prior chemotherapy, the
19 patients did not tolerate the radionuclide therapy as well.

20 Wessels looked at a number of factors,
21 including age, gender, prior radiation, prior chemotherapy,
22 and found that if he developed a formula that took into
23 effect some accounting of this and applied this to the
24 radiation dose, that the correlation between toxicity and
25 the reported dose was improved with r value going from 0.57

1 | to 0.80.

2 | There are also agents that can impact on the
3 | biologic effectiveness of radionuclide therapy that don't
4 | contribute to dose estimates. There are a number of agents
5 | or factors that can contribute to this. Chief among them
6 | in the studies may be chemotherapy, but also other biologic
7 | response modifiers such as radiosensitizing agents,
8 | including BuDR; cytokines, interleukin-1 and interleukin-2,
9 | have been studied to some extent; and growth factor
10 | inhibitors such as antibodies to the epidermal growth
11 | factor receptor or anti-tyrosine kinase inhibitors.

12 | As an example of this, a study of radiolabeled
13 | chimeric L6 antibody was given as therapy for breast cancer
14 | xenographs in a study published by the DeNardos. In this
15 | case, the patients received the radiolabeled antibody
16 | alone. There were 79 percent responses but no cures, but
17 | the addition of Taxol 6 or 24 hours after this, the same
18 | dose, resulted in an increase in response rate and nearly
19 | 50 percent of the animals having cures.

20 | How accurate are comparisons between
21 | radionuclide dose estimates? There are a number of things
22 | that one can consider in terms of trying to compare doses
23 | from different studies and different institutions. Some
24 | things that one may want to take into account are variance
25 | in dosimetry methods, such as did they use measured organ

1 volumes such as in the myeloablative studies at the
2 University of Washington, or are these phantom studies
3 based on a single model such as one-size-fits-all for a
4 male of adult size, one-size-fits-all for a female adult?

5 Do the calculations use computer programs? Are
6 they the same programs, such as MIRDOSE 2 or MIRDOSE 3?

7 Was attenuation correction applied for the
8 regions of interest or a transmission scan technique used?

9 Was there background subtraction?

10 What was the frequency and appropriateness of
11 data collection? Some examples are if the peak
12 concentration is missed in a normal organ such as liver,
13 the dose may be lower than normal. If there were no early
14 scans and there was an assumption that there was immediate
15 full dose, then the dose estimate will be over that which
16 actually was received.

17 How accurate are the doses reported in the
18 literature? Barry Wessels looked at this and finds that in
19 the 1980s, in terms of reporting marrow toxicity based on
20 the radiation dose reported, it was about a 700-fold
21 difference. By the 1990s, it was down to 200 percent and
22 now it's about 30 percent.

23 In his recent analysis, he actually took data
24 from seven institutions and recalculated it using each
25 institution's own data, and his calculations varied from

1 | what was reported from minus 35 percent to plus 6 percent.

2 | An example of this also, in terms of looking at
3 | methods, such as the bone marrow, the AAPM task group
4 | report by Dr. Sgouros looked at a concentration factor of
5 | .19 for radioactivity in the blood as that portion of the
6 | blood in the marrow that should be taken into account for
7 | the dose estimate. He came up with a dose estimate of
8 | about 200 centigray versus another report of a similar
9 | agent where they looked at the radioactivity in the whole
10 | blood, and the dose estimate was approximately three-fold
11 | greater.

12 | Dr. Mills has asked me to look at when does
13 | imaging or dosimetry have a great impact, when should it
14 | absolutely be done. So, some things that may make a
15 | difference.

16 | One is when there is good correlation of the
17 | data between organ toxicity or antitumor effects with the
18 | radiation reported.

19 | The second is when there's a normal organ that
20 | can be somewhat accurately assessed and may be dose-
21 | limiting such as in the myeloablative studies for organs
22 | such as liver and lung.

23 | As a couple of examples of this, this comes
24 | from a myeloablative study at the University of Alabama at
25 | Birmingham, and you see here that each of these bars

1 represent dose to individual patients to the whole body,
2 liver, or spleen. You can see that despite different size
3 of patients and different amounts dosed, that there's not
4 much difference in the whole body dose received, but
5 there's a great difference in the individual organ doses
6 for liver and spleen.

7 This example also comes from the University of
8 Washington studies using high-dose I-131 labeled antibody
9 for lymphomas and leukemia. In this case, they looked at
10 the amount of radiation per unit of injected activity and
11 compared this to the injected activity per body weight.
12 You can see there's a large spread here. Now, the tracer
13 study showed about a 30 percent plus or minus difference.
14 Here you have a very wide range for individual patients.

15 Other areas that it may be very important to do
16 imaging and dosimetry may be when tumor is adjacent to a
17 normal critical organ and there's a high chance that the
18 tumor will receive a high dose that would affect the normal
19 organ.

20 Areas where distribution may be highly
21 variable. One antibody against CEA studied in this regard
22 had variable distribution between patients, and it was
23 noted that colorectal patients generally had twice the
24 clearance rate as those with other types of diseases.

25 Another thing would be when the distribution is

1 unknown for a particular agent and the distribution could
2 be critical. An example here is some of our work at the
3 University of Alabama at Birmingham giving radiolabeled
4 antibodies into the peritoneal cavity for ovarian cancer.
5 You can see on the left that when a trace element was put
6 in, all the activity is loculated here in the lower part of
7 the abdomen and there's nothing up in the rest of the
8 abdomen. This patient has catheter revision, and you can
9 see on later image that this is distributed well through
10 the abdomen.

11 In this one you can see that these sort of look
12 like loops of bowels. This is another patient that had a
13 test dose before radiolabeled antibody. Indeed, the
14 catheter had eroded into the bowel, and this patient could
15 not be treated until that catheter was removed, the area
16 healed and a new catheter placed.

17 There's concern about the addition of
18 radioimmunotherapy or radionuclide therapy with external
19 beam. There's not a lot of information in the literature,
20 but some of it goes back to the early days of
21 radioimmunotherapy when hepatomas were treated. In this
22 instance, 2,100 centigray were used of external beam
23 radiation concomitant with Adriamycin alternated with 5-FU
24 and the patients also received Flagyl. Then they received
25 2 months of intensity increased chemotherapy. Subsequently

1 they received radiolabeled anti-ferritin which delivered a
2 calculated dose of 400 to 1,000 centigray to normal liver.
3 So, if you add this dose to their external beam, this was
4 well tolerated and is within the reasonable numbers that
5 were noted with external beam radiation alone.

6 Other information comes from myeloablative
7 studies, and I've taken this first one as an example from
8 leukemia studies at the University of Washington where
9 patients received between 76 and 612 millicuries of I-131
10 anti-CD45 antibody. This was delivered in conjunction with
11 cyclophosphamide and 1,200 centigray total body radiation
12 as preparation for bone marrow transplantation. The MTD of
13 the radiolabeled antibody was at 1,050 centigray, and again
14 this is added to the external beam given concomitantly of
15 1,200 centigray.

16 Some of our studies at the University of
17 Alabama at Birmingham treating breast and prostate cancer
18 patients with I-131 labeled CC49 therapy included a higher
19 dose of total body radiation with the cyclophosphamide. In
20 this case, the liver dose was slightly less than that
21 reported at the University of Washington. Some liver
22 toxicity was seen. However, the patients that had liver
23 toxicity are those that also got thiotepa and those that
24 had had many cycles of chemotherapy prior to this
25 intervention. Again, the toxicity seen was increase in

1 | liver function tests and these were very transient.

2 | In terms of tissue tolerance to retreatment,
3 | from animal studies, it's found that some acutely responding
4 | tissues can tolerate a full course several months later.
5 | In terms of late responding tissues, there's virtually no
6 | recovery, however, in these studies for the heart, the
7 | bladder, or the kidney. There was partial recovery for the
8 | skin, mucous membranes, the lung, and spinal cord.

9 | We don't have quite as clean data for human
10 | studies, but we do have a fair amount of practical
11 | experience in giving retreatment of external beam
12 | radiation. Some of these examples include head and neck
13 | studies at our own institution, as well as others, where
14 | patients initially receive a tolerance dose to the head and
15 | neck of at least 70 gray. At least 6 months later, they
16 | may be treated as salvaged and can get pretty close to a
17 | full dose of radiation again with concomitant chemotherapy.
18 | This has resulted in reasonably good 2-year control, and
19 | there is some increased fibrosis, but this has been done
20 | without severe complications such as fistulas or necrosis
21 | of bone.

22 | Spinal cord. Most people would usually tell
23 | you that it remembers all the radiation and cannot be
24 | retreated. However, most recent information from animal
25 | studies and selected human data indicates that there is

1 | some partial recovery with time and that after about a full
2 | dose of around 40 gray, some patients have tolerated almost
3 | the same dose again without developing myelitis.

4 | In terms of prostate cancer, many patients have
5 | been treated with a full dose of 70 gray or higher and then
6 | salvaged for local recurrence by implants which deliver
7 | more than 9,000. Again, this has been done without severe
8 | toxicity when a time period elapses between these two.

9 | Nasopharynx cancer has been treated twice. In
10 | most instances, patients get a full dose the first time and
11 | then if they relapse. The M.D. anderson has found that you
12 | can give a total of 10,000 centigray with only a 4 percent
13 | complication rate, and Massachusetts General has used
14 | another 6,000, sometimes with brachy therapy, to result in
15 | a 50 percent survival without a large complication rate.

16 | There's not as much data about radionuclide
17 | retreatment, but there are some instances in the
18 | literature. I've listed here that strontium-89 has been
19 | given more than five times. I believe in some instances in
20 | the literature it's actually been given more than 10 times.
21 | Generally this has been separated by at least 6 weeks and
22 | often much longer periods.

23 | Some information about the agent under study
24 | today from Stanford University. 3 patients with
25 | unfavorable characteristics received a second dose of Y2B8

1 and some received a total dose of 70 millicuries with a
2 maximum of 40 at one administration.

3 Our own experience at the University of
4 Alabama. We have a few patients with various radionuclides
5 that have received retreatment, and in general with all of
6 these things, what we could say is that there is a trend of
7 somewhat longer recovery, mildly increased toxicity with
8 the retreatment, especially if it's done at short interval,
9 but for the most part, these have been tolerated.

10 To summarize some of these points I've tried to
11 make today, more radionuclide data is needed to be able to
12 improve dose and toxicity relationships. This may come
13 about by improved data collection, processing methods, that
14 will increase the accuracy and perhaps the standardization
15 between institutions.

16 There are a number of modifiers that need to be
17 taken into account in terms of the biologic effect as
18 opposed to just the radiation number calculated. These
19 include chemotherapy, as well as other radiosensitizing
20 agents, cytokines, other agents, such factors as prior
21 therapies, the disease status. All of these things can
22 affect toxicity or tumor response, but they do not change
23 the dose estimates.

24 Thank you.

25 DR. NERENSTONE: Thank you very much, Dr.