

TRANSCRIPT OF PROCEEDINGS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICAL EVALUATION AND RESEARCH

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BIOLOGICAL RESPONSE MODIFIERS ADVISORY COMMITTEE

NINETEENTH MEETING

Pages 1 thru 200

Bethesda, Maryland
July 25, 1997

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Friday, July 25, 1997

8:15 a.m.

Holiday Inn Bethesda
8120 Wisconsin Avenue
Bethesda, Maryland

MILLER REPORTING COMPANY, INC.
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P R O C E E D I N G S

Opening and Administrative Remarks

DR. FREAS: Good morning and welcome. Again, I apologize for the delay. I am Bill Freas. I am the Executive Secretary for the Biological Response Modifiers Advisory Committee and we would like to welcome you to the second day of our meeting.

The good news is I do not have to read the conflict of interest statement that was read into the public record yesterday. The bad news, however, though, it still applies to today's meeting. As a result, our Chair, Dr. Julie Vose, has been excluded from today's topic and our new Chair is Dr. Virginia Broudy.

I would like to go around the table and introduce the members of the committee for those of you who were not here yesterday. I will be starting down here at the end of the table and if the members would raise their hands so the people in the audience could identify who you are.

First we have Dr. French Anderson, Director, Gene Laboratory, University of Southern California School of Medicine. Next is Dr. Hugh Auchincloss, Associate Professor of Surgery at Harvard Medical School. Next is Dr. Ellin Berman, Associate Professor, Memorial Sloan Kettering Cancer Center.

The empty seat will soon be filled with Dr.

1 Richard Hong, Professor, Vermont Cancer Center, University
2 of Vermont. Next is Dr. Eugenie Kleinerman, Professor,
3 University of Texas, M.D. Anderson Cancer Center. Next is
4 Dr. William O'Fallon, Chair, Department of Health Sciences
5 Research, Mayo Clinic.

6 Around the corner is Dr. Richard Goldsby,
7 Professor, Amherst College. Next is our Acting Chair for
8 this morning's topic, Dr. Virginia Broudy, Associate
9 Professor of Medicine, University of Washington School of
10 Medicine. Next is our patient rep, Christine Heinemann.
11 Next is our consumer advocate, Abbey Meyers, President and
12 Executive Director, National Organization of Rare Disorders,
13 New Fairfield, Connecticut.

14 Next is Dr. Charles August, Division of Hematology
15 and Oncology, Miami Children's Hospital. Next is Dr. Paul
16 McCurdy, Director, Blood Resources Program, Division of
17 Blood Diseases and Resources, NIH. Next is Dr. Carole
18 Miller, Assistant Professor of Oncology at the Johns Hopkins
19 University. Next is Dr. Pamela Hartigan, Senior
20 Biostatistician, Westhaven V.A. Medical Center.

21 At the table, we also have three members of FDA to
22 help coordinate the meeting. They are, continuing around
23 the table, Dr. Pat Keegan, Chief, Oncology Branch; Dr. Karen
24 Weiss, Director, Division of Clinical Trial Design and
25 Analysis; and Dr. Jay Siegel, Director, Office of

1 Therapeutics, Research and Review.

2 We were to have a voting patient representative at
3 this morning's meeting. At the very last minute, David Larr
4 contacted us and he was too ill to participate. His name
5 will be mentioned frequently throughout this morning because
6 he did receive the briefing materials and he does have some
7 comments to bring to the committee.

8 Fortunately, Christine Heinemann was contacted by
9 our Office of Special Health, and volunteered at the last
10 minute -- and I do mean at the last minute -- to join the
11 panel as a non-voting patient representative.

12 Normally the patient representative has a vote,
13 however, at the last minute we were unable to process the
14 paperwork through the chain to get the vote approved on the
15 advisory committee, but we would like to welcome to the
16 table Christine, who at the last minute did manipulate her
17 schedule to join us here this morning.

18 At this time I would like to turn the microphone
19 over to our Chair, Dr. Broudy.

20 **Open Public Hearing**

21 DR. BROUDY: The first item on the agenda is the
22 open public hearing.

23 DR. FREAS: Dr. Broudy, if you don't mind, let me
24 just read the responses or address the responses that we
25 received from the advertisement that we placed in the

1 Federal Register notice about requesting members of the
2 public to speak at the open public hearing.

3 We have received one request, and that is from
4 Kathryn Adams from the Cure for Lymphoma Foundation.

5 Kathryn, would you please come to the microphone
6 this morning and make your statement, and also at the close
7 of the statement, please, in the interest of fairness,
8 address any affiliations that you may have with any of the
9 products that you may wish to comment upon.

10 MS. ADAMS: My name is Kathryn Adams. I am Vice
11 President of the Cure for Lymphoma Foundation based in New
12 York City.

13 The Cure for Lymphoma Foundation is a nationwide
14 not-for-profit organization dedicated to funding research
15 and to providing support and education for those whose lives
16 have been touched by Hodgkin's disease and non-Hodgkin's
17 lymphoma. I am here today to represent the Foundation and
18 two our patients we know and love.

19 David Larr, who had planned to be a member of this
20 panel this morning, could not be here. He is very
21 enthusiastic about rituximab and asked me to pose the
22 following question.

23 After pursuing the material sent to him by the
24 FDA, his question is this: Since there is only a 1 percent
25 HACA response from the patient's own immune system, does

1 this mean that the patient can be retreated many times?
2 There was no information regarding retreatment in his
3 packet.

4 It seems as if a patient may be able to be
5 retreated on a chronic basis, with a so-called "booster"
6 shot every year. It would mean that a low grade non-
7 Hodgkin's lymphoma could be considered then a chronic
8 condition.

9 I would also like to read a statement faxed to me
10 late last night by Dr. Wendy Harpham, who is actually on our
11 board and a non-Hodgkin's lymphoma patient. It is
12 handwritten, so please bear with me.

13 It is entitled "C2B8 - Life and Hope." I am a
14 doctor of internal medicine, mother of three young children
15 and a seven-year survivor of small cleaved cell follicular
16 non-Hodgkin's lymphoma.

17 In 1990, I developed a rash, enlarging lymph
18 nodes, and excruciating pain in my groin and back. Two
19 surgeries disclosed disseminated low-grade lymphoma. In
20 light of my debilitating symptoms, and the recent work
21 suggesting that more intensive therapies might increase the
22 durability of remission, and possibly effect a cure, I
23 received Promace-MOPP chemotherapy.

24 My course was complicated by esophagitis,
25 phlebitis, colitis, and the usual host of side effects.

1 Needless to say, I was unable to care for my patients, and
2 could tend to my children only with major help from family
3 and friends.

4 Fatigue, persistent pain, colitis, and recurrent
5 infections slowed my recovery. Almost one year following
6 treatment, I was diagnosed with a local recurrence. It was
7 a devastating time, not because I had to close my beloved
8 medical practice but because, despite my being in a most
9 favorable subgroup at the beginning and end of chemotherapy,
10 I knew I wasn't cured.

11 Remission again achieved, I had my bone marrow
12 harvested. A few months later, the rash reappeared. Scans
13 appeared clear. In hopes of preventing the development of
14 measurable disease, I was started on interferon alpha.
15 After four long months of debilitating fatigue and nausea,
16 scans revealed disseminated disease.

17 As a physician-patient, it was again a very
18 terrifying time. The pace of my disease suggested that I
19 would fall on the shorter end of the average life expectancy
20 after diagnosis. The fact that I had had a rapid and
21 complete response to chemotherapy but recurrence less than a
22 year later, and the new data coming in on recurrence of low
23 grade lymphoma after bone marrow transplants, made me
24 fearful that not only would transplant be a traumatic
25 experience, it may very well not provide a durable

1 remission.

2 I worried about the possible late effects of
3 repeated exposure to intensive chemotherapy. Since I had
4 never had a chance to recover from my first courses of
5 treatment before recurrent lymphoma was diagnosed, I worried
6 about feeling sick for the rest of my life, however long
7 that might be. And, most important of all, there was the
8 heart-wrenching fear that I would not live to raise my
9 children.

10 Balancing all the risks and benefits, short term
11 and long term, of all my treatment options, in 1993, I
12 entered the Phase I trial of IDEC anti-CD20 MAB at Stanford.
13 Although I felt nauseated during the infusion, I fell back
14 to baseline when the infusion was over.

15 My husband and I went out to dinner and marveled,
16 "Can it really be working? It's not making me sick or
17 bald."

18 The single infusion resulted in a good partial
19 remission, during which time I regained all the weight I had
20 lost on interferon, wrote most of my second book, "After
21 Cancer: A Guide To Your New Life," and raised my children.

22 Eight months later, the remaining disease
23 progressed, the same month that, for the first time since
24 the antibodies were infused, my peripheral B cell count was
25 rising, indicating less of an effect of the IDEC Mab.

1 I then entered a Phase I/II trial and received
2 four infusions. Ill effects were minor and transient. The
3 infusions gave me another partial remission and eight more
4 months of good quality of life, and delayed further exposure
5 to toxic chemotherapies.

6 In December of 1994, the remaining lymphoma
7 progressed. The next trial of antibodies wasn't open, so I
8 did nine months of -- I can't read this -- based
9 chemotherapy. Although I did not lose my hair, the fatigue
10 was debilitating. At the end of the treatment, there were
11 minimal abnormalities on the scans, which continued to
12 improve over the subsequent few months.

13 In May of this year, scans revealed progressive
14 disseminated lymphoma. Biopsy confirmed the same SCCFNHL.
15 In June 1997, I received four weekly infusions of C2B8. As
16 far as I know, I am the first person ever to receive the
17 IDEC Mab three times.

18 I had more flu-like symptoms for a couple of days
19 after the first doses, and a six-day bout of diffuse
20 tenosynovitis after the second dose. None of these problems
21 required hospitalization or intervention other than oral
22 Tylenol.

23 The first set of scans, done four weeks after the
24 last dose, were obtained 7-18 and showed -- just this recent
25 July 18 -- and showed dramatic improvement in all areas.

1 After living with this disease for seven years,
2 through seven various courses of treatment, here is what
3 C2B8 treatment means to me.

4 One. The availability of this treatment tames my
5 greatest fear - not living to raise my children. Each of
6 the last two courses of C2B8 brought me eight months with
7 minimal toxicity. Repeated courses appear to be at least as
8 effective for me as my first courses.

9 It is very possible that C2B8 alone can keep me
10 alive with a good quality of life for many, many years.
11 Even if it doesn't cure me, although it is possible that the
12 third time is the charm, any amount of time I can get is
13 invaluable.

14 It is time with my family, it is time for other
15 treatments to be developed, it is time for bone marrow
16 transplant to become even safer, it is time for scientists
17 to learn more about the best treatments (conditioning
18 regimens), and it is time without the toxic effects of
19 chemotherapy.

20 Two. C2B8 has been an effective treatment for me
21 that I could take as an outpatient. The fact that I had
22 hair, a good appetite, and good blood counts meant
23 relatively little disruption in my children's lives. Bone
24 marrow transplant, or less intensive chemotherapy, would be
25 harder on me and my entire family.

1 Three. C2B8 allowed me to avoid the acute and
2 long-term toxicities of chemotherapy for 16 months in 1993-
3 1995, and again now. I have still never recovered my
4 stamina.

5 Four. C2B8 has not eliminated any standard
6 treatment options for me should the C2B8 no longer be
7 effective against my lymphoma at some time in the future.

8 In summary, I had chemotherapy, radiation therapy,
9 interferon, and IDEC-C2B8. C2B8 has given me years of life
10 with minimal toxicity especially if compared against
11 chemotherapy or radiation therapy.

12 C2B8 has given me real hope for a long life.
13 Without C2B8, I would have undergone high-dose chemotherapy
14 with marrow or stem cell salvage in June. At best, I would
15 face the post-bone marrow transplant problems and risks
16 during a durable remission and possible cure. At worst, I
17 would not survive the bone marrow transplant.

18 Most importantly, I would deal with the usual
19 treatment-related problems, achieve remission, and then
20 spend enormous energy -- I can't read her writing -- fear of
21 recurrence, because recurrence would mean more treatment for
22 shorter remissions.

23 With C2B8, I see myself as having a chronic
24 disease like diabetes. During remissions or partial
25 remissions, fear of recurrence is more easily managed

1 because the implications of recurrence are less frightening.

2 C2B8 treatment is relatively easy, I don't close
3 treatment options when I get C2B8, and C2B8 is effective,
4 giving me a good quality of life.

5 Thank you very much.

6 DR. FREAS: Thank you, Kathy. Before you leave,
7 would you please state any affiliations that you or your
8 organization may have with either the sponsor or any
9 competing firms.

10 MS. ADAMS: We have none.

11 DR. FREAS: Thank you.

12 Again, the FDA welcomes the participation of the
13 public at these advisory committee meetings.

14 Is there any other member in the audience at this
15 time who would like to address the committee?

16 [No response.]

17 DR. FREAS: I see none. We will have another open
18 public hearing after lunch. If you would like to speak at
19 that open public hearing, you are encouraged to do so.
20 Please contact me during the morning.

21 Dr. Broudy, I turn the microphone over to you.

22 DR. BROUDY: Thank you, Dr. Freas.

23 The next item on the agenda is the presentation on
24 the C2B8 antibody by IDEC Pharmaceuticals.

25 **OPEN COMMITTEE DISCUSSION: TOPIC III**

1 BLA 97-0260

2 Rituximab, IDEC Pharmaceuticals

3 Presentation by IDEC Pharmaceuticals

4 Opening Remarks

5 MS. WEI: Good morning, Ms. Chairperson, members
6 of the Biological Response Advisory Committee and FDA staff
7 from the Office of Therapeutic Research and Review.

8 [Slide.]

9 I am Alice Wei, Director of Regulatory Affairs at
10 IDEC Pharmaceuticals. We are here to share with you our
11 promising efficacy and safety data regarding the use of a
12 novel new agent Rituxan or rituximab, a mouse/human chimeric
13 monoclonal antibody.

14 [Slide.]

15 Specifically, IDEC is requesting approval of
16 rituximab for the treatment of patients with relapsed or
17 refractory low-grade or follicular B-cell non-Hodgkin's
18 lymphoma. If approved, rituximab will be the first
19 therapeutic monoclonal antibody for an oncologic indication.

20 [Slide.]

21 Non-Hodgkin's lymphoma is an incurable disease
22 with limited treatment options. It is predominantly of B-
23 cell origin and expresses the CD20 antigen. Low grade or
24 follicular, non-Hodgkin's lymphoma, according to 1997 Cancer
25 Statistics and the latest SEER statistics, represents 32

1 percent of incidence and approximately half of the
2 prevalence for all B-cell and non-Hodgkin's lymphoma.

3 The incidence is approximately 17,000 to 18,000
4 cases and the prevalence is approximately 120,000 cases with
5 survival of 6.2 years from the time of diagnosis or less
6 than 5 years from the time of first relapse.

7 [Slide.]

8 Rituximab is a genetically engineered chimeric
9 murine/human monoclonal antibody produced in Chinese hamster
10 ovary cells. The [fab] domain contains the murine sequence
11 with binding specificity for the human CD20 antigen. The Fc
12 domain is of human IgG-1 origin and has the ability to
13 affect human immune functions.

14 [Slide.]

15 Rituximab was engineered by IDEC Pharmaceuticals.
16 It is being developed for use in the global market through
17 the collaborative efforts of four companies: IDEC,
18 Genentech, Inc., of South San Francisco, F. Hoffmann-La
19 Roche of Basel, Switzerland, and Zenyaku Kogyo of Tokyo,
20 Japan.

21 Development was initiated in 1993 by IDEC
22 Pharmaceuticals and was conducted primarily in the United
23 States and Canada. Since 1995, development has continued
24 through the combined efforts of IDEC Pharmaceuticals and
25 Genentech, Inc.

1 Data from the studies were used in support of
2 joint biologic license applications which were filed on
3 February 28th, 1997. A simultaneous marketing authorization
4 application was also filed by F. Hoffman LaRoche in Europe
5 in February 1997.

6 The primary data for these applications are
7 derived from two U.S. studies, a single pivotal trial that
8 evaluated the clinical safety and efficacy of rituximab
9 including overall response rate, time of progression, and
10 duration or response in 166 patients. Also, a key
11 supportive study was conducted in 37 patients.

12 Thus, at the recommended dosing schedule, the
13 primary efficacy information is based upon a total of 203
14 patients

15 [Slide.]

16 The data we will present today demonstrate that
17 rituximab, when given in repeated courses of 375 mg/m² for
18 four doses, or over a 22-day period, has consistent activity
19 and limited toxicity in the treatment of patients with
20 relapsed or refractory low-grade or follicular B-cell non-
21 Hodgkin's lymphoma.

22 Rituximab is not associated with the morbidity and
23 the mortality typically seen with chemotherapy.

24 At this time, we wish to express our gratitude to
25 the FDA for working with IDEC in a collaborative manner and

1 providing guidance through the development of rituximab. We
2 also wish to acknowledge their efforts in working with us to
3 establish the response criteria used in our pivotal study.

4 [Slide.]

5 IDEC is pleased to have in attendance today
6 individuals who have been instrumental in the development of
7 rituximab. These include a number of investigators who were
8 involved in various clinical studies.

9 [Slide.]

10 These clinical scientists, as well as our
11 clinicians and biostatisticians, have played important roles
12 in development of rituximab and are available to answer any
13 questions you may have.

14 [Slide.]

15 Dr. Antonio Grillo-Lopez, Senior Vice President of
16 Medical and Regulatory Affairs, at IDEC Pharmaceuticals, and
17 a clinical hematologist/oncologist, will provide further
18 background information on the product and review the safety
19 and efficacy data we feel support our indication.

20 During the question and answer period, Dr.
21 Christine White, Senior Director of Oncology/Hematology at
22 IDEC, and also a clinical oncologist, will join Dr. Grillo-
23 Lopez.

24 Now, I would like to introduce Dr. Antonio Grillo-
25 Lopez, who will present the scientific and medical summary

1 for rituximab.

2 **Scientific and Medical Summary of IDEC-C2B8**

3 DR. GRILLO-LOPEZ: Good morning, Dr. Broudy,
4 members of the BRM committee, FDA staff, ladies and
5 gentlemen. It is a privilege for me to be here with you
6 today to discuss IDEC-C2B8 rituximab, a monoclonal antibody
7 for the treatment of relapsed or refractory low-grade or
8 follicular non-Hodgkin's lymphoma.

9 [Slide.]

10 I have divided my talk into three parts. I would
11 first like to address some background information relative
12 to the natural history and treatment options for this
13 disease, and then go on to discuss with you the safety and
14 efficacy results from our clinical trial

15 Low-grade or follicular non-Hodgkin's lymphoma is
16 subclassified into Types A, B, C, and D in the International
17 Working Formulation. The IWF formulation is the clinical
18 pathologic classification that has been the standard in the
19 United States over the past 15 years, and I would like to
20 utilize the 1,200-patient multicenter database that was used
21 in putting together that formulation to show you the typical
22 characteristics that this patient population has.

23 On the next two slides we will be talking about
24 the 433 patients from that 1,200-patient database who were
25 in the A, B, C, and D classes of the IWF.

1 [Slide.]

2 As you see, the median age for these patients was
3 55.8 years, the sex ratio was 1.2 males to females, 60
4 percent of the patients were Class B, and about 20 percent
5 were Class C, 10 percent D, and 10 percent A.

6 In most of these patients, 80 percent, the stage
7 at diagnosis is III or IV, and about 47 percent of the
8 patients have bone marrow invasion at the time of diagnosis.
9 As you will see later on in my presentation, the patient
10 characteristics for the patients included in our study are
11 fairly similar to these.

12 [Slide.]

13 On the next slide, you see that these patients had
14 a 69 percent CR rate with their first ever chemotherapy, and
15 there our patients are a little bit different because the CR
16 rate in our patient population with their first even
17 chemotherapy was around 40 percent, so lower than this.

18 Also, this is an important figure. The median
19 survival from diagnosis for this patient population was 6.2
20 years, and this is important in a number of ways. First of
21 all, it serves as the basis for comparison to our patient
22 population because you will see later on in my presentation
23 that our patients had 4.1 years on the median since
24 diagnosis at the time they were entered into our study,
25 which would indicate that about two-thirds of the natural

1 history of their disease had already elapsed.

2 This figure is also is important and has been
3 further documented in the Eastern Cooperative Group
4 experience. ECOG has published a number of years ago, as
5 you will see on the next slide, their experience with over
6 400 low-grade or follicular lymphoma patients, and they have
7 established a model to predict survival following first
8 relapse.

9 [Slide.]

10 In that particular 400-patient database, what they
11 found was that the patients with best survival, as shown on
12 this curve at the top, were those patients who had a CR
13 greater than one year in duration.

14 The next curve was for those patients who had a PR
15 greater than one year in duration, and at the bottom, those
16 patients who had either a CR or a PR, but less than one year
17 in duration, and the median survival figures declined from
18 5.9 to 4.8 to 2.4, and in fact, all patients greater than
19 age 60 had a median survival following first relapse of 2.4
20 years. For the patient population as a whole, for those
21 400+ patients, the median survival following first relapse
22 as less than 5 years.

23 [Slide.]

24 This disease is characterized by a series of
25 remissions and relapses, eventually leading to death either

1 from the disease itself or from complications. This is very
2 nicely shown in studies reported by Gallagher and others,
3 from St. Bartholomew's Hospital in London, where they have
4 very elegantly shown how the percent of responding patients
5 remaining in remission declines over time with the first
6 ever chemotherapy treatment reaching a median of about 16
7 months, and then declines with second and third remissions
8 and fourth remission.

9 [Slide.]

10 Likewise, the response rate drops from the first
11 treatment, 70 percent, to 60 percent, to 44 and 39 percent
12 with subsequent treatments.

13 [Slide.]

14 As I said, the duration of remission also declines
15 from 16 months to 11, to 9.6, to 3.2 months, and this is
16 very characteristic of this disease, declining response rate
17 with subsequent remissions, declining duration of remission.

18 [Slide.]

19 In our database, we see a similar phenomenon. In
20 our database, our patients with prior chemotherapy before
21 receiving the antibody, with the first relapse, remission
22 duration had been 19 months, dropping to 11 months, second
23 relapse 6 months, third relapse, and fourth relapse 5
24 months.

25 [Slide.]

1 We have performed a review of the literature, a
2 15-year review of the literature, looking at response rates
3 and duration of response for a variety of different
4 treatment options that are available to these patients with
5 relapsed low-grade or follicular lymphoma, including single
6 agents, biologicals, immunotherapy, aggressive combinations,
7 and ABMT.

8 We particularly focused on fludarabine and
9 cladribine because they are the more frequently reported
10 single agents evaluated in this patient population, and for
11 the same reason interferon.

12 As you see, the overall response rates with those
13 single agents ranged from 45 percent to 52 percent. Some of
14 these studies did include previously untreated patients, so
15 they are not all relapsed patients, and that inflates the
16 results slightly.

17 Likewise, if you pay attention to the Time to
18 Progression column and the Duration of Remission column, you
19 see that those range from 3 to 12 months.

20 This review of the literature was important
21 because it served as the basis for discussions in
22 establishing our efficacy endpoints, as I will explain later
23 on.

24 [Slide.]

25 So this disease is usually fatal in patients who

1 are relapsed. There are limited treatment options for these
2 patients. The chemotherapy that is used does have
3 significant toxicities and limited durability.

4 I would now like to turn to IDEC-C2B8 or
5 rituximab, again, a chimeric anti-CD20 antibody. It was
6 genetically engineered at IDEC laboratories in San Diego,
7 and that we have evaluated in patients with relapsed or
8 refractory, low-grade of follicular B-cell non-Hodgkin's
9 lymphoma.

10 This antibody is safe with limited adverse events,
11 and it is effective with a 48 percent overall response rate
12 and greater than 11 months median time to progression in
13 responders.

14 [Slide.]

15 Clinical development of IDEC-C2B8 was initiated in
16 early 1993. Enrollment in the pivotal trial was completed
17 in early 1996. During these three years, four studies were
18 conducted. First, a single dose study followed by a
19 multiple dose study.

20 We also carried out a pilot study of the
21 combination of the antibody with CHOP chemotherapy and the
22 pivotal trial with 166 patients entered. These four studies
23 were completed, reported, and submitted to the FDA in the
24 BLA that was submitted as hardcopy and CD-ROM in February of
25 this year, so four years after the first patient was entered

1 in the Phase I trial.

2 Simultaneously, applications for approval were
3 submitted in Europe with the EMEAA following the centralized
4 procedure.

5 [Slide.]

6 A number of studies were ongoing at the time that
7 the BLA was submitted to the Agency, and those included a
8 Phase II study that addressed two separate patient
9 populations, a patient population with bulky disease, that
10 is, lesions greater than 10 cm in diameter, and a patient
11 population consisting of those patients who had received the
12 antibody, responded, had relapsed with progression of
13 disease, and needed to be retreated.

14 Additionally, there was a study of an eight-
15 infusion schedule, so that we could compare beyond the four
16 infusions that had been used in most patients; a Phase II
17 pilot study of the combination with interferon; a study
18 where IDEC-C2B8 was used as cold antibody preceding
19 radioimmunotherapy with IDEC Y2B8; a Phase II pilot study
20 intermediate grade lymphoma, and this was a combination
21 again with CHOP chemotherapy; and currently, there is an
22 open label study that is ongoing.

23 So all of these studies were ongoing at the time
24 of the BLA, however, as many patients as were available for
25 safety information have been included in the submissions.

1 In addition to these studies, the NCI has planned
2 four studies at this time. One of them has already been
3 initiated at the Dana Farber by Dr. Shippe and Dr. Cheson,
4 who is in the audience, tells me that the Intergroup study
5 of CHOP+ antibody versus CHOP versus CHOP followed by
6 antibody, a three-arm randomized study, will be initiated
7 this year.

8 We will also be doing some additional studies with
9 the antibody.

10 [Slide.]

11 Today, the safety database that we will be talking
12 about includes 315 patients from all of the studies shown on
13 this table, and for efficacy, the 203 patients that have
14 been mentioned previously and 166 of those come from the
15 pivotal trial and 37 from the Phase II part of the multiple
16 dose Phase I/II study.

17 [Slide.]

18 The CD20 antigen is a hydrophobic phosphoprotein
19 of 35kd. It is expressed on mature B cells and most B-cell
20 malignancies, but not on stem cells or pre-pre B cells or
21 mature normal plasma cells.

22 It is thought to be important for cell cycle
23 initiation and differentiation. Interestingly, this antigen
24 does not shed, internalize, nor does it modulate upon
25 antibody binding.

1 The anti-CD20 antibody has murine variable regions
2 and human constant regions. In vitro, it has been shown to
3 activate complement-dependent cytotoxicity, antibody
4 dependence, cellular cytotoxicity to induce apoptosis and to
5 sensitize chemoresistant cell lines.

6 [Slide.]

7 This antibody is a B-cell depleting antibody and
8 our experience in experimental animals, and specifically as
9 shown on this graph, in monkeys, was that B cells in
10 peripheral blood were rapidly, selectively, and profoundly
11 depleted after a single infusion or multiple infusions with
12 subsequent recovery occurring over the next two or three
13 months.

14 The same effect was noted in the lymph nodes and
15 in the marrow of these experimental animals.

16 [Slide.]

17 In humans, as shown on this next slide, we
18 likewise saw profound depletion as measured by CD19 absolute
19 counts on FACS analysis in patients immediately following
20 the first infusion, and the B-cell count remained at very
21 low levels for 6 months when recovery started, and entered
22 the range of normal between 9 and 12 months, so there was
23 recovery between 9 and 12 months.

24 This phenomenon is not unprecedented, however, it
25 is very interesting, and we think that there is a

1 relationship between B-cell depletion and many of the
2 adverse events that we see with this antibody, so that there
3 may in fact be a biological effect of the antibody.

4 [Slide.]

5 As you will see on the next slide, the majority of
6 the adverse events do occur with the first infusion, and
7 subsequent infusions are characterized by much lower
8 incidence of adverse events.

9 Interestingly, most adverse events are Grade 1 or
10 Grade 2, and there are very few Grade 3's and 4's, as you
11 see on this very simple bar graph.

12 [Slide.]

13 Most adverse events are infusion related and are
14 associated with the first infusion. Primarily, they consist
15 of fever and chills, mild nausea, pruritus, fatigue, mild
16 hypotension, tumor-related pain, bronchospasm, and sensation
17 of tongue or throat swelling.

18 Just to give you a couple of examples, hypotension
19 was Grade 3 and 4 only in three patients. None of these
20 patients required vasopressors, and the median duration of
21 hypotension was less than two hours.

22 Bronchospasm likewise was Grade 3 and 4 in only
23 three patients, and some of the patients having bronchospasm
24 did require bronchodilators, in fact, six patients required
25 bronchodilators. Now, bronchospasm is a term that we have

1 used for any patient with dyspnea, shortness of breath, or
2 wheezing, so it includes those three categories, and the
3 median duration of these symptoms was less than 45 minutes.

4 Sensation of tongue or throat swelling likewise
5 occurred only in a few patients. Only in one case was it
6 Grade 3 or 4, and again the median duration was less than 45
7 minutes.

8 Infusion-related events are usually mild, resolve
9 in less than one to two hours. They usually resolve with
10 slowing or temporary interruption of the infusion. They are
11 usually managed with acetaminophen or diphenhydramine.

12 [Slide.]

13 Less than 3 percent Grade 3 and 4 neutropenia or
14 thrombocytopenia were reported. B cells were rapidly
15 depleted and recover in 9 to 12 months.

16 T cells and NK cells are not affected. The mean
17 serum immunoglobulin levels remained normal, and on the next
18 slide I will show you a graphic representation of this, and
19 there are few opportunistic or serious infections.

20 [Slide.]

21 Here it the graph showing the mean serum
22 immunoglobulin G levels in all patients. As you see, the
23 mean levels remained fairly stable throughout treatment and
24 the observation period and within the range of normal.

25 I could show you similar graphs for IgA and IgN

1 likewise.

2 [Slide.]

3 Nevertheless, we were concerned about the
4 incidence of infections in these patients and we did collect
5 all infections regardless of severity, regardless of
6 attributability in these patients. In fact, in the 315
7 patients in the safety database during the treatment period,
8 and that treatment period was defined as the 50 days
9 following the first infusion, and also during one year
10 followup.

11 As you see, during the treatment period, 53
12 patients had some kind of infection, any infection, and
13 during followup, 50 patients had any infection. Those were
14 viral, bacterial, fungal, and some were unknown as to
15 etiology.

16 The viral infections were predominantly colds,
17 URIs, and some recurrences of herpes simplex and herpes
18 zoster. The bacterial infections, many of those were UTIs,
19 sinusitis, and so on. There were only three fungal
20 infections. One was an onychomycosis, and two were
21 mucocutaneous infections. There were no systemic fungal
22 infections.

23 In the bacterial infections, we did enter all
24 patients who were prescribed antibiotics because we presumed
25 they had bacterial infections.

1 [Slide.]

2 HACA responses. In the 325 patients, only 3 had
3 HACA responses, and they are shown on this slide, Patients
4 A, B, and C. As you can see, 2 patients had detectable but
5 not quantifiable levels of HACA and only 1 patient had a
6 quantifiable level of HACA, 120 ng/mL.

7 Our HACA test assay can detect and quantify down
8 to 100 ng/mL. As you see, two of these patients were re-
9 treated and both of them, in spite of the quantifiable
10 detectable and detectable here, HACA, did go on to have
11 partial responses, one of them lasting over 10 months,
12 another one over 6.2 months. This one patient did have
13 progression of disease and was not retreated.

14 [Slide.]

15 There were no deaths reported during the treatment
16 period. During one-year followup, 15 patients died of
17 progressive lymphoma and 5 patients died of the conditions
18 shown here - acute promyelocytic leukemia, bronchiolitis
19 obliterans, one patient with a CNS papovavirus,
20 meningoencephalitis, and respiratory failure as shown on
21 this slide.

22 [Slide.]

23 The more frequent adverse events. I would like to
24 summarize the safety. They included fever, chills, nausea,
25 asthenia, headache, pruritus. These events are usually mild

1 to moderate. They may be related to B cell depletion. They
2 occur primarily with the first infusion and decrease with
3 subsequent infusions. They are usually ameliorated by
4 acetaminophen and diphenhydramine.

5 [Slide.]

6 We looked at the incidence of adverse events
7 relative to the prior history. For example, infusion-
8 related bronchospasm, as I said, which includes any patient
9 with dyspnea, wheezing, or shortness of breath, the
10 incidence of bronchospasm was not increased in patients with
11 prior history of allergy, allergic rhinitis, COPD, asthma,
12 or any pulmonary disorder.

13 Likewise, the incidence of Grade 3 or 4 adverse
14 events was not increased in patients with prior history of
15 asthma, allergy, congestive heart failure, arrhythmia, or
16 myocardial infarction.

17 [Slide.]

18 B cells are rapidly and selectively depleted.
19 This is also observed after chemotherapy and ABMT. Recovery
20 occurs within 9 to 12 months. As I mentioned earlier, stem
21 cells, pre-pre B cells, dendritic cells, and plasma cells
22 are not depleted. They do not express the CD20 antigen.

23 T cells and NK cells are not affected. This is
24 very selective B-cell depletion. Mean serum immunoglobulin
25 levels remain within normal limits.

1 There is no apparent increase in the incidence of
2 infections, and there is no apparent or significant
3 impairment of clinical immunity due to the B-cell depletion
4 that occurs in these patients.

5 [Slide.]

6 The effects on platelets and neutrophils are
7 reported in less than 10 percent of patients, and are Grade
8 3 and 4 in less than 3 percent of patients.

9 This effect is probably peripheral and does not
10 appear to affect marrow reserves.

11 [Slide.]

12 Grade 3 or 4 clinical adverse events. Only 32 of
13 315 patients, that is 10 percent, had Grade 3 or 4 clinical
14 adverse events. Grade 3 events were reported in 9 percent,
15 and Grade 4 in 1 percent of patients.

16 [Slide.]

17 Fifteen of 20 deaths, as I mentioned earlier, were
18 lymphoma related. Other therapies are reported to have
19 treatment-related mortality as high as 5 to 30 percent.

20 [Slide.]

21 No HAMA responses were observed. Less than 1
22 percent HACA response, that is, 3 out of 315 patients, and
23 this was in low concentrations. Again, the highest level
24 was 120 ng/mL, and these were transient.

25 No clinical or laboratory parameters were affected

1 in the patients, and retreatment with the antibody was not
2 precluded, and tolerability was not affected in these
3 patients.

4 [Slide.]

5 This is outpatient treatment. Hospitalization is
6 not required. Premedication consists of oral acetaminophen
7 and diphenhydramine. Antiemetics, sedatives, and other
8 medications are usually not required. Treatment is well
9 tolerated, and retreatment is feasible, and in fact, we have
10 retreated 22 patients who received treatment twice, and 2
11 patients who have received treatment three times.

12 [Slide.]

13 I would like to now turn to efficacy. We will be
14 discussing the pivotal study with 166 patients enrolled. In
15 the Phase I/II supportive study, the 37 patients in that
16 study who were in the Phase II part. So the combined
17 database for these studies includes a total of 203 patients.

18 [Slide.]

19 The pivotal study was for relapsed or refractory,
20 low-grade or follicular B-cell non-Hodgkin's lymphoma, and
21 was designed as an open-label, single-arm, safety and
22 clinical efficacy trial.

23 Treatment consisted of the antibody at 375 mg/m²
24 by intravenous infusion given once weekly times 4. This
25 treatment is given over a 22-day period.

1 A total of 166 patients were entered at 31 centers
2 across the U.S. and Canada. The response criteria were
3 established by a panel of lymphoma experts and were
4 presented to this committee at the October meeting.

5 The responders were subject of an independent and
6 blinded audit by the LEXCOR panel, and I will explain this
7 further.

8 [Slide.]

9 We did agree on efficacy endpoints with the FDA
10 prospectively at a meeting that occurred in October of '94.
11 These decisions were made after discussing the literature
12 review, the results with other single agents and other
13 therapies, and the decisions were to utilize as primary
14 efficacy endpoints the overall response rate with a goal of
15 35 to 40 percent, and as secondary efficacy endpoints, time
16 to progression in responders with a target of equal to or
17 greater than 8 months, and duration of response with a
18 target of equal to or greater than 6 months.

19 [Slide.]

20 These are the patient characteristics for the
21 pivotal trial. Again, 166 patients were enrolled. All of
22 these patients were relapsed or refractory, and all of these
23 patients had progressive disease. This was required by the
24 protocol prior to study entry.

25 There was a predominance of males with a ratio of

1 1.8 males to females. A median of 58 years of age, and as
2 you see, there were a number of older patients included in
3 this study.

4 The time since diagnosis, as I mentioned earlier,
5 showed a median of 4.1 years compared to the 6.2 year median
6 survival time in the IWF database. All of these patients
7 were low-grade or follicular in histology, IWF classes A, B,
8 C, and D.

9 Their stage at diagnosis was predominantly Stage
10 III or IV. These patients were heavily pretreated with a
11 median of two prior chemotherapy regimens, however, some
12 patients had received up to seven prior chemotherapy
13 regimens. Additionally, 23 patients had had ABMT, 6
14 patients had been treated with immunotherapy, and 42
15 patients had received radiotherapy.

16 [Slide.]

17 Let me go through the quality assurance measures
18 that were implemented for this pivotal trial. First of all,
19 the response criteria were established by a panel of
20 lymphoma experts, and this was done in consultation with the
21 FDA.

22 [Slide.]

23 These were the experts that participated in
24 putting together those response criteria - Dr. Cheson from
25 the National Cancer Institute, Dr. Horning, who chairs the

1 ECOG Lymphoma Committee, Dr. Peterson, who chairs the CALGB
2 Lymphoma Committee.

3 [Slide.]

4 Responses were assessed at the clinical site by
5 the principal investigator at that site, and subsequently,
6 there was a centralized response audit conducted by IDEC.

7 Additionally, there was a third party audit for
8 Good Clinical Practices, and finally, there was a blinded
9 third party audit of all patients with 40 percent or greater
10 reduction in tumor size by the LEXDOR Panel.

11 [Slide.]

12 LEXCOR stands for Lymphoma Experts Confirmation of
13 Response. This was a panel of experts separate from the
14 panel of experts that put together the response criteria.
15 This particular panel was responsible for the response
16 evaluation and here is the process that they went through.

17 The conducted a blinded audit of baseline, first
18 efficacy evaluation, and confirmation of response CT scans.
19 All -- and I underline "all" -- measurable lesions were
20 identified and measured on CT scan using calipers.

21 The sum of the product of the perpendicular
22 diameters and the percent change from baseline was
23 calculated for each patient.

24 Clinical data and non-measurable lesions were
25 reviewed by the panel. They then assigned a response

1 classification, and this is the response classification that
2 we have utilized for all of our reports, all of our
3 presentations, all of our analyses.

4 [Slide.]

5 These are the lymphoma experts that participated
6 in the LEXCOR Panel. As you see, they are a group of expert
7 hematologists and oncologists and cancer radiologists.

8 [Slide.]

9 On our intent-to-treat basis, and that means
10 including all patients enrolled on the study regardless of
11 whether they actually got treatment or not, in the Phase II
12 trial, there was an overall response rate of 46 percent, in
13 the pivotal study 48 percent, and for the combined 203
14 patient database there were 6 percent complete responders,
15 41 percent partial responders, for an overall response rate
16 of 97 of 203 patients, that is, 48 percent.

17 [Slide.]

18 That is shown graphically on this slide. For the
19 pivotal trial, the point estimate for overall response rate,
20 as well as the 95 percent confidence limits, similarly for
21 the Phase II trial, and for the combined database, and this
22 is just to show you the consistency between these two
23 studies.

24 [Slide.]

25 Interestingly, the median reduction in tumor size

1 in complete responders was 100 percent. In partial
2 responders was 89 percent. Even the patients with stable
3 disease had a 33 percent median reduction in tumor size.

4 [Slide.]

5 The mean SPD over time for all responders, that
6 is, the 97 responders in the combined database, is shown on
7 this slide, and as you see, the mean SPD sharply dropped
8 after -- even during -- but after treatment during that
9 first month, and then continued to drop over time, so that
10 there was still some additional shrinkage occurring in
11 responders even at 10 and up to 16 months.

12 [Slide.]

13 If we look at the individual patients in terms of
14 what reduction, what maximum reduction in lesion size the
15 individual patients had, as you see, only a few patients had
16 immediate progression of disease, so the majority of
17 patients had some reduction in lesion size, and of course,
18 there were a number who had 100 percent reduction and 50
19 percent or greater reduction in all of those were CRs and
20 PRs, but 70 patients with stable disease had some reduction
21 in tumor size likewise.

22 [Slide.]

23 The duration of response is shown on this slide,
24 and the duration, of course, is defined as the time interval
25 between first evidence of 50 percent or greater overall

1 shrinkage and progression and disease.

2 For the Phase II trial, the median was 8.6 months.
3 For the pivotal study, it was 9.2 months, the median was not
4 been reached. So for the combined database, a median has
5 not been reached after 9+ months of observation.

6 [Slide.]

7 Time to progression in responders is shown on this
8 slide. For the Phase II trial, the median was 10.2 months.
9 For the pivotal study, it is 11.8 months and ongoing, and
10 thus, for the combined database, 97 responders, we have not
11 reached a median at 11.4+ months.

12 [Slide.]

13 This is shown graphically on this Kaplan-Meier
14 curve where you can see the time to progression curve for
15 responders on the pivotal trial with an N of 80, and for the
16 Phase II trial with an N of 17. The C's indicate patients
17 who are censored on this Kaplan-Meier analysis and are
18 ongoing responders.

19 [Slide.]

20 We also conducted an analysis, a univariate
21 analysis of baseline prognostic factors. I would like to
22 stress that this is an exploratory analysis and thus the
23 data has to be cautiously interpreted.

24 We included 22 prognostic factors and most of
25 these are the usually reported factors that I considered in

1 studies reported in the medical literature.

2 We also included number of relapses, number of
3 prior chemotherapy courses, and five criteria for clinical
4 chemoresistance including resistance to first chemotherapy
5 to last chemotherapy, 20 intervening chemotherapy, or to all
6 chemotherapy ever received by the patient, as well as those
7 patients whose last chemotherapy response was less than 3
8 months. We are also curious to find out about patients with
9 prior ABMT or prior anthracycline therapy.

10 [Slide.]

11 The highlights of this exploratory univariate
12 analysis are shown on the next two slides.

13 Older patients had an overall response rate
14 similar to that of younger patients. Patients with bulky
15 disease showed a trend towards a lower overall response rate
16 and yet in patients with lesions greater than 7 cm, the
17 response rate is 38 percent in this study.

18 IWF Types B, C, and D patients did show a higher
19 overall response rate of 58 percent. Patients who had had
20 ABMT showed a higher overall response rate at 78 percent,
21 and that was intriguing.

22 Patients who were bcl-2 positive in peripheral
23 blood at baseline had a higher overall response rate at 60
24 percent. I have shown those that were significant at the
25 0.05 level with an asterisk.

1 [Slide.]

2 Patients whose bone marrow was not involved by
3 lymphoma had a higher overall response rate, 59 percent.
4 Those with absence of extranodal disease showed a trend for
5 higher overall response rate.

6 Patients with a lower number of relapses had a
7 higher overall response rate, and patients with resistance
8 to the last chemotherapy course had a lower overall response
9 rate, and yet the overall response rate in those patients is
10 36 percent.

11 [Slide.]

12 This summarizes the logistic regression analysis
13 versus response. On the next slide I will show you the
14 results of the logistic regression analysis versus TTP and
15 versus duration of response.

16 As you see, at the 0.05 level, there were only
17 three factors that emerged as significant, and one of them
18 was histologic type, the Type A patients have a lower
19 overall response rate at 11 percent as compared to the B, C,
20 and D patients. We do think that these patients, however,
21 do have important clinical benefit, and we will be glad to
22 discuss that further with you during the Q and A period.

23 These patients, in spite of that low response
24 rate, of the 37 patients, 28 had some tumor shrinkage, and
25 of those 28 who did have some tumor shrinkage -- and I will

1 be glad to show you that graph later on -- 5 were
2 symptomatic from their lymphoma, and 1 of those was a
3 responder and his symptoms disappeared after treatment.

4 Four of those were patients with stable disease,
5 and in 2 cases, the symptoms disappeared. So we believe
6 that there is a clinical benefit, an important clinical
7 benefit for the A patients, despite the somewhat lower, 11
8 percent, response rate.

9 Also significant was prior ABMT, as I have
10 mentioned, the 78-80 percent response rate in patients who
11 did have prior ABMT, and also significant, bcl-2 at
12 baseline. Bulky disease, not significant, but approach
13 significance, and so on.

14 [Slide.]

15 Both for time to progression and for duration of
16 response, it was only resistance to last chemotherapy that
17 emerged as significant at the p 0.05 level. Again, these
18 patients did have a response rate of 34 percent.

19 The bulky disease patients approached
20 significance, however, they do have an important response
21 rate, 38 percent in those patients with lesions greater than
22 7 cm, and we will be glad again to discuss that further in
23 the Q and A period. Suffice it to say that we do have some
24 preliminary data from the separate study that we conducted
25 including patients with lesions greater than 10 cm, and that

1 preliminary data, which has been included in the 120-day
2 update, shows a 48 percent response rate, 10 of 21 patients.

3 [Slide.]

4 We initially established the primary and secondary
5 efficacy endpoints. The study was then initiated and
6 subsequently, after discussions with the Agency, we agreed
7 to also conduct additional analysis utilizing patients as
8 their own controls, that is, a comparison to last
9 chemotherapy results and a comparison to last therapy.

10 Also, from the literature review, a comparison to
11 reported results with fludarabine and cladribine in similar
12 patient populations.

13 [Slide.]

14 On this table, I would like to show you the
15 duration of response to IDEC-C2B8 compared with duration of
16 response to prior therapies.

17 As you can see, the median duration in the
18 combined database of Phase II and pivotal trial has not been
19 reached after 9+ months of observation. For last
20 chemotherapy, the median was 12 months, and for last therapy
21 of any kind, the median was 11 months.

22 [Slide.]

23 Graphically, on the next slide, in the form of a
24 Kaplan-Meier analysis, you can see that the duration or
25 response curves for the responders to IDEC-C2B8, for the

1 responders to last prior therapy, and for the responders to
2 last prior chemotherapy, these curves overlap and there is
3 no significant difference on the Kaplan-Meier analysis.

4 [Slide.]

5 As I said, we looked at studies in the literature
6 where fludarabine was used in the treatment of similar
7 patient populations, and we found four such studies that met
8 the criteria prospectively established for comparator
9 studies, and those were the ones reported by Whelan,
10 Hiddeman, Falkson, and Pigaditou, and the point estimate for
11 overall response rate and 95 percent confidence limits are
12 shown here for each of those four studies.

13 Then, if you combine those four studies, a total
14 of 138 patients, the overall response rate was 41 percent
15 with these confidence limits, whereas, for IDEC-C2B8, in our
16 203 patients, it is 48 percent with those confidence limits,
17 so you can compare these two bars.

18 [Slide.]

19 For cladribine, we found two studies, that of Kay
20 with 40 patients, Hoffman 21 patients, combined database of
21 61 patients, and in the combined database, the overall
22 response rate was 43 percent with these confidence limits,
23 and you can compare that to the response rate with IDEC-
24 C2B8.

25 [Slide.]

1 So, in summary, for efficacy, the overall response
2 rate is 48 percent in the intent-to-treat patient
3 population. This was the primary efficacy endpoint, and the
4 results exceeded the 35 to 40 percent goal that had been
5 prospectively established.

6 Favorable reponse rates are also seen in
7 clinically chemoresistant patients.

8 [Slide.]

9 Secondary endpoints, the median duration of
10 response was not reached after 9+ months of observation, and
11 this exceeds the goal of equal to or greater than 6 months
12 that had been prospectively established.

13 [Slide.]

14 Likewise for median time to progression in
15 responders, that median has not been reached after 11.4+
16 months. That exceeds the goal of equal to or greater than 8
17 month that has been prospectively established.

18 [Slide.]

19 So, in conclusion, IDEC-C2B8, given once weekly
20 for four 375 mg/m² intravenous infusions, is safe and
21 effective in the treatment of patients with relapsed low-
22 grade or follicular non-Hodgkin's lymphoma, that is, IWF
23 Classes A, B, C, and D.

24 It has significant clinical activity, a novel
25 mechanism of action, and compares favorably with alternative

1 therapies in response rate and response duration.

2 It is administered over a shorter period of time,
3 22 days, and has a more favorable safety profile.

4 I cannot end my presentation without acknowledging
5 the very significant and very personal contribution of the
6 patients who participated in those studies. This treatment
7 is for them, however, had it not been for those patients, we
8 would have no data to present to you today, so we are
9 grateful to them.

10 [Slide.]

11 I would also to acknowledge our consultants and
12 investigators, and some of them are sitting here in the
13 audience today. Also, our colleagues from Roche and
14 Genentech, and very specially, the 300 professionals at IDEC
15 Pharmaceuticals that are represented here today by the team
16 sitting at this table.

17 Thank you very much. We will be glad to take
18 questions, and if Dr. Broudy would like us to do that now, I
19 would like to call to the podium my colleague, Dr. Christine
20 White, who is our Senior Director of Clinical Oncology.

21 DR. BROUDY: Thank you very much. Yes, this is
22 the time for questions.

23 **Committee Discussion**

24 DR. BROUDY: Are there any questions for Dr.
25 Grillo-Lopez or Dr. White? Dr. Berman.

1 DR. BERMAN: I would just like to comment that the
2 company did a very careful series of investigations and a
3 very clear presentation, but I have a question, and you
4 mentioned it, Dr. Grillo-Lopez, about the fact that patients
5 who had had a prior autologous transplant seemed to have a
6 higher overall response rate.

7 Was this a group of patients that had a long
8 interval between their transplant and the treatment with the
9 monoclonal antibody or can you speculate why this may be so?

10 DR. GRILLO-LOPEZ: The question is was there a
11 long period of time between transplant and antibody therapy
12 and to speculate on the reasons why this high response rate
13 has been observed.

14 This has been intriguing and in fact we have
15 looked carefully at that patient population. They are
16 predominantly males and they are younger with a median age
17 of 48 years. However, when we analyzed for bulky disease,
18 there was no statistically significant difference in the
19 range of tumor volume or tumor size as measured as SPD,
20 these patients compared to the overall population.

21 They had received more prior chemotherapy. In
22 fact, 80 percent of these patients had received three or
23 more courses of chemotherapy previously. They had also
24 received more anthracycline therapy, 92 percent of these
25 patients had received anthracyclines.

1 We also looked at bone marrow invasion and
2 extranodal disease, and there was significant difference in
3 the incidence of bone marrow positivity or extranodal
4 disease in these patients compared to the rest of the
5 patient population.

6 So frankly, I am left without a good explanation
7 for why these patients had a higher response rate, but this
8 is our finding.

9 DR. BERMAN: What about the interval from
10 transplant to treatment with the antibody, was it long?

11 DR. GRILLO-LOPEZ: Some patients received antibody
12 upon progression of disease following transplant, but many
13 patients had received some other chemotherapies, maybe even
14 two courses of chemotherapy following transplant, so not
15 even half of these patients were treated immediately
16 following ABMT.

17 DR. BROUDY: Yes.

18 DR. MILLER: Could you please comment or show the
19 correlation between therapy LEXCOR gradation of CR and PR
20 and the primary investigator's definition in the patients of
21 CR and PR?

22 DR. GRILLO-LOPEZ: Certainly. Can I see the
23 LEXCOR slides.

24 The question is what was the correlation between
25 the results of this blinded independent panel that we have

1 called LEXCOR and the response classifications assigned by
2 the investigators at the sites.

3 [Slide.]

4 On this slide you can see the concordance on
5 response classifications for the 166 patients in the pivotal
6 trial. The investigator called 90 of these patients
7 responders, so according to the investigators, the response
8 rate was 54 percent.

9 LEXCOR agreed with the investigators in 77 of 90
10 cases for a concordance rate of 85 percent. In turn, LEXCOR
11 called 80 patients responders for the 48 percent overall
12 response rate that we have reported, and the investigator
13 agreed with LEXCOR in 77 of these 80 cases, for a
14 concordance rate of 96.3 percent.

15 DR. MILLER: Thank you.

16 My second question, you mentioned that you thought
17 the neutropenia and thrombocytopenia was peripheral. Do you
18 mean peripheral and unrelated to the drug or related to
19 peripheral destruction due to the drug?

20 DR. GRILLO-LOPEZ: I will ask Dr. White to address
21 that.

22 DR. WHITE: It was our impression, particularly in
23 the case of thrombocytopenia that it was peripheral and
24 possibly related to the drug. The possible mechanism would
25 be FC receptors binding the neutrophils or platelets. In

1 particular, we have seen in one patient, a patient who was
2 treated on the single agent study, who had some
3 thrombocytopenia at the time that wasn't thought to be too
4 clinically significant, was then retreated on a retreatment
5 study, who right after infusion developed what looked like
6 an immune thrombocytopenia, possibly hemolytic anemia, at
7 that time resolved with steroids. That was a single case,
8 but that was what led us to believe that there could have
9 been a peripheral immune mechanism.

10 In the case of neutropenia, the neutropenias we
11 have seen during the treatment period, and during the
12 follow-up period, have been predominantly mild, but there
13 have been a small number of cases of Grade 3 and 4
14 neutropenia. In all of those cases, there doesn't seem to
15 be any particular time that it occurs and in all these
16 cases, the patients when treated with G-CSF have been very
17 G-CSF sensitive.

18 In the case of neutropenia in the follow-up
19 period, it is not absolutely clear that it is drug related.
20 We are picking up a total of 8 patients out of 315 who had
21 less than 500 granulocyte counts in the follow-up period,
22 and in a couple of those cases, the next time the blood was
23 drawn it was normal, but in a few of those cases, they were
24 persistent for a period and responsive to G-CSF and whether
25 that is remotely drug related or whether that is heavily

1 pretreated patients cycling into neutropenia and occult
2 infection or some other mechanism, we just don't know the
3 answer to that right now.

4 DR. MILLER: One final question. Do you have any
5 molecular data in the patients that were bcl-2 positive?

6 DR. GRILLO-LOPEZ: Yes. We did an assay for bcl-2
7 translocation. We used the BCR assay methodology that was
8 described by Gribben and others, and has been modified and
9 is currently used to Roswell Park and a number of other
10 institutions.

11 That methodology gives us a sensitivity of 1 in
12 100,000 cells, but at times we pick up even 1 in a million
13 cells. What we found was that with the single agent, about
14 75 percent of patients will clear the translocation from
15 peripheral blood by three months after therapy, and about 50
16 percent of patients will clear bone marrow following
17 treatment.

18 We did do the bcl-2 studies because in the pilot
19 CHOP study that we had done, we had found that of 8 patients
20 who in that study happened to be tested for bcl-2 and found
21 to be positive, 7 also cleared and had long-term remissions.
22 At the time that this happened, clearing bcl-2 from
23 peripheral blood had not been reported.

24 Subsequently, Cabanillas, McLaughlin, and others
25 have reported clearance of bcl-2 from peripheral blood and

1 marrow with intensive chemotherapy treatments like FMD, ATT,
2 and so on.

3 DR. MILLER: Thank you.

4 DR. BROUDY: Yes, Dr. Hong.

5 DR. HONG: I was surprised to see that the
6 immunoglobulin levels didn't drop, and it is an interesting
7 biological phenomenon. You have exceeded the half-life of
8 all those immunoglobulins by several times, so there must be
9 synthesis.

10 I wonder if, one, you have any thought about how
11 that is being maintained. What is more relevant, I think,
12 in the clinical situation, is that if a person is presented
13 with an infectious agent to which he must mount a B-cell
14 response, he has to have the ability to give a recall
15 response.

16 Do you have any studies that relate to the ability
17 of such individuals to respond in a recall manner?

18 DR. GRILLO-LOPEZ: I would ask Dr. White to
19 address that.

20 DR. WHITE: Although our mean immunoglobulin
21 levels did remain in the normal limits for the 315 patients
22 in our database, there were in fact 13 percent of patients
23 who had a fall in either their IgG, IgM, IgA, or some
24 combination to 50 percent from their baseline into the
25 abnormal range.

1 In most of those, we have started to see recovery
2 although some of the patients, it has been most recent and
3 we don't yet have recovery on those patients.

4 With regard to why that might be, well, we are not
5 destroying plasma cells, and so mature plasma cells should
6 still be in the circulation, and of course, there is
7 persistent immunoglobulin. B cells are depleted and
8 immediately the median recovery time is 9 to 12 months, but
9 some patients recover obviously earlier, and that is our
10 explanation for why we are not seeing change in the mean
11 immunoglobulins, our potential explanation.

12 With regard to specific function, we do not have
13 any direct data with regard to rechallenging patients with
14 particular antigens, but we have actually set up a trial
15 which is just starting, that will look at whether patients,
16 with normal controls and with cancer controls, that will
17 look at whether patients who had prior immunity to
18 vaccinated antigens maintain that immunity or whether they
19 need revaccination, but that will be some time before we
20 have that answer.

21 DR. GRILLO-LOPEZ: If I may, let me add that
22 although recovery occurs within 9 to 12 months, this is in
23 peripheral blood, and although we haven't shown this, I
24 would have to assume that recovery occurs earlier in the
25 lymph nodes and in the marrow.

1 DR. WHITE: Thank you, Antonio. In fact, in a
2 single instance, anecdotal as it may be, we did see a
3 patient who recovered immunoglobulin. This was a patient
4 that we were considering for retreatment, and when we
5 initially started retreatment studies we looked at the B
6 cells and in the immunoglobulin to make sure patients were
7 in a safe range before we went ahead and retreated them, and
8 we did have, in fact, a patient who had had an
9 immunoglobulin nadir, had recovered immunoglobulin even
10 though B cells were still low in the peripheral circulation,
11 and that was a single patient who actually was biopsied,
12 just a needle biopsy, and the node had B cells at the time.

13 DR. ANDERSON: Actually, Dr. Hong asked my exact
14 questions, but let me extend it just slightly, and that is,
15 since what you are doing is removing the B-cell arm of the
16 body's immune defense system, have you given thought to the
17 concern that the primary threat to these patients might very
18 well be an exposure to a new antigen, a new pathogen, which
19 they had not seen before, therefore, there would not be the
20 B plasma cells, but an inability to mount a B-cell response?

21 DR. GRILLO-LOPEZ: Yes, and I would like to see
22 the Petracini slides.

23 [Slide.]

24 The question is are these patients going to be
25 immunocompromised and develop infections to new antigens

1 that they haven't seen before because of the B-cell
2 depletion, despite the IgG, A and M levels remaining fairly
3 stable.

4 Well, I would like to say that B-cell depletion is
5 a phenomenon that we are not setting a precedent for.
6 Obviously, as you know, this has been reported with ABMT,
7 and this is the study reported by Petracini and others back
8 in '89 from the Dana Farber experience with ABMT, where they
9 also showed a sharp drop in the CD20 counts in patients
10 treated with ABMT, where 50 percent of these patients had
11 recovered by four months, but full recovery in 100 percent
12 of patients did not occur until eight or nine months.

13 So this is true of ABMT. And if I can see the
14 Mackall slide.

15 [Slide.]

16 This has also been reported with chemotherapy. Of
17 course, with both chemotherapy and ABMT, you are depleting
18 not only B cells, but practically all lineages. So with
19 chemotherapy, Mackall from the NCI reported in Blood the
20 experience at the National Cancer Institute and what they
21 have seen will be on the next slide as soon as we are ready.

22 [Slide.]

23 Basically, what they have seen is that with
24 chemotherapy, regardless of the type of intensive
25 chemotherapy regimen that you might use, you also see a very

1 profound depletion of B cells which lasts for as long as the
2 chemotherapy is being administered.

3 So it stays down there for each and every cycle of
4 chemotherapy up to 10, 18 cycles were given in the studies
5 particularly reported by Mackall in this article. So they
6 are expressing it. We are not setting some new precedent
7 here. B-cell depletion has been with us for a long time,
8 and the concerns that we might have with the antibody are
9 the same that you would have with patients treated with ABMT
10 or with chemotherapy except that with the antibody, the B-
11 cell depletion is selective, specific, and you are not
12 affecting T cells, and you are not affecting other lineages
13 like you do affect them with ABMT and chemotherapy, so we
14 should perhaps less of a concern.

15 However, I think the study that Dr. White has
16 mentioned will more directly address the concerns that you
17 have expressed.

18 DR. BROUDY: Dr. Goldsby.

19 DR. GOLDSBY: One of your slides mentions a novel
20 mechanism of action of the agent. Could you comment on that
21 novel mechanism, please?

22 DR. GRILLO-LOPEZ: The question is relative to the
23 mechanism of action of the agent. We don't know that this
24 agent has one mechanism of action. In vitro, we have of
25 course shown CDC, ADCC, and we have shown that in our labs

1 in IDEC at San Diego, and scientists at UCLA, Bonavida,
2 Demidem, and others, have shown induction of apoptosis in
3 human lymphoma cell lines and also the ability for the
4 antibody to sensitize those resistant, chemotherapy-
5 resistant cell lines to the effects of chemotherapy.

6 Likewise, Dr. Maloney, who is here in the
7 audience, has done a number of very elegant mechanistic
8 studies, and if I could ask please ask Dr. David Maloney
9 from the Fred Hutchinson Cancer Center to come to the
10 microphone, he might speak to those studies that he has
11 performed.

12 DR. MALONEY: We have investigated this IDEC
13 antibody and found that it can directly induce apoptosis in
14 resistant cell lines that are growing in culture, and this
15 appears to be a mechanism where the antibody, by directly
16 binding to the cells, can inhibit cell proliferation and
17 directly induce apoptosis.

18 It doesn't occur in all cell lines, and it is a
19 focus of my laboratory to figure out what cell lines are
20 more sensitive. Unfortunately, we don't really have yet
21 low-grade lymphomas that can be maintained in culture to
22 answer these questions directly, but I think the mechanisms
23 are three: complement antibody-dependent cell media and
24 cytotoxicity, and then this direct effect of either
25 inhibition of proliferation directly or by inducing

1 apoptosis.

2 DR. GOLDSBY: One follow-up question. If you look
3 at cell populations from individuals who have resisted the
4 agent, do you find that those B cells are resistant to ADCC
5 or do you find any change in their P53 status?

6 DR. MALONEY: We have been attempting to make cell
7 lines in vitro that are differentially sensitive, and I
8 don't have really any results on that yet. It appears that
9 cells that are more rapidly proliferating, interestingly,
10 are the more sensitive. That is actually in contrast to
11 low-grade lymphomas where we think the proliferative rate is
12 actually quite low. We don't have those correlative studies
13 yet.

14 DR. BROUDY: Dr. O'Fallon.

15 DR. O'FALLON: Yes, a few questions regarding
16 statistical things. Slide 31, one of your safety slides,
17 you reported the number of infections during the treatment
18 period and then during the one-year followup.

19 Are these the same people experiencing these
20 infections or overlap, how many total people experienced
21 infections?

22 DR. WHITE: In just a couple of those cases, they
23 were the same people experiencing two infections, but most
24 of those were separate. We actually realized that having B-
25 cell depletion for a median of 9 to 12 months raised the

1 question of whether there was going to be long-term
2 infections.

3 So although in the follow-up period, in general,
4 we collected serious adverse experiences and adverse
5 experiences that were probably possibly related to the study
6 drug, or of unknown relationship, we specifically instructed
7 both our investigators, their coordinators, and our auditors
8 to collect every single infection no matter how trivial, and
9 in addition, if we saw on the concomitant med sheet that the
10 patient had been given antibiotics, even if there was no
11 adverse event, we went back and queried and asked for the
12 adverse event that had precipitated the antibiotics.

13 For that reason, we picked up, in addition to
14 significant infections and serious infections, we picked up
15 some colds and sore throats and viral infections that were
16 common infections.

17 So I will show you a series of three slides now
18 that I will show you all infections in this population over
19 one year time and break them out for type.

20 [Slide.]

21 This was the viral infections. Most of these were
22 upper respiratory infections, colds, something called a
23 viral syndrome. There were a number of labial herpes
24 simplex uncomplicated, a bronchitis, a pharyngitis, a
25 diagnosis of viral pneumonia. The only significant

1 infections on this slide were one hospitalization for a
2 diagnosis of disseminated zoster that actually was just a
3 few vesicular lesions that took actually a couple of days to
4 diagnose. It wasn't a typical syndrome, and there was one
5 case of segregation facial herpes.

6 [Slide.]

7 We attributed to the category of bacterial any
8 infection in which the patients received anti-bacterial
9 antibiotics. Again, we picked up a lot of just standard
10 upper respiratory infections, a patient with a single
11 pustule on the skin, a minor skin infection, runny noses,
12 diagnoses of sinusitis even without x-rays, but there were
13 also a few significant infections in this list.

14 One was a myofascial infection that required
15 intravenous antibiotics, and there were two cases of sepsis,
16 actually three, but one is not listed under the word sepsis.
17 One case of sepsis was a catheter-related sepsis where the
18 patient came into the clinic quite well with no complaints
19 for routine exam, and had a catheter flushed, and then a
20 couple of hours later had fever and chills in a way that all
21 of us who have treated patients have sometimes seen, and a
22 single patient who had fever and chills and had Listeria
23 grow from the blood on day 15.

24 But the majority of these were minor infections
25 including infections that were clearly unrelated to the

1 study drug, like this is a patient who had an operation for
2 a fracture and had a post-op infection that the investigator
3 felt was unrelated.

4 [Slide.]

5 For fungal infections, they were the three that
6 Dr. Grillo-Lopez mentioned a few minutes ago, two oral
7 candidas and one nail fungal infection. Under the Unknown
8 list, we listed anything that was not attributed to viral or
9 bacterial, and again the majority were minor like a
10 sebaceous cyst, a pharyngitis, a skin infection, but we did
11 have a couple of more significant infections although not in
12 this category.

13 The overlap between these patients is relatively
14 minimal. There is about two or three patients who are
15 represented on more than one of those lines.

16 DR. O'FALLON: So although the infections are not
17 terribly serious, there is about 100 different patients over
18 the course of the therapy plus the year who experienced --

19 DR. WHITE: Actually, I apologize, within the
20 treatment period and with the follow-up period, there is not
21 significant overlap, two or three patients, however, from
22 treatment to followup, I don't have that answer right now,
23 but I think I can give it to you in a few minutes if you
24 could give us a few minutes to work on that.

25 DR. O'FALLON: So you misunderstood my first --

1 DR. WHITE: Yes.

2 DR. O'FALLON: Let me move on to more specific
3 statistical questions. You showed a logistic regression
4 analysis that was Slide No. 61, but you didn't tell me
5 whether this was a multivariate logistic regression or a
6 series of univariate regressions that you were summarizing.

7 DR. GRILLO-LOPEZ: Let me call to the microphone
8 Dr. David Shen, who is our head biostatistician, and can
9 address that question very nicely. Dr. Shen.

10 The question was regarding the methodology used in
11 the logistic regression analysis, was it a series of
12 univariates or what of analysis was it?

13 DR. SHEN: It is a multiple logistic, stepwise
14 multiple logistic regression analysis where you have a
15 logistical model with all the prognostic factor as a
16 dependent variable and had the responder as an independent
17 variable.

18 DR. O'FALLON: Okay. So these p values that were
19 summarized were not independent p values because all the
20 variables are in the model at the same time.

21 DR. SHEN: That is correct.

22 DR. O'FALLON: The very next slide you used the
23 expression logistic regression in terms of analyzing time to
24 progression and duration of response.

25 May I assume that that was a mistake in the

1 labeling of the slide?

2 DR. SHEN: That one -- can we see the slide,
3 please?

4 DR. O'FALLON: Slide No. 62.

5 DR. SHEN: That is a univariate analysis.

6 DR. O'FALLON: I am questioning whether it was a
7 logistic regression analysis or some other type of analysis
8 that might have been appropriate for time to progression and
9 duration of response.

10 DR. SHEN: We did a Cox regression analysis
11 afterward, so it is an ad-hoc analysis. If you give me some
12 time, I can go back and show you what the p values look
13 like.

14 DR. O'FALLON: Okay. The last two questions
15 pertain to the analysis where you were comparing the
16 individuals who responded to their experience in their prior
17 round of chemotherapy. Slide No. 64, for example, shows the
18 97 responders that you are reporting here and 141 from the
19 last chemotherapy.

20 I am confused by the fact that it is 141. It
21 would seem like it should be 97 since we are presumably
22 going to do a paired analysis in which we would compare the
23 same people who responded in this period of time to what
24 they had done in the previous analysis, and if we didn't do
25 it, I don't understand quite how we compared them because

1 there must have been an awful lot of overlap, so there would
2 have been a lot of dependency among the variables.

3 DR. SHEN: You are absolutely right, that it was
4 done by assuming those two groups of independent, in fact,
5 is a pair comparison. What we did was we took all the
6 patients who respond to CTPA and all the patients who
7 respond to last chemotherapy assuming those are two
8 independent groups, and compared them.

9 DR. O'FALLON: But they won't be independent
10 groups.

11 DR. SHEN: That is correct.

12 DR. O'FALLON: And the same comment about the
13 Kaplan-Meier, the very next slide.

14 DR. GRILLO-LOPEZ: May I address your first
15 question first? We did the analysis both ways. We prefer
16 this analysis because here, the denominator remains fixed,
17 it is 97 of the 203 patients, and likewise, 141 of the 203
18 patients, and 125 of the 203, so you have a fixed
19 denominator throughout.

20 As you see, when you analyze the p values are not
21 significant, however, we also did the analysis as you said
22 originally, using 97 as the denominator, and in that case --
23 and I think you will see that in Dr. Bernard Parker's
24 presentation, that he will show that -- the difference is
25 that for last chemotherapy, if I remember correctly, David,

1 it was 19 months when you used 97 as a denominator, however,
2 the p values are still not significant, so we did both, and
3 we did the Kaplan-Meier both ways, and it is not
4 significant.

5 DR. WHITE: May I go back to the question on
6 infection? Twenty-nine percent of patients had one or more
7 infections over the entire course of counting those types of
8 infections.

9 DR. O'FALLON: Thank you.

10 DR. BROUDY: Dr. Grillo-Lopez, could you comment
11 on the lower response rate in the Working Formulation A, the
12 small lymphocytic lymphoma patients and whether that relates
13 to the density of the CD20, or do you have some other
14 mechanism to explain their 11 percent response rate in
15 contrast to the 48 percent in the other groups?

16 DR. GRILLO-LOPEZ: Yes.

17 [Slide.]

18 That has turned out to be very interesting and
19 challenging. I have to say first, of course, that the study
20 was not designed to show what the response rate was in the
21 Class A patients, it was designed and powered to show the
22 overall response rate as a primary efficacy parameter across
23 A, B, C, D, and we did do that.

24 However, this was interesting, so we did look at
25 it, and let me share some of that information with you.

1 These patients were predominantly heavily pretreated males.

2 In fact, 76 percent of these patients were males.

3 There were a number of situations, like, for
4 example, one patient was judged inevaluable by LEXCOR
5 because they could not determine that there was measurable
6 progressive disease, and on histology, was found to have
7 mostly CD4 T cells and less than 10 percent B cells on
8 biopsy.

9 Another patient was reported by the
10 investigational site to have faint CD20 on FACS analysis, and
11 these patients may benefit from higher doses and/or more
12 doses of the antibody, and in answer to your question, yes,
13 when we looked at our entire database of low-grade lymphoma
14 patients and compared them to the Class A's, the Class A's
15 tend to have a lower antigen density on the cell surface.

16 We also looked at a small group of CLL patients,
17 samples that we obtained courtesy of Dr. Susan O'Brien from
18 M.D. Anderson Hospital, and as previously reported by
19 others, the CLL's have a lower and more heterogenous CD20
20 expression.

21 [Slide.]

22 So the Class A patients in our population did have
23 a lower response rate. It was 11 percent. However, the
24 patients that did respond had a time to progression and a
25 duration of response which was not significantly different

1 from the rest of the population, so they did have responses
2 that were as durable as that of the other B, C, D patients.

3 Interestingly, they had had a shorter time to
4 progression and duration of response with their last
5 chemotherapy as compared to the B, C, D's. We talked about
6 this. They did not deplete their circulating cells as well
7 as the B, C, D's, and there is a correlation between
8 response and B-cell depletion.

9 More heterogenous histologies were included. For
10 example, in the pivotal trial, where there were 33 Class A
11 patients, interestingly, only 18 were really small
12 lymphocytic well-differentiated, 18 of the 33. The rest
13 were plasma cytoids. There were a couple of diffuse small
14 cleaveds. There were a couple of mantle cells, and there
15 was a Waldenstrom's and a couple of not well characterized
16 lymphomas lumped into Class A's.

17 These patients, the Class A's in our studies were
18 more likely to have marrow involvement as you would expect
19 and extranodal disease. Interestingly, they had received
20 more courses of chemotherapy, in fact, 55 percent had
21 received three or more courses of chemotherapy, so they were
22 more heavily pretreated than the B, C, D patients.

23 [Slide.]

24 Again, interestingly, although the response rate
25 was lower, and it was 11 percent, when you look at the

1 percent change in lesion size for these patients, you see
2 that 28 of the 37 patients did have some tumor regression.
3 In fact, as I mentioned during the presentation, there were
4 5 of these patients or 4 of these patients that were
5 symptomatic with B symptoms or other disease-related
6 symptoms.

7 One of those was a responder, and his symptoms
8 went away. The others were stable and in two cases, the
9 symptoms also went away, so there is some clinical benefit,
10 there is some biological effect as manifested by the tumor
11 reduction, and these patients we believe do benefit from the
12 antibody.

13 Your question, and of course, there is the
14 implication here that these patients may benefit from higher
15 doses or more doses of the antibody, and that will surely be
16 explored in future studies.

17 DR. BROUDY: Dr. Berman.

18 DR. BERMAN: Can you comment on the role for
19 individual dosing especially in patients with bulky disease
20 greater than 7 cm or 10 cm?

21 DR. GRILLO-LOPEZ: Yes. That has been an issue
22 for discussion, and of course, our first attempt has been to
23 establish a practical regimen for every-day outpatient use,
24 so we have looked at dose and schedule that is fixed and
25 stable across all patients, of course, dosing based on m^2 .

1 What we have found, of course, is that this
2 particular dose and schedule is effective, as you have seen,
3 but that there may be some patient populations that could
4 benefit from individualized or higher, more frequent doses.

5 In spite of that, we have seen pretty good
6 response rates even in the bulky disease patients.

7 Did I answer your question?

8 DR. BROUDY: Dr. August.

9 DR. GRILLO-LOPEZ: I think she said no.

10 DR. BROUDY: Did you say no? Oh, I am sorry.

11 DR. BERMAN: The pharmacokinetics are somewhat
12 unusual. They are nonlinear pharmacokinetics and especially
13 in people with bone marrow involvement. Has this been
14 looked at before for clinical trials, were there patients
15 with marrow involvement, in fact, have a different pattern
16 than in patients who don't have bone marrow involvement?

17 DR. GRILLO-LOPEZ: The question is do the patients
18 with marrow involvement have a different pharmacokinetic
19 pattern. That question is hard to respond to.

20 If you are thinking of tumor bulk versus
21 pharmacokinetics, I think the answer is clearly yes. The
22 patients that have a larger number of circulating B cells,
23 the patients that have larger tumor volume as measured by
24 the diameter and the maximum diameter of the largest lesion,
25 as measured by SPD, there is a correlation between those

1 measures of tumor volume or circulating B-cell mass and
2 serum levels of the antibody, and the patients that have the
3 larger tumor volume have lower levels of circulating
4 antibody.

5 We do know that serum levels of circulating free
6 antibody do correlate with response. There is a significant
7 correlation where patients with the higher peak and trough
8 levels of circulating free antibody, that correlates
9 directly with response.

10 So I still haven't answered your question, but I
11 tried to give you a lot of information.

12 DR. BROUDY: Last question. Dr. August.

13 DR. AUGUST: I would like to go back to the area
14 that Dr. Hong and Dr. Anderson began to explore, and my
15 first question is sort of a housekeeping one.

16 I assume that HACA, which you never explained,
17 means human antichimeric antibody?

18 DR. GRILLO-LOPEZ: I apologize and that is
19 correct.

20 DR. AUGUST: And you found little or no
21 responsiveness, and that raises the question as to whether
22 the material was non-immunogenic or the patients were
23 incompetent, which gets us back to Dr. Anderson's and Dr.
24 Hong's area.

25 In spite of the fact that you showed us some

1 immunoglobulin data, and we have seen a lot of information
2 about your infections, we really don't know anything about
3 these patients' immunologic competence either with respect
4 to secondary immune responses or primary immune responses.

5 I would just comment that the occurrence of herpes
6 simplex reactivations and herpes zoster provide you with an
7 opportunity to look at that, because in normal populations,
8 both of those events are associated with anamnestic
9 responses, and you should have antibody rises, and I presume
10 at some point you collect serum and bank it at the beginning
11 of your studies, and so you simply can wait a few weeks,
12 draw blood on those patients, and get some information on
13 it.

14 I would also like to comment that your analogize
15 also your treatment to the immunosuppression that follows
16 chemotherapy or autologous bone marrow transplantation, but
17 I would just say that what an autologous bone marrow
18 transplant does to the immune system is like hitting it with
19 a hammer, and what you are doing is really inserting an ice
20 pick, and you have a very specific and very neat sort of an
21 immunosuppressive reagent and that is worth studying in and
22 of itself, but I would also remind you that in recovering
23 from the immunosuppression following a bone marrow
24 transplant, the recovery recapitulates ontogeny, and what I
25 mean by that is that some antigens are responded to very

1 early, for example, the EBB virus, and some antigens are
2 responded to much, much later, for example, diphtheria and
3 tetanus toxoids, so that this -- I don't think you can make
4 any assumptions about your patients' immunologic competence
5 or incompetence based on what we think we know about past
6 experience.

7 I mean you have a unique reagent, and these
8 patients are obviously very, very much affected by it, and
9 that their B cells completely disappear, so I wouldn't
10 presume you know the answer to any of these questions before
11 you look.

12 DR. GRILLO-LOPEZ: Absolutely. I agree with
13 everything you have said, and I will never forget the hammer
14 versus ice pick analogy. That's a good one. Thank you very
15 much.

16 DR. BROUDY: Thank you for that graphic image. We
17 are going to take one more question and then we are going to
18 take a five-minute break for audiovisual reasons.

19 Dr. Auchincloss.

20 DR. AUCHINCLOSS: Back to Dr. Goldsby's question
21 about mechanism of action. Do you have any information to
22 suggest that other agents, and in particular I am thinking
23 about steroids, would interfere with the mechanism of
24 action, and I am asking the question for the I guess obvious
25 reason that most of your first dose effects probably would

1 be blocked by steroids, but I think you avoided giving them,
2 if I remember correctly.

3 Was there a reason for that or have you tried
4 using the drug with steroids?

5 DR. GRILLO-LOPEZ: Yes. As you say, we were
6 concerned that, one, there might be an interference by
7 steroids with the mechanism of action of the antibody. We
8 were also concerned that since occasionally, some patients
9 might respond to steroids, they might cloud the accurate
10 determination of response in some patients, so we did make
11 that an exclusion criterion and we did not permit the
12 administration of steroids in this study.

13 Nevertheless, eight patients did receive steroids
14 during or close to the treatment period. In our evaluable
15 patient analysis, we excluded those patients. However, the
16 overall response rate remained the same because, in fact,
17 four of those patients did respond.

18 So there is small patient numbers, but four of the
19 eight patients who received steroids did respond. Now, we
20 also had I think an interesting experience in the study
21 where we looked at the CHOP combination with the antibody,
22 and, of course, with the CHOP chemotherapy, those patients
23 all got five days of steroids with each CHOP cycle, and the
24 results of that particular study were very interesting.

25 Dr. Myron Czuczman, who was the principal

1 investigator in that study, is here with us. I would like
2 to call Dr. Czuczman to the microphone and maybe he can
3 address this question also.

4 DR. AUCHINCLOSS: Could you perhaps comment at the
5 same time about whether the B cells were cleared when you
6 gave steroids or CHOP in addition to the monoclonal
7 antibody?

8 DR. GRILLO-LOPEZ: Yes.

9 DR. AUCHINCLOSS: They were.

10 DR. GRILLO-LOPEZ: They were.

11 DR. CZUCZMAN: We used CHOP chemotherapy and
12 prednisone course with each regimen, and did not see any
13 indication that the efficacy or the patients' response was
14 affected by the steroids. However, they were receiving the
15 CHOP chemotherapy every three weeks for six cycles, and then
16 the antibody in this specific trial was given twice at the
17 beginning of the treatment, twice at the end, and then prior
18 to the third and fifth cycles of treatment for potential
19 synergistic effect and priming effect.

20 So it is very difficult to ascertain what exact
21 response, but the patients did not seem to be having any
22 problem, actually responded continuously through the trial
23 and did benefit.

24 DR. BROUDY: I think we are going to take a five-
25 minute break here just to change the audiovisual equipment.

1 [Recess.]

2 DR. BROUDY: The FDA perspective. Dr. Mark
3 Brunswick will start.

4 **FDA Perspective**

5 DR. BRUNSWICK: Good morning. My name is Mark
6 Brunswick. I am in the Division of Monoclonal Antibodies.
7 I am the product reviewer and chair of this committee. On
8 the first slide is the rest of the members of my committee.

9 [Slide.]

10 CD20 is a pan B cell marker on the majority of B
11 cell lineages from pre-B cell to mature B cells, but
12 excluding plasma cells, as you heard already this morning.

13 It is a cell surface glycoprotein of 35 kD, that
14 does not modulate upon antibody binding.

15 [Slide.]

16 IDEC-C2B8 is a chimeric human/mouse IgG1 against
17 the CD20 antigen. The function is not absolutely clear in
18 vivo, but in vitro the C2B8 mediates complement mediated
19 cytotoxicity, antibody-dependent cellular cytotoxicity, and
20 also apoptosis, but as I said before, the exact mechanism of
21 action is not known.

22 There remain some major manufacturing issues
23 related to product consistency and process validation, but
24 we are working closely with the sponsor to resolve these,
25 and the resolution of these issues will be performed prior

1 to final consideration for approval.

2 I will pass on to Dr. Parker, who is going to
3 discuss the clinical perspective. Thank you.

4 DR. PARKER: I am Bernard Parker. I am with the
5 FDA. I am a clinical reviewer for this biologics licensing
6 application, and I will discuss the FDA review of this data
7 submitted in this application.

8 [Slide.]

9 This slide illustrates all of the studies
10 pertinent to this application. Before I get to that, I just
11 want to mention that these are the subtypes of non-Hodgkin's
12 lymphoma that this study will target.

13 Notice that the frequency is the highest with the
14 IWF Class B non-Hodgkin's lymphoma. This is the follicular,
15 small cleaved cell. Also, notice the relatively long median
16 survival time. Again, I have to mention that these are the
17 diseases which will serve as the focus of this therapy.

18 [Slide.]

19 This slide illustrates all of the studies
20 pertinent to this application. The studies which are shaded
21 were used to obtain a pharmacokinetic profile of C2B8.
22 These studies were 102-01, which was the Phase I/II single-
23 dose study in which C2B8 was given as a single dose in the
24 range of 10 to 500 mg/m²; 102-02, the Phase I/II multiple-
25 dose study in which C2B8 was given in a dose range of 125 to

1 375 mg/m² weekly for a total of four doses; and 102-05, the
2 pivotal, single-arm, single agent study, again, in which
3 C2B8 was given as a dose of 375 weekly for a total of four
4 doses.

5 Various pharmacokinetic parameters were calculated
6 for C2B8 including the area under the curve as a measure of
7 overall exposure. The observed maximal plasma
8 concentration, there are the Cmax, the terminal elimination
9 half-life, and the clearance.

10 [Slide.]

11 Rituximab or C2B8 exhibits nonlinear
12 pharmacokinetics and change with increasing dosage due to
13 saturation of the elimination.

14 A tumor-burden/tumor response relationship is
15 noted with C2B8. The tumor cells function as routes of drug
16 elimination, thus, the clearance of drug is decreased with
17 decreasing tumor burden.

18 [Slide.]

19 With regard to responders to C2B8, serum levels
20 were lower with the first dose due to high tumor burden. As
21 tumor burden decreases, successive infusion and responses
22 lead to higher serum levels due to decreased clearance.
23 This pharmacokinetic finding reflects the pharmacodynamic
24 relationship with the responders.

25 [Slide.]

1 The sponsor has conducted five clinical studies
2 using single drug treatment with C2B8. The data submitted
3 in support of efficacy are derived from 203 subjects
4 enrolled in these two protocols.

5 102-05 again with a total of 166 patients and 102-
6 02, in which 37 of 47 subjects enrolled were treated at the
7 same dose and schedule as in the IDEC-102-05.

8 [Slide.]

9 Protocol 102-05 is a single-arm, multiple-dose,
10 multicenter study conducted at 31 sites in the U.S. and
11 Canada. The eligibility criteria included the following:
12 IWF Subtype Classes A, B, C, and D, which were low-grade or
13 follicular non-Hodgkin's lymphoma. The patients had to be
14 CD20+, at least one prior chemotherapy regimen with or
15 without other therapy including radiotherapy, immunotherapy,
16 and/or bone marrow transplantation.

17 All patients were to have refractory or
18 progressive disease. Patients without bulky disease were
19 also included, and bulky meaning single mass greater than 10
20 cm in its greatest diameter. No patients with CLL were
21 included, and small lymphocytic lymphoma patients had to
22 have a total lymphocyte count of less than 5,000/microliter,
23 and finally, patients could not have malignant pleural
24 effusion or ascites.

25 [Slide.]

1 C2B8 was administered at 375 mg/m² at an initial
2 rate of 50 mg/hour and increased to a maximal rate of 150
3 mg/hour intravenously. Again, it is 375 mg/m² once weekly
4 for four weeks. The use of steroids prophylactically or
5 during infusion was specifically prohibited.

6 During the therapy, the patients were monitored
7 for changes in vital signs and symptoms frequently. Serum
8 for pharmacokinetics and serum human antichimeric antibody
9 titers or HACA levels were also assessed during and after
10 the treatment period, and quantitative serum immunoglobulin
11 levels and peripheral blood lymphocytes for flow cytometry
12 were monitored up to one year after the treatment.

13 [Slide.]

14 The prespecified primary efficacy variable was the
15 overall response rate. The secondary efficacy variables
16 were the time to progression in responders, the response
17 duration, the CR rate, and the PR rate.

18 [Slide.]

19 In addition to the intent-to-treat population,
20 which encompassed all of the registered patients,
21 subpopulations in which efficacy analysis were to be
22 performed included the efficacy population in which all
23 patients received at least one dose of IDEC-C2B8, and the
24 evaluable population, which encompassed all patients who had
25 satisfied all of the eligibility criteria, who had received

1 at least four doses of C2B8, who had no concomitant
2 antineoplastic therapy, and were assessable for tumor
3 response.

4 [Slide.]

5 As discussed with CBER, a clinically meaningful
6 result meant that you had to have an overall response rate
7 of greater than or equal to 35 to 40 percent, a complete
8 response rate of greater than or equal to 15 percent, and
9 response duration of greater than or equal to 6 months.

10 In addition, this could be supported by resolution
11 of tumor-related symptoms, such as the B symptoms.

12 [Slide.]

13 The baseline entry characteristics for the study
14 population is presented in the following two tables. 166
15 patients, which consisted of 105 males and 61 females, were
16 enrolled. The numbers in terms of characteristics with
17 regards to age, ethnicity, and IWF classification, are
18 consistent with the general population with this disease
19 with the exception of the IWF Class A being overrepresented
20 in this study.

21 [Slide.]

22 As a group, the population that received a
23 significant amount of prior therapy with a median of two
24 prior chemotherapy regimens and 14 percent of the population
25 had undergone progenitor cell transplantation, the median

1 time from initial diagnosis to study entry was 4.1 years.

2 Additional baseline entry characteristics included
3 whether the patients were considered chemosensitive, 73
4 percent, or chemoresistant at 27 percent, and
5 chemoresistance was defined as the nonresponse to the last
6 course or a response duration of less than three months
7 after the last chemotherapy.

8 [Slide.]

9 The primary and secondary efficacy analysis were
10 performed in the intent-to-treat, efficacy, and the
11 evaluable patient populations. Out of the total 166
12 patients in the intent-to-treat analysis, 5 subjects did not
13 receive all four infusions. One patient withdrew consent,
14 and four other patients withdrew due to the adverse events.

15 This constituted the efficacy population of 161
16 patients, 10 excluded due to major protocol violations.
17 Here is the efficacy population.

18 The evaluable efficacy population was 151 patients
19 with a total of 15 patients being judged by the sponsor not
20 being evaluable for efficacy.

21 [Slide.]

22 This table illustrates the efficacy analysis from
23 Protocol 102-05. Of 166 total patients in the intent-to-
24 treat population, 10 or 6 percent had a CR rate and 70 or 42
25 percent had a PR rate, for an overall response rate of 48

1 percent.

2 The median time to onset of response as 50 days.
3 The median response duration had not yet been reached in
4 this study, however, based on the number of patients who
5 have already relapsed, the median is between 9 and 12
6 months. 38 of the 80 responders, or 50 percent, are
7 continuing in remission at 13 months followup.

8 The overall response rates being greater than 40
9 percent, and the response durations being greater than 6
10 months, were similar for the efficacy and for the evaluable
11 subpopulations, and met the target designation for
12 successful results. On the CR rate was lower than the
13 target of greater than 15 percent.

14 [Slide.]

15 When reviewing the data from 16 sites which
16 enrolled 5 or more patients, the response rates range from
17 17 percent to 67 percent. At least responsive patient was
18 noted in each site.

19 [Slide.]

20 A total of 39 patients had tumor-related symptoms,
21 which included B symptoms, which consisted of night sweats,
22 fever, and/or weight loss. Also pain, urticaria in one
23 patient, nodal itching was also noted in one patient.
24 Twenty-three of those patients had objective clinical
25 responses.

1 The relief of tumor-associated symptoms was more
2 consistently observed in patients with objective clinical
3 responses. All tumor-related symptoms resolved following
4 C2B8 by the fourth week of treatment and 17 of 23 patients
5 with objective tumor responses. In this case, 8 resolution
6 of symptoms in 8 of 16 patients occurred without the
7 objective tumor responses.

8 [Slide.]

9 A prespecified secondary analysis was conducted to
10 compare the response rate and the duration to C2B8 with that
11 of the most recent chemotherapy regimen. 161 patients had
12 previous chemotherapy. 78 of these patients who had prior
13 chemotherapy responded to C2B8. So, the overall response
14 rate for these patients to C2B8 was 48 percent with a
15 response duration of 9.2+ months.

16 Of 161 patients who had received prior
17 chemotherapy, there were 117 who had responded, for an
18 overall response rate of 73 percent and a CR rate of 37
19 percent with a median response duration of 12 months.

20 [Slide.]

21 In looking at the C2B8 responders who had received
22 previous chemotherapy, we noted that the majority of
23 patients who responded to C2B8, or 63 out of 78 patients, or
24 81 percent, had also responded to the most recent
25 chemotherapy regimen. Approximately half, or 41 of 78

1 patients, had a complete response to the most recent
2 chemotherapy regimen, and the median duration of response to
3 the most recent chemotherapy was 20 months.

4 [Slide.]

5 Now, this table provides the results of an
6 exploratory analysis of overall and complete response rates
7 and response duration according to the number of prior
8 chemotherapy regimens.

9 A notable observation is that with increasing
10 number of chemotherapy regimens, the response rate is
11 unchanged. The response duration data does not have
12 sufficient followup to make an assessment on whether the
13 duration of response to C2B8 varies according to the extent
14 of prior therapy.

15 [Slide.]

16 Ninety-five percent of the patients reported
17 adverse reactions. That is 158 patients out of 166, with 85
18 percent of those adverse events reported during the
19 treatment period. The majority were Grade 1 to 2 in
20 severity, and the most frequent adverse events were infusion
21 related, being fevers, chills, and nausea. The incidence
22 was highest during the first infusion.

23 [Slide.]

24 Listed here are the incidence rates for the
25 adverse events of particular concern which were associated

1 with study drug infusion. 32 episodes of angioedema
2 occurred in 25 patients. 19 episodes of hypotension
3 occurred in 16 patients. 19 episodes of bronchospasm in 17.
4 9 episodes of arrhythmia in 5 patients. Finally, 8 episodes
5 of bradycardia was noted in 6 patients.

6 [Slide.]

7 Four patients, or 2 percent, discontinued the C2B8
8 therapy due to Grade 3 or Grade 4 adverse events. Three
9 patients were discontinued to study day 1 following the
10 onset of these infusion-related symptoms. One other patient
11 experienced Grade 2 arrhythmia during the first two
12 infusions and was hospitalized for the third infusion.
13 During this infusion, Grade 4 arrhythmia was observed and
14 the infusion was stopped. The patient recovered and was
15 discontinued from the study.

16 [Slide.]

17 The next set of data to review from the efficacy
18 studies will be from Protocol 102-02. The eligibility
19 criteria include the following. Patients had to be CD10
20 positive, had to have relapse/refractory non-Hodgkin's
21 lymphoma of any subtype, and there were no restrictions in
22 this case on bulky disease.

23 The treatment plan was weekly treatment I.V.
24 infusions times 4 weeks. The Phase I aspect consisted of
25 escalating dose cohorts receiving either 125, 250, or 375

1 mg/m², and the Phase II aspect, the patients received 375
2 mg/m².

3 I want to mention also that with regards to the
4 Phase I study, 14 to 30 patients were to be enrolled at the
5 biologically active therapeutic dose level in the Phase II
6 trial. The BATD was determined to be at 375, which is why
7 we have 375, and all patients will be treated once weekly
8 for 4 doses.

9 [Slide.]

10 Forty-seven subjects were enrolled in the study,
11 20 in the Phase I portion of the study, and 27 in the Phase
12 II portion. Three subjects were accrued in the 125 mg/m²
13 dose level, 7 were accrued in the 250 mg/m², and 10 were
14 accrued in the 375 mg/m².

15 All the subject in the Phase II portion of the
16 study received 375 mg/m² for 4 infusions. The efficacy
17 results for the last 10 patients enrolled in Phase I and the
18 27 enrolled in the Phase II portions of the study, all of
19 whom were receiving 375 mg/m² four times were combined.

20 [Slide.]

21 The baseline entry characteristics for the study
22 population are presented in this following table. The
23 numbers in terms of characteristics, with regards to age,
24 ethnicity, and IWF class are consistent with the general
25 population.

1 [Slide.]

2 In the Phase I study, there were 6 PR's, that is 2
3 out of 7 patients having a PR in the 250 mg/m² group and 4
4 out of the 10 in the 375 mg/m² group. Among the combined
5 Phase I and Phase II populations, which received 375 mg/m²,
6 3 complete and 14 partial responses were observed.

7 The median time to onset of response was 50 days,
8 and the median duration of response was 8.6 months.

9 [Slide.]

10 There was no clear pattern between the dose
11 frequency or severity of adverse events. At 375 mg/m²,
12 notable were some toxicities observed, which included a
13 myocardial infarction on study day 5, laryngismus in 4
14 patients, and the laryngismus was at Grade 1 to 2.
15 Coagulopathy, thrombocytopenia, and vasodilatation was also
16 noted.

17 [Slide.]

18 The three withdrawals in this study due to adverse
19 events were due to hyperbilirubinemia that was attributed to
20 viral hepatitis following the first infusion, a Grade 4
21 thrombocytopenia, which was a Grade 4 thrombocytopenia with
22 Grade 3 anemia occurring in a patient during the first
23 infusion, and a patient who had suffered a myocardial
24 infarction on study day 5 following Infusion 1.

25 [Slide.]

1 As mentioned before, the data submitted in support
2 of efficacy are derived from 203 subjects enrolled in these
3 two protocols. Again, 102-05 has a total of 166 patients,
4 and 102-02 with 37 of the 47 patients included.

5 [Slide.]

6 The results of 102-02 and 102-05 are confirmatory
7 in demonstrating similar response rates and durability in
8 multicenter settings using the same dose and schedule for
9 C2B8.

10 [Slide.]

11 The following factors strongly correlated with
12 response to therapy. The follicular histology, that is,
13 Types B, C, and D, a history of prior autologous bone marrow
14 transplantation, and the absence of bone marrow involvement
15 with lymphoma. Here is the histology at p value, bone
16 marrow transplant, and bone marrow involvement.

17 There appeared to be no pattern between response
18 rate and the number of prior chemotherapeutic regimens.

19 [Slide.]

20 Safety data are submitted for all the patients,
21 that is, 282 enrolled in the single-agent studies listed in
22 this table. This data is from the original BLA submission,
23 and does not include the 120-day update.

24 [Slide.]

25 This slide demonstrates the number of patients

1 having a respective grade of toxicity during a particular
2 infusion of C2B8. The patients having more than one grade
3 of toxicity were counted only in the highest grade of
4 toxicity. 95 percent of patients experienced the toxicity,
5 80 percent experienced toxicity during the first infusion,
6 and subsequent infusions led to a lower percentage of
7 toxicity around 40 percent.

8 The percentage of patients experiencing Grade 3
9 and 4 toxicity were higher during the first infusion as
10 compared to subsequent infusions. In addition, more
11 subjects discontinued treatment due to adverse events
12 associated with the first infusion as compared with
13 subsequent infusions.

14 [Slide.]

15 The infusional toxicities predominantly were
16 constitutional: fever, chills, hypotension, GI symptoms,
17 and headache. In addition, we noted cardiovascular
18 toxicities with arrhythmia, bradycardia, and
19 hypersensitivity toxicities, angioedema, bronchospasm,
20 laryngismus, and urticaria.

21 [Slide.]

22 The most frequent adverse events were fever, at 54
23 percent, followed by chills 35 percent. We also noted GI
24 symptomatology, headache, and hypotension.

25 [Slide.]

1 Cardiovascular toxicity was noted with arrhythmias
2 being at 1.8 percent and bradycardia at 1.8 percent in 10
3 patients, 4 percent. Two patients had Grade 3 to 4
4 arrhythmias. Myocardial infarction occurred in 1 patient.
5 0.4 percent.

6 [Slide.]

7 Hypersensitivity reactions included angioedema in
8 13 percent of patients, one patient having a Grade 3 to 4
9 angioedema. Bronchospasm occurred in 10 percent, pruritus
10 13, and urticaria in 8 percent.

11 [Slide.]

12 To summarize the total incidence of Grade 3 and 4
13 adverse events, 53 patient, or 20 percent, experienced Grade
14 3 adverse events, and 13 patients, or 5 percent, experienced
15 Grade 4 adverse events.

16 There was a 2 percent incidence of Grade 3
17 headache and a 1 percent incidence each of Grade 3 fever,
18 nausea, abdominal pain. Abnormal laboratory findings
19 included neutropenia, thrombocytopenia, and anemia in a
20 small percentage of the patients.

21 [Slide.]

22 Three patients had documented sepsis, one of these
23 patients with Listeria occurred early in the study period,
24 and one with polymicrobial sepsis and one with pneumonia,
25 occurred later, during the treatment period.

1 Other infections included sinusitis in two
2 patients, one of which requiring hospitalization on study
3 day 3, gastroenteritis, and reactivation of herpes simplex.

4 Because of the prolonged lymphopenia observed
5 during the C2B8 treatment, we noted all the serious
6 infections occurring in the follow-up period.

7 [Slide.]

8 Patients who had infections during the follow-up
9 period, and the follow-up period is from 30 days after the
10 fourth infusion to one year later, included four patients
11 with pneumonia, two patients with herpes simplex infections,
12 and one each with sepsis, upper respiratory tract infection,
13 which the patient was hospitalized, and herpes zoster
14 reactivation, and also a myofascial infection.

15 [Slide.]

16 In two multicenter trials, C2B8 had demonstrated
17 an overall response rate of 46 percent and 48 percent, and
18 CR rates with 6 percent and 8 percent.

19 The median response durations were 8.6 months and
20 9 to 12 months. Toxicity was noted in 95 percent of
21 patients, 75 percent of adverse events being Grade 1 and 2.

22 [Slide.]

23 The pharmacokinetic-pharmacodynamic relationship
24 exists for C2B8. The toxicity profile includes some
25 atypical toxicities. These would include constitutional

1 symptoms, cardiovascular events, and hypersensitivity-like
2 reactions. It also included prolonged sustained
3 lymphopenia.

4 Thank you.

5 DR. BROUDY: Thank you, Dr. Parker.

6 Are there any questions for either Dr. Brunswick
7 or Dr. Parker?

8 MS. MEYERS: Yes, I have a question.

9 DR. BROUDY: Abbey.

10 MS. MEYERS: The control group seems so unusual.
11 Do you accept this control group? It is really historical
12 controls and patients acting as their own controls.

13 DR. PARKER: We noticed that there were studies
14 done in which the patients were used as their own control,
15 and it is sort of difficult in terms of looking for other,
16 you know, having another type of control group.

17 They did historical controls from other studies,
18 from publications, and that was sort of hard for us to
19 review also because there are a lot of factors that we
20 couldn't extract from those publications, so it was pretty
21 difficult to have control groups, and so the best that could
22 be done in this case was to review those patients who had
23 previous chemotherapy.

24 DR. KEEGAN: Ms. Meyers, because the patient
25 population for consideration was relapsed or refractory,

1 there was not very good consensus on the appropriate control
2 population. In part, the comparison to patient as their
3 last control was one of the specific remedies recommended by
4 this committee or discussed by this committee as an optimal
5 comparison for this kind of a patient population where it
6 would be difficult to find a concurrent control group.

7 So, there really are two reasons. One is that
8 this was intended to be a relapsed and refractory
9 population, and for which while there might be alternatives,
10 an optimal alternative was not readily identified. That was
11 the reason for choosing this type of a control.

12 MS. MEYERS: Is it usual for the Oncology Division
13 to accept control groups from historical controls?

14 DR. KEEGAN: In a relapsed, refractory setting,
15 where there may not be adequate alternative therapy, that
16 is, in fact, the comparison which is most frequently used,
17 and this is not only CBER, but CDER follows this policy to
18 look at what available information there is on the
19 alternatives or potential alternatives or if there is no
20 perceived alternative, to use what would be expected to be
21 the natural history in the population.

22 MS. MEYERS: On the other hand, no, CDER usually
23 doesn't in many diseases where the consumer community feels
24 that historical controls could be used, the divisions won't
25 accept it, and so it doesn't seem like there are rules

1 within all divisions that are the same. Every division
2 seems to do what it wants. I just want to register with you
3 that this is a matter of utmost concern.

4 DR. SIEGEL: Let me add a couple of things in
5 terms of perspective. There is in development, I was
6 working on this morning a document through the ICH process
7 on utilization of control groups that will address some of
8 the issues you raise. It is not at present available for
9 public comment in that it is in a very preliminary draft
10 form.

11 However, there are principles that are used to
12 determine when historical controls are acceptable. It is
13 not simply everybody doing what they want. In the case of
14 refractory disease, an oncology part of it relates just to
15 issues depending on the situation, either feasibility or
16 ethics. It can be hard to find an appropriate control group
17 in some populations, but in this case, part of it relates to
18 the choice of endpoints.

19 In those settings where tumor response endpoint is
20 acceptable as opposed to a survival endpoint, and as you
21 know, the Oncology Initiative addresses this at great
22 length, the role of the historical control is going to be
23 very different in those settings, for the simple reason, one
24 doesn't need to treat patients with placebo or no treatment
25 in most diseases to know what the response rate will be.

1 The nature of most tumors in terms of tumor size
2 is fairly consistent. They occasionally remain stable,
3 usually progress, and only very rarely regress, and
4 responses therefore can be reliably compared to historical
5 controls to be measures of drug activity. Then, the issue
6 becomes is that the adequate and most important measure, and
7 as I say, that is addressed in the Oncology Initiative.

8 Obviously, the most important measure is survival.
9 Survival is very difficult, probably impossible to assess
10 with historical controls unless one had a drug of such
11 extraordinary efficacy that it would be hard to imagine any
12 we have seen where one could make that sort of
13 determination.

14 But as discussed with this committee, as discussed
15 in Oncology Initiative, all survival outcomes are of course
16 critically important in this and in all malignant diseases.
17 It is not the hurdle, if you will, set for marketing
18 approval.

19 DR. BROUDY: I would also just like to briefly
20 comment that this study included patients who had very
21 heterogeneous prior therapies, and there wouldn't be any
22 standard next therapy, so it was difficult for them to
23 divide the patients into 50 percent the IDEC antibody and 50
24 percent "standard" next therapy for the low-grade lymphomas.
25 There wouldn't have been an identifiable standard next

1 therapy, and I think that was probably one of the other
2 reasons for the design in this way.

3 If you look at some other agents that have been
4 studied in low-grade lymphomas, such as fludarabine, the
5 initial reports also were in multiple-relapsed patients
6 assessing the response rate and progression-free survival,
7 that sort of thing.

8 MS. MEYERS: But I think that that is the issue.
9 There seems to be this special standard for cancer and for
10 nothing else.

11 DR. SIEGEL: I don't think so. As I say,
12 historical controls are most useful in diseases with
13 relatively predictable natural history, because it is only
14 then that you can look at -- and its response to treatment
15 is markedly different from that natural history, it is only
16 then that you can draw any reasonable conclusions in those
17 comparisons given all the variables between historical
18 control and non-historical populations.

19 In this disease nor in any other disease, if this
20 had been compared to alternative chemotherapy, there would
21 not necessarily be a standard that it had to do better in
22 some sense than alternative chemotherapy. The standard
23 would be that it would have to give responses that added up
24 to efficacy and could lead to a reasonable presumption of
25 benefit, and that can be determined from this sort of

1 historical control trial, as well as from a treatment
2 controlled trial, which isn't to say that there isn't
3 important additional information to be gathered from
4 treatment controlled trials, but I think the aspect of your
5 comment that I would like to address, and address clearly,
6 is that this is not a cancer-specific standard.

7 The use of controls is determined by the nature of
8 the disease and the nature of the indication, and as it
9 applies in refractory, malignant disease, the Agency has
10 determined that historical controls are appropriate, but it
11 is not a different determination for cancer for other
12 diseases. In another disease in which there was a highly
13 predictable consistent outcome that was radically
14 demonstrably different enough for treatment that one could
15 determine that that wasn't due to other factors or variables
16 that differed in the population, a similar trial design
17 would be acceptable.

18 MS. MEYERS: I will remember to tell that to
19 another division director when they are looking at a
20 neurologic -- and they refuse to say that nobody has to go
21 on placebo.

22 DR. SIEGEL: I would be interested to know which
23 neurologic disease you have in mind that has such a
24 consistent outcome.

25 MS. MEYERS: How about Lou Gehrig's disease? You

1 are dead in three to five years.

2 DR. BROUDY: Maybe we could address this more
3 during the lunch hour. Are there other questions?

4 [Laughter.]

5 DR. BROUDY: Seriously, it is a very important
6 question and I think we should. Are there other questions
7 for either Dr. Parker or Dr. Brunswick from the committee?

8 Not seeing any, thank you very much for your
9 presentation.

10 What we would like to do now is go ahead with the
11 questions. I think Dr. Freas would like to comment on who
12 is eligible to vote and not vote.

13 **Committee Discussion**

14 DR. FREAS: Yesterday, it was read into the public
15 record the conflict of interest statement for this topic.
16 Of course, the conflict of interest statement pertains to
17 both days of the meeting.

18 For this topic, everybody at the table, both
19 standing members and temporary voting members will be
20 allowed to vote with the exception of Dr. Auchincloss, who
21 received a limited waiver and therefore cannot vote, and
22 also our patient representative, Christine Heinemann, who is
23 a non-voting patient representative.

24 DR. BROUDY: I would also like to announce that we
25 will be voting on two questions, Question No. 1, and the

1 first sentence of Question No. 2. Those are the two voting
2 issues.

3 I would like to read the first question. Does the
4 committee believe that C2B8 is effective for the treatment
5 of relapsed or refractory, low-grade and follicular non-
6 Hodgkin's lymphoma?

7 Would anybody like to begin the discussion of this
8 question? Carole.

9 DR. MILLER: Given the data in this heterogeneous
10 group of patients with what is truly a chronic disease, I
11 think the data supports clinical efficacy in well done and
12 carefully collected clinical trials.

13 DR. BROUDY: Thank you.

14 Dr. Berman, any comment?

15 DR. BERMAN: I would agree completely with that.
16 I think the data are very clear and was very concisely
17 presented this morning.

18 DR. BROUDY: Dr. August?

19 DR. AUGUST: Although the representatives from the
20 FDA didn't stress this, I think that the data are clear that
21 this is as good as cladribine and fludarabine, I guess they
22 were, and it actually the data are very respectable to a
23 host of other anticancer drugs which have been approved by
24 the FDA and are on the market today.

25 DR. BROUDY: Thank you. Are there other comments?

1 I would have to say I completely concur that this
2 is an agent that we should add to our armamentarium in this
3 patients with low-grade lymphomas. It has got a very
4 convincingly demonstrated 50 percent response rate even
5 though a few of those are complete responses and a
6 reasonable duration, and I would completely support also
7 adding it to our armamentarium.

8 Are there other comments before we proceed to
9 voting on No. 1?

10 Okay. So let's take a vote. Should we just take
11 a hand vote here?

12 DR. FREAS: Yes.

13 DR. BROUDY: Does the committee believe that C2B8
14 is effective for the treatment of relapsed or refractory,
15 low-grade and follicular non-Hodgkin's lymphoma?

16 Let's see a show of hands for the yes votes.

17 [Show of hands.]

18 DR. FREAS: Twelve yes votes.

19 DR. BROUDY: Are there any abstentions?

20 [No response.]

21 DR. BROUDY: Any no votes?

22 [No response.]

23 DR. BROUDY: Thank you very much.

24 We will move on now to Question No. 2. I think
25 you can all read the first paragraph. I won't read it

1 aloud, it has been gone over twice.

2 The question is: Does the committee find that the
3 risks of C2B8 therapy are acceptable given the efficacy
4 data?

5 Would anyone like to comment on this issue?
6 Carole.

7 DR. MILLER: Again, given the spectrum of
8 toxicities of most of the drugs we give for this efficacy, I
9 feel that the risks are certainly acceptable, and I think it
10 does represent a drug that we can use -- given the toxicity
11 profile, which is not overlapping with many other drugs that
12 we use, it does present a good opportunity for future
13 studies, as well.

14 DR. BROUDY: Dr. August.

15 DR. AUGUST: I think it should be pointed out for
16 the record that most of the toxicities are toxicities that
17 are pretty easily controlled with rather simple therapies,
18 and although it was never mentioned, pretreatment would be
19 available to prevent these toxicities after individuals had
20 experienced them in subsequent treatments.

21 From my point of view as a clinician, this would
22 be a pretty easy drug to use.

23 DR. BROUDY: Are there other comments weighing the
24 side effects versus the potential benefit?

25 I would just like to comment that I, too, think

1 this sounds like the risk-benefit ratio is definitely in
2 favor of approving this medication, particularly attractive
3 is that it is not very myelosuppressive, a very low
4 incidence of thrombocytopenia and neutropenia in contrast to
5 many of the other drugs that we use in patients with low-
6 grade lymphomas, and we always get into difficulty, having
7 used one group of drugs, another group, and getting into
8 profound myelosuppression, and its lymphopenia doesn't seem
9 to be really any worse from what I can see so far than
10 fludarabine, really.

11 Are there other comments on the toxicity, other
12 concerns committee members would like to raise?

13 Let's go ahead and vote.

14 Does the committee find that the risks of C2B8
15 therapy are acceptable given the efficacy data?

16 All in favor, please raise your hand.

17 [Show of hands.]

18 DR. FREAS: Twelve votes stating the risks are
19 acceptable.

20 DR. BROUDY: Any abstentions?

21 [No response.]

22 DR. BROUDY: Any no votes?

23 [No response.]

24 DR. BROUDY: I think the other questions are more
25 for discussion than for votes.

1 The next question is: Should the labeling
2 discourage use in any particular populations which might be
3 at increased risk for adverse events, for example, those
4 with underlying cardiovascular disease or atopic history?

5 Any thoughts about that, should we discourage its
6 use? Dr. Berman.

7 DR. BERMAN: I thought the company did a very good
8 job in trying to determine which patients would have
9 hypotension or allergic reactions, and it doesn't appear to
10 be, so I don't think there can be a group defined as being
11 at increased risk. So I would say no.

12 There didn't seem to be any predictive factors
13 that would allow you to identify the patients that would
14 have allergic reactions or low blood pressure.

15 DR. BROUDY: Other thoughts on that issue?

16 MS. MEYERS: Does this disease apply to children,
17 are there any pediatric concerns, has it been tested on
18 children?

19 DR. BROUDY: Would you like to comment, Dr.
20 Kleinerman? Ms. Meyers' question is does this apply to
21 children.

22 DR. KLEINERMAN: I don't treat pediatric
23 lymphomas, so I really don't know whether -- I think that
24 should probably go to the company. I don't know what the
25 incidence is of the expression of this antibody.

1 DR. BROUDY: Dr. Grillo-Lopez.

2 DR. GRILLO-LOPEZ: We have not studied any
3 pediatric population at this point. That is something that
4 will be done in the future. However, in the pediatric
5 patient population, low-grade or follicular lymphomas are
6 very limited in incidence. Dr. August might help me here,
7 but I think it is about 200 or fewer cases a year in the
8 United States.

9 DR. AUGUST: In fact, it is very rare. Actually,
10 the lymphomas that we see tend to be Burkitt type or large
11 cell. The comment that I made earlier in private was that
12 this antibody's potential usefulness is perhaps in the CD20+
13 acute lymphoblastic leukemia patients rather than lymphoma,
14 which would be a whole new area of investigation that we
15 will just have to wait and see about, I guess.

16 MS. MEYERS: But the concern is that when it is
17 approved and out on the market, oncologists are going to use
18 it for a lot of things, as they do all cancer drugs. The
19 question is should it be studied in the pediatric population
20 for something in a post-marketing study to make sure that
21 the pediatricians or pediatric oncologists get the right
22 dosage.

23 DR. AUGUST: I think the answer to that question
24 is yes, but I think it would be reserved for investigator-
25 initiated studies, to be perfectly frank, and they probably

1 will happen.

2 DR. KLEINERMAN: I think Abbey, her point is well
3 taken because I think often companies are reluctant to start
4 studies in pediatrics, and because of the small numbers, and
5 that is why I think her point is well taken. I think the
6 company should be encouraged to try to define a dosage
7 because, as we have seen in other cases, pediatric doses
8 cannot be the same.

9 Children can tolerate higher doses of various
10 types of therapies, so determining an effective dose may not
11 be utilizing the same dose that is applicable to adults, so
12 I think it is very important that post-marketing studies in
13 children be encouraged with all the agents that ultimately
14 are approved.

15 DR. AUGUST: Absolutely.

16 DR. WEISS: The largest concern -- and I think Ms.
17 Meyers' question is very good -- but the largest concern
18 about something that is approved and had not yet been
19 studied in children is diseases that are very common in
20 children, as well as in adults, and while I agree, I always
21 like to encourage studies in broad populations, it is very
22 true that low-grade lymphoma is an extremely rare entity in
23 pediatric diseases, and we will talk with the sponsor
24 subsequently about their potential populations.

25 The concern and the issues with pediatric use is

1 the idea that if it is approved, investigators, physicians
2 will -- if something is a very common disease in children --
3 investigators, physicians will likely use the product, and
4 it behooves all of us to try to give the investigators as
5 much information on the label regarding safe dosing,
6 appropriate dosing, whether or not doses should be higher
7 because it is more likely to have higher clearance, et
8 cetera, and more information on perhaps toxicities that may
9 be more apparent in children that investigators should be
10 aware of.

11 DR. BROUDY: My understanding is there is no data
12 available in children, no pharmacokinetic data or other data
13 at all, so that guidance would be difficult to provide.

14 DR. WEISS: But part of it, too, is this a disease
15 that affects children. Certainly, in diseases such as
16 thrombolytics for myocardial infarction, you know, you
17 wouldn't ask that this be studied in children, other
18 diseases, prostate cancer, breast cancer, something that is
19 targeted to specifically an adult population, if there are
20 other uses in pediatrics, certainly, this can be studied,
21 but it isn't the same issue as something like
22 thrombocytopenia that is going to affect adults and children
23 equally and where you would want to get some infection for
24 pediatric use.

25 DR. BROUDY: Dr. Keegan, did you want to comment,

1 as well?

2 DR. KEEGAN: My comment was basically what Dr.
3 Weiss has just said, that the indication appears to be
4 limited to the adult population, therefore, to require
5 pediatric information doesn't seem to apply here, but were
6 the indication to be one which is present equally or is
7 present both in adults and pediatric patients, it would be a
8 different issue.

9 DR. KLEINERMAN: If I could just say one more
10 thing. I just think that Abbey's point -- and I agree with
11 her -- is to get the message out to these companies that if
12 they do have a drug that is applicable, that they should
13 think about starting pediatric studies early, and not
14 disregarding the pediatric population.

15 I think that is starting to be done, and I think
16 we have to send the message that we consider that to be very
17 important.

18 DR. KEEGAN: As does the FDA, and we completely
19 agree.

20 MS. MEYERS: And I think that the 200 children who
21 have this type of cancer would like to know that the FDA
22 cares about this subject.

23 DR. BROUDY: Other comments on this issue?

24 Okay. Let's move on to the next point for
25 discussion. We have basically discussed should the sponsor

1 be encouraged to perform additional studies to evaluate the
2 toxicity profile and relative safety in these or any other
3 patient populations?

4 What other patient populations should be studied?

5 We have commented on children. Anyone? Dr. Miller, any
6 other thoughts?

7 DR. MILLER: No.

8 DR. BROUDY: Dr. Kleinerman?

9 DR. KLEINERMAN: I don't know if it applies here,
10 but I think a great deal of discussion we had in terms of
11 the immunologic profiles, the long-term immunologic profiles
12 of patients who have received this antibody, and I think the
13 company should be encouraged to start that trial that they
14 talked about, looking at the ability of these patients to
15 mount an antibody response to new antigens and to recall
16 antigens, and I think that is a very important follow-up
17 study that needs to be done.

18 DR. BROUDY: And Dr. Grillo-Lopez, that study is
19 underway at present or could you comment on its status?

20 DR. GRILLO-LOPEZ: Yes, that study has started,
21 and in that study we are looking at normal controls,
22 patients with lymphoma, second group, patients with lymphoma
23 who have not received the antibody, and a third group of
24 patients with lymphoma who have been treated with the
25 antibody, and that study has started.

1 DR. BROUDY: What sort of data will you be
2 collecting? Could you comment on what sort of studies you
3 will be doing?

4 DR. GRILLO-LOPEZ: These patients are going to be
5 immunized with a variety of different antigens, and then
6 will be studied for their antibody responses to these
7 antigens. That work is being centralized at the laboratory
8 of the University of Maryland Cancer Center, Dr. Cross, Dr.
9 Borden, and others are working on that.

10 DR. BROUDY: Other thoughts?

11 DR. O'FALLON: Since it seems highly likely that
12 patients will ultimately be treated with this multiple
13 times, although we have heard that only one has been
14 treated, or maybe it was two, three times already, it would
15 seem that the company could be encouraged to keep a bit of a
16 registry or something as to whether the rates are the same
17 in these subsequent therapeutic --

18 DR. BROUDY: Would you like to comment on that
19 issue, Dr. Grillo-Lopez?

20 DR. GRILLO-LOPEZ: We have, in fact, treated close
21 to 50 patients twice, however, a lot of that has happened
22 recently, and it is not in the database submitted to the
23 Agency. In the database that has been submitted to the
24 Agency, there are 22 patients that have been treated twice
25 with the antibody. Most of those patients responded the

1 first time, and then upon progression of disease were
2 retreated in another protocol.

3 For those 22, data is available on 10. That
4 allows us to assess efficacy, and of those 10, 5 have
5 responded. There are 2 patients that have been treated 3
6 times, and those 2 patients have also responded.

7 DR. AUCHINCLOSS: Until we get the data
8 immunizations, I think you would have to assume that these
9 patients are pretty B-cell suppressed, and that therefore
10 labeling would probably want to indicate that some kinds of
11 immunizations or most kinds of immunizations would be
12 unlikely to be effective, and some might actually be
13 dangerous.

14 DR. BROUDY: I guess I would like to see more
15 trials in the bone marrow transplant setting. That is very
16 intriguing that uniquely this group of patients, that the
17 post-transplant patients seem to respond better to the IDEC-
18 C2B8 antibody than the pre-transplant patients, and this is
19 really unique that you get an agent that works better post-
20 transplant than pre-transplant, and this might offer some
21 very encouraging options for people that often don't have
22 very many options when they relapse after auto-transplant.
23 I am sure those studies are planned, as well.

24 Should internally controlled trials be performed
25 to evaluate the clinical impact of sustained B cell

1 depletion on the relative risk of infection?

2 Anyone like to comment on this? Yes, Dr.

3 Anderson.

4 DR. ANDERSON: I would just like to get back to
5 Charley August's ice pick model. For those of us interested
6 in immunodeficiency diseases, this really is a very unique
7 agent, and certainly sort of basic studies on what happens
8 to the B cell arm of the immune system probably isn't
9 highest priority for the company, but certainly to the
10 extent they could be encouraged to add additional studies
11 and to encourage investigators to look into what happens
12 just at the basic biology level would be very useful.

13 DR. SIEGEL: The question I guess is about
14 clinical trials. It is not important necessarily to get an
15 answer, but I wonder if there is advice. I am struck
16 looking at the smattering of infections that have occurred
17 in this population, that it is pretty hard to determine
18 given that they have underlying lymphoma, prior
19 chemotherapy, or whatever, and that they are out there in
20 the world getting infected like everybody else.

21 The extent to which this agent is really impacting
22 infections, so the question that was posed was about a
23 controlled trial, for example, which would be the only way I
24 guess to really get a handle as to whether there is a
25 significant increase in certain types of infections,

1 notwithstanding the importance of the immunologic data, and
2 so I guess the question is does anybody care to comment on
3 the importance or their perception of the significance of
4 such a trial.

5 DR. BROUDY: I guess I am not impressed that the
6 infections were at all out of line from what I would expect
7 to see in a low-grade lymphoma patient with two prior
8 regimens, which may or may not have included fludarabine. I
9 thought this was a very reasonable and modest rate of
10 infection.

11 Dr. Miller?

12 DR. MILLER: I would also like to comment that
13 they followed these patients out for a year, which
14 considering a study population like this for infections, I
15 have not seen in this type of study, or I have not noticed
16 it very frequently or I don't know about at least, it may
17 have happened, but the bottom line is these patients, you
18 can't follow them much longer, because it is very likely
19 that they will have released, get further therapy, so I
20 think a one-year followup is adequate.

21 It may be possible that the randomized trial that
22 is being started, with CHOP plus or minus IDEC, with be able
23 to give you that answer in a more long-term fashion. Those
24 patients I assume are less heavily pretreated, you are going
25 to expect some longer term responses, and you are going to

1 see, I think, a patient population where you are going to be
2 able to follow long term, so I think they are providing
3 that, and I don't think further randomized trials are really
4 needed.

5 DR. BROUDY: Dr. Anderson.

6 DR. ANDERSON: I would agree with that. Jay, my
7 feelings in looking at it is that it would take an
8 internally controlled trial or enormous proportions to see a
9 difference.

10 The issue is whether or not an exposure to new
11 infections, there is a danger, but that isn't something that
12 can be done in sort of an internally controlled trial, but
13 if one isn't keeping one's eyes open to it and thinking
14 about it, and doing tests to look for it, then, you wouldn't
15 see it. I mean it is going to happen too randomly.

16 But my bias is that these patients are going to be
17 more at risk when exposed to a new pathogen than if they
18 were not on the agent. Now, how much of an increased risk
19 that is, probably not much, but on the other hand, if they
20 take a trip to South America, probably a lot. If they spend
21 a lot of time around a primate colony, probably a lot. But
22 for most other situations, probably not.

23 I guess the third thing, if they spend a lot of
24 time in a New York subway.

25 [Laughter.]

1 DR. BROUDY: Dr. Anderson, would you like those
2 specifically introduced in the package inserts?

3 [Laughter.]

4 DR. BROUDY: Any other comments on that issue?

5 No.

6 We will move on to Question 3. Does the committee
7 believe that an overall response rate of 4 out of 37, 11
8 percent, observed in the patients with Working Formulation A
9 subtype provides sufficient evidence of efficacy for an
10 indication in this patient subpopulation?

11 Would anyone like to comment on this? Dr. Berman.

12 DR. BERMAN: I think we already heard that this
13 Group A population contained a number of patients with
14 different types of disease, some with Waldenstrom's,
15 presumably some with a lymphomatous phase of CLL. So I
16 think this is a very small population, and 11 percent is not
17 to be disregarded. So I would say that it does provide
18 sufficient evidence of efficacy.

19 DR. BROUDY: Dr. Miller.

20 DR. MILLER: I agree. I wouldn't break it down
21 any further and say excluding this subgroup. I think
22 whether or not what the long-term response are going to be
23 will be in other clinical practice trials that hopefully
24 will be done in these patient populations.

25 DR. BROUDY: I don't think we really have adequate

1 data in this subgroup since many of the patients actually,
2 as you clarified, were sort of atypical patients for this
3 subgroup, but many of them did have a significant shrinkage
4 in tumor bulk, although they didn't meet your stringent
5 criteria for response.

6 So I guess I would also not X these patients out,
7 although I think it probably should say in the package
8 insert that there was an 11 percent response rate in the
9 initial trial with so many patients, and then the clinician
10 can make his or her own judgment about whether to use this
11 agent or not.

12 Are there other comments on this issue? No. Okay.

13 Let's move on to Part b. Given the availability
14 of alternative therapies, does the committee believe that an
15 overall response rate of 40 to 60 percent, CR rate of
16 approximately 8 percent, and response duration of 9+ months
17 provide evidence of efficacy for an indication in less
18 heavily treated patients?

19 Dr. Siegel, could you clarify for in brevity what
20 you mean by less heavily pretreated?

21 DR. SIEGEL: I will defer to Dr. Weiss.

22 DR. WEISS: And I am going to defer to Dr. Keegan.

23 DR. KEEGAN: The database included about 5
24 patients in the pivotal study who had never received prior
25 chemotherapy and a number of patients who had only received

1 one prior regimen, and the response rate there appeared to
2 be somewhat lower than one might expect with traditional
3 chemotherapy agents, and the question was should there be
4 some distinction made with regards to the relative benefits
5 of this therapy as either a first-line therapy or the first
6 salvage therapy given that the response rate and
7 particularly the complete response rate was not as high as
8 one might expect.

9 DR. BROUDY: Who would like to comment on this
10 issue? Dr. August.

11 DR. AUGUST: I think for the reasons that we heard
12 so eloquently expressed albeit in a group of one in the
13 letter that was read to us at the outset, when offered to a
14 patient, this might be quite a preferable therapy early on
15 to more intensive chemotherapy.

16 You can imagine a person just wanting a rest, in a
17 sense, from intensive chemotherapy and all the side effects
18 that it entails. So I would think that it ought to be
19 offered to earlier patients, but also, my feeling is that it
20 ought to be used in the context of clinical studies.

21 DR. BROUDY: Dr. Kleinerman.

22 DR. KLEINERMAN: Well, not treating lymphoma
23 patients, but just from a perspective of a laboratory
24 investigator, presumably there is some immune mechanism of
25 action of this monoclonal antibody since it stimulates ADCC

1 and other arms of the immune system, and usually, we think
2 of patients who have had less chemotherapy being more
3 immunoresponsive, so I would think in that type of context,
4 you may, even though the data -- I guess it is a small
5 number -- didn't show that, but I would think that perhaps
6 patients who have been less heavily pretreated would have a
7 potential of responding better.

8 DR. KEEGAN: We presented the data, and the data
9 were that four patients have been more heavily pretreated,
10 the response rates were better than one might expect for
11 traditional antineoplastic therapies.

12 We all saw the curves that were presented by the
13 company with regards to response rates and response
14 durations that fell relative to the initial treatment or the
15 first salvage treatment, this was lower than what might be
16 expected.

17 We are just discussing that these are the data
18 that were obtained.

19 DR. KLEINERMAN: Again, I don't think there is
20 enough. Maybe that could be presented in the package
21 insert, and the company could be encouraged to do more
22 studies to look at that, but I don't think I would limit it,
23 and strongly, particularly for one of the reasons that Dr.
24 August said, that this patient should be offered, should be
25 able to have the opportunity to choose, and know that maybe

1 the response rate isn't as terrific, but that they would get
2 a rest from the therapy.

3 DR. BROUDY: I guess my feeling is we just don't
4 have sufficient data by any means in patients who have not
5 had prior chemotherapy with low-grade lymphomas to assess
6 what the PR and CR rates are going to be, and so I wouldn't
7 include that as an indication when we have standard front-
8 line -- several options of front-line chemotherapy that have
9 a higher CR rate than this appears to have, at least in the
10 subset of patients who had a 6 to 8 percent CR rate.

11 I think the exciting thing is that the response
12 rate does not seem to decline with number of prior regimens
13 unlike most other chemotherapeutic regimens in which you
14 have a lower response rate and a shortened duration with
15 each subsequent regimen.

16 This does not apply to this novel mechanism of
17 action of this antibody, and so I think where I would feel
18 at least that we should recommend its use presently in
19 patients who have relapse from front-line therapy.

20 DR. WEISS: As I said, the sponsor is certainly
21 not asking for an indication other than for people with
22 refractory, relapsed, low-grade lymphoma. I guess our only
23 concern was when we did these subset analyses and looked at
24 people by the number of prior chemotherapy regimens, indeed,
25 it is comforting that people at the larger end, who had had

1 a number of prior chemotherapy regimens, still had
2 acceptable response rate, but by the same token, those at
3 the shorter end, at the one prior chemotherapy regimen, when
4 you compare a historical database or to prior chemotherapy,
5 seemed to have perhaps a little less than what you would
6 expect.

7 So that is what we were just asking about, and I
8 think Dr. Kleinerman's advice about just putting it in the
9 label, so people realize that if this is your first salvage
10 regimen, if you were on this, your response rate might be
11 lower, but it is a choice that one would be able to make.

12 DR. GRILLO-LOPEZ: We have, of course, requested
13 an indication only for relapsed or refractory patients, as
14 you have said. I think it would be very interesting to
15 study this antibody in patients at front line prior to
16 chemotherapy, and to look at that in a scientific and well-
17 designed study. We have not done that, and that is for
18 future studies.

19 We have, however, treated patients in the CHOP
20 study, in the combination with CHOP chemotherapy, who were
21 previously untreated, and that was an uncontrolled, single-
22 arm study, so the results have to be interpreted cautiously,
23 but all of those patients responded.

24 We had a 100 percent response rate in 38 evaluable
25 patients with clearance of bcl-2 translocation from the

1 peripheral blood and marrow and marrow harvests in 7 of 8
2 patients who were positive at baseline.

3 There didn't seem to be in that study any apparent
4 increase in adverse events because of the combination or in
5 infections, but again this is uncontrolled data.

6 I would like, if I may, to clarify -- because this
7 issue I think is very interesting relative to how many
8 regimens the patient has received -- and you can slice this
9 a number of different ways. You can look at number of
10 regimens or you can look at number of courses, and it is
11 different because a patient may have received several
12 courses of only one regimen, or they may have received
13 several regimens.

14 We have also looked at it in terms of relapses.
15 Some of that information may be interesting to look at.

16 DR. BROUDY: I think he is going to show some
17 slides. Go ahead.

18 [Slide.]

19 DR. GRILLO-LOPEZ: Here is the information
20 relative to number of prior chemotherapy courses, and there
21 were 5 patients who had not received any chemotherapy, had
22 received radiotherapy and/or bioimmunotherapies, and 2 of
23 those patients did respond.

24 For one course, the overall response rate was 59
25 percent, 33, 46, and 54 percent and there were no

1 statistically significant differences, which is what has
2 been mentioned.

3 Now, when you look at it, interestingly, in terms
4 of the number of relapses, we had a number of patients, 21
5 patients, who had had zero relapses. Now, what that means
6 is they had received chemotherapy, but never responded, so
7 by definition, since they never responded, they never had a
8 relapse, so these are your worst category patients, and yet
9 there was a response rate of 29 percent in those 21
10 patients.

11 As you proceed to one, two, three, and four
12 relapses, here, you see I think what Drs. Weiss and Keegan
13 were referring to, that is not seen when you analyze based
14 on number of courses, and that is that the higher, at least
15 numerically, and there is statistically significant
16 difference here, the higher overall response rate is for
17 patients who have had just had just one relapse. That
18 declines to 46 and to 38 percent for one, two, and three
19 relapses.

20 So it is interesting information and thank you for
21 allowing me to clarify that point.

22 DR. BROUDY: Dr. Auchincloss.

23 DR. AUCHINCLOSS: Just to comment that when you do
24 your front-line study, which will be a very interesting
25 study, you had better have a quality of life component to

1 that. The treatment of this disease at that stage is very
2 complicated, obviously, and I don't know what you are going
3 to choose if it is 50 percent response versus 70 percent
4 with chemotherapy where this is such a milder treatment.

5 DR. BROUDY: Dr. Miller.

6 DR. MILLER: I just wanted to comment that in this
7 disease, the absence of localized radiation therapy for
8 localized disease, no chemotherapy regimen is curative, and
9 so by definition, we are palliating or with the treatment,
10 with any of these agents, and therefore I think it is
11 important to keep that in mind when you are looking at when
12 to use a drug with potentially less side effects.

13 I just wanted to comment on that, that there is no
14 data that attainment of a complete remission with the
15 initial therapy prolongs survival. There is some good data
16 that it prolongs disease-free survival, but not survival.

17 DR. BROUDY: Are there other comments? No.

18 Let's move on to the next question then. Pending
19 the results of Study 102-08, a study in patients with
20 lesions greater than 10 cm, and given these pharmacologic
21 properties, does the committee agree that the labeled
22 indication of C2B8 should be restricted to patients who do
23 not have evidence of high tumor burden as described above?

24 Dr. Berman.

25 DR. BERMAN: I think given what we have heard this

1 morning, that it should be in the package insert, but I
2 think it should be available to the patients. It is clearly
3 not going not going to be dangerous to them, and there may
4 be some efficacy. I just don't think there are any data.
5 You haven't treated anybody with lesions greater than 10 cm?

6 So I think it should be in the package insert and
7 these patients should be allowed to use that.

8 DR. GRILLO-LOPEZ: If I may, I would like to start
9 responding to that issue with an anecdote. Please forgive
10 me for showing an anecdote here, but it is an interesting
11 one and illustrative.

12 [Slide.]

13 This patient was a 30-years old white male with
14 follicular, small cleaved lymphoma diagnosed in '90. He
15 initially received chemotherapy with a CVP regimen, and had
16 only a partial response lasting for 10 months. Upon
17 progression of disease, he was treated with ABMT with
18 cytoxan VP 16 and total body irradiation, and had a complete
19 response which lasted for 18 months. He progressed and was
20 treated with CVP, had a CR lasting 11 months.

21 Following this, he had progression of disease and
22 was treated with IDEC-C2B8 back in December of '93. This
23 patient had a very good partial response, I will show you on
24 the next slide, which in fact lasted 22 months.

25 The lesion measurements in this patient are shown

1 on this slide.

2 [Slide.]

3 There were a variety of cervical, axillary, and
4 other lymph nodes with the diameters in centimeters as shown
5 here, and one very large upper periaortic mass that measured
6 6 by 12 cm.

7 Following treatment, most of those lesions and all
8 of those lesions three months later had disappeared except
9 this very large periaortic mass, which was reduced 3 by 9,
10 and in fact, this was March, but a month later, at CT,
11 already showed that it had decreased 2.5 by 7.5, which is a
12 greater than 50 percent shrinkage for that mass alone. This
13 patient again had a PR that lasted 22 months.

14 [Slide.]

15 On the next slide I would like to show you the CT
16 scans at baseline, the 12 by 6 cm periaortic mass, and then
17 in April, already 2.5 by 7.5.

18 [Slide.]

19 This is more of the same, a sequence showing the
20 reduction in the size of that mass.

21 [Slide.]

22 The very large mass.

23 [Slide.]

24 Then reduced to a small size by February.

25 [Slide.]

1 Next.

2 [Slide.]

3 And then 2.5 by 7.5, and it remained at that size
4 for the 22 months that this remission lasted. Upon
5 progression of disease, this patient who was wiser than we
6 were, insisted that he get the antibody again. At that
7 time, amongst other lesions, he had a thoracic paraspinal
8 mass which was causing neurologic symptoms.

9 His decision -- and we agreed -- thought that he
10 needed radiotherapy rather than the antibody, and insisted
11 on that. The patient, however, was wiser and he did want
12 the antibody, but in any case, the medical opinions
13 prevailed. He started radiotherapy and we also treated him
14 with the antibody after radiotherapy had been started, at
15 which point he discontinued radiotherapy having received
16 only three doses of 250 rads, and went on to have a very
17 good partial response again with disappearance of that
18 thoracic mass and all other lesions that were present, and
19 that response is ongoing for another 20+ months.

20 So this is an interesting patient from the point
21 of view of your question.

22 Let me now show you, in the pivotal trial,
23 although we did have an exclusion criterion for patients
24 with lesions greater than 10 cm, that was not necessarily
25 heeded by our investigators, and we did have patients in

1 that study with lesions whose maximum diameter was as large
2 as 15 cm.

3 In fact, 25 percent of the patients had single
4 lesions larger than 6 cm.

5 [Slide.]

6 So in the Phase III pivotal trial, the bulky
7 disease patients were 21 of 166 patients. These 21 had
8 lesions greater than 7 cm, and 8 of these 21 patients
9 responded, for a response rate in the 21 patients of 38
10 percent. The duration of response median for these patients
11 was 7.9+ months ongoing, and their time to progression
12 median 9.5+ months and ongoing.

13 Some patients have a TTP out as far as 15+ months.

14 [Slide.]

15 Then, in the study that I mentioned during my
16 presentation, that was ongoing at the time of BLA
17 submission. This is a study where there is one patient
18 population which specifically includes only those patients
19 who have at least a single lesion greater than 10 cm in
20 diameter. The data is early and preliminary. The
21 investigators have reported 28 patients to us, and the
22 response rate in those 28 patients is 43 percent, 12 of the
23 28, with the median durations and TTP as shown here,
24 ongoing.

25 Our own evaluation, we find 21 patients were

1 currently evaluable out of those 28 with a similar response
2 rate and duration of response and time to progression.

3 So this data is early, we have not analyzed all of
4 the patients on this study, however, the patients that we
5 are showing on this slide have been reported to the Agency
6 and they are in the electronic database as of the update.

7 So we do believe that patients with bulky disease,
8 although there is a trend for lower response rate, there is
9 a clinically important response rate in these patients, that
10 is 38 percent in the pivotal trial, and in this study it
11 looks like it is going to be in the 40, 45 percent range or
12 thereabouts.

13 Thank you.

14 DR. BROUDY: I guess I would feel that it would
15 micromanagement in a certain sense to say but don't use it
16 over 10 cm, and maybe if this information can just appear in
17 the package insert, then, the clinician can make their own
18 decision about whether to go ahead with this approach or
19 some other approach.

20 Are there other thoughts on this issue? Does
21 anyone else want to comment on the use of IDEC-C2B8 in
22 patients with large masses?

23 DR. AUGUST: I agree with what you have just said,
24 Dr. Broudy, and for an additional reason, and that is, that
25 the problem that Abbey Meyers alluded to yesterday, about if

1 a restriction were to be put in the package insert, it would
2 be used as an excuse by insurers not to pay for the
3 treatment and the outpatient visit and whatever else it
4 entailed, and I would just not want to see that happen at
5 all.

6 DR. BROUDY: Are there final comments? Dr.
7 Berman.

8 DR. BERMAN: I would like to commend IDEC for what
9 really has been a model of clarity in presentation, and they
10 clearly have an exciting product here, and certainly a novel
11 one, but the command of the data this morning and the
12 presentation, I think to us serves as a model for new
13 comment, so I would like to have that on the record and
14 really compliment all of you. I have no affiliations with
15 IDEC.

16 DR. BROUDY: I would have to agree the quality of
17 the data, the numbers of patients, the clarity of the
18 presentation were absolutely superb.

19 Given that there are no other comments, I think we
20 will close this session.

21 [Whereupon, at 11:45 a.m., the proceedings were
22 recessed, to be resumed at 12:45 p.m.]

1 A F T E R N O O N S E S S I O N

2 [12:55 p.m.]

3 DR. FREAS: I would like to resume with a
4 discussion of Neupogen by Amgen, Inc.5 For this topic we have one change to the table --
6 well, actually, we have several changes to the table. Dr.
7 Vose, our chair, is back and presiding. We have a new
8 patient representative, and I would like to welcome to the
9 table, Helaine Baruch. Welcome, Helaine. Would you raise
10 your hand, so they can identify you. Thank you.11 Also, Dr. Auchincloss, your vote has been restored
12 for this topic.13 **Open Public Hearing**14 DR. FREAS: Dr. Vose, I have not received any
15 inquiries or a request to speak during the open public
16 hearing as was advertised in the Federal Register.17 Is there anyone in the room at this time who would
18 like to address the committee during the open public
19 hearing?

20 [No response.]

21 DR. FREAS: I see no response, Dr. Vose. I turn
22 the microphone over to you.

23 DR. VOSE: Thank you, Dr. Freas.

24 We will go ahead with the presentation for
25 Application No. 4, for Neupogen by Amgen. I will turn it

1 over to Dr. Morstyn.

2 OPEN COMMITTEE DISCUSSION: TOPIC IV

3 BLA, Supplement Reference 96-1136

4 Neupogen, Amgen, Inc.

5 Presentation by Amgen, Inc.

6 Introduction

7 DR. MORSTYN: Good afternoon. My name is George
8 Morstyn. I am Vice President for Clinical Development at
9 Amgen.

10 [Slide.]

11 I would like to thank Dr. Vose and members of the
12 panel and the FDA for the opportunity to present data on the
13 use of Neupogen or so called Filgrastim or G-CSF in patients
14 with acute myeloid leukemia.

15 [Slide.]

16 To help the panel with the discussion, we have a
17 number of people from Amgen who will make presentations.
18 Dr. Alan Barge is Director of Hematology at Amgen, and Mr.
19 James Matcham is a biostatistician at Amgen.

20 We have also invited several consultants to help
21 the committee with discussions if they would so like. We
22 have invited Dr. Charley Schiffer, who is Professor of
23 Medicine at Wayne State University in Detroit, and is
24 Director of the Division of Hematology and Oncology there,
25 and a former Chairman of the CLG Leukemia Group.

1 We have also invited Dr. Heil, who is a consultant
2 hematologist at Hannover Medical School, and was the
3 principal investigator of the study that we will be
4 presenting, and Dr. Jeff Szer, consultant hematologist at
5 the Royal Melbourne Hospital, another principal investigator
6 of the study.

7 In addition, we have Dr. Lloyd Fisher, who is
8 Professor of Biostatistics at Washington University in
9 Seattle.

10 [Slide.]

11 As you know, Neupogen or Filgrastim was approved
12 in 1991 as an adjunct to chemotherapy to reduce the
13 complications that patients suffer including febrile
14 neutropenia and the concomitant treatments that are required
15 for this including intravenous antibody and prolonged
16 hospitalization.

17 In 1994, the label was extended to the use of
18 Neupogen in patients undergoing bone marrow transplantation.
19 Here, Neupogen was shown to reduce the duration of
20 neutropenia and the neutropenia-related sequelae, such as
21 the duration of febrile neutropenia in patients undergoing
22 this intensive chemotherapy.

23 This setting is analogous to induction
24 chemotherapy of acute myeloid leukemia since these patients
25 also suffer prolonged myelosuppression and the benefits of

1 Neupogen here were in reducing the duration of the
2 complications of the treatment.

3 In 1994, Neupogen was also approved for use in
4 children with severe chronic neutropenia and there are now
5 some children who have received it continuously for five to
6 10 years.

7 In addition, in December of '95, it was approved
8 for mobilization of peripheral blood progenitor cells for
9 use in transplantation, and since 1991, Neupogen has
10 certainly proved to be a safe and effective medicine
11 reducing the side effects that patients undergoing these
12 various treatments suffer.

13 [Slide.]

14 What we are now here to discuss is an additional
15 label extension, which is on this slide, that is, that
16 Neupogen is indicated for the reduction in the duration of
17 neutropenia, fever, antibiotic use and hospitalization, in
18 patients undergoing induction and consolidation treatment
19 for acute myeloid leukemia.

20 To be able to discuss this, we have conducted with
21 our investigators the largest placebo-controlled, randomized
22 trial of a colony-stimulating factor that has ever been done
23 in this disease. Obviously, there is a rich array of data
24 since the trial involved more than 500 patients, and to aid
25 the discussion, what we have focused on is the questions

1 that the FDA has asked the panel to review. We are
2 obviously also happy to provide any additional information
3 that the panel would like.

4 So what I would now like to do is hand over to Dr.
5 Alan Barge to introduce the topic.

6 Thank you.

7 **Overview of Disease, Treatment and Study Design**

8 DR. BARGE: Thank you, Dr. Morstyn. Dr. Vose,
9 members of the committee.

10 [Slide.]

11 The FDA have raised for your discussion this
12 afternoon a number of issues in relation to our submission,
13 and we would like to integrate our discussion of these
14 issues into the main body of our presentation, which reviews
15 the entire data from our study.

16 The questions that they have raised have revolved
17 around the efficacy of Neupogen following induction and
18 consolidation chemotherapy for AML, and the safety of
19 Neupogen in the same setting.

20 They have asked whether or not it is reasonable to
21 extrapolate the data that we have generated in adults to
22 children with AML. They have also asked about the impact of
23 the prophylactic use of antibiotics in this study on the
24 incidence of documented infection, and have inquired about
25 label recommendations for bone marrow evaluation prior to

1 the administration of a growth factor.

2 They have also asked whether or not these results
3 can be extrapolated to secondary AML.

4 [Slide.]

5 Well, the background to AML is obviously well
6 known to you. AML is the primary malignancy of the myeloid
7 lineage in the bone marrow, and there are about 7,000 new
8 cases in adults every year in the United States and a
9 further 400 cases in children.

10 Severe neutropenia is a universal consequence of
11 the disease and the very aggressive chemotherapy that is
12 used to treat it.

13 The prolonged pan-cytopenia that results from that
14 is associated with significant morbidity, an intensive
15 requirement for supportive care in hospital and prolonged
16 durations of hospitalization.

17 Current optimal treatment for the disease achieves
18 an overall CR rate in adults of approximately 65 percent
19 with median survivals between 9 and 15 months.

20 [Slide.]

21 Well, Filgrastim, as you have heard, have been
22 extensively shown to significantly reduce the duration of
23 neutropenia and its associated infection-related
24 consequences following chemotherapy for a variety of non-
25 myeloid malignancies.

1 We were obviously interested to determine whether
2 it would do the same in the chemotherapy for AML, but
3 because the blasts from patients with AML express the
4 receptors for G-CSF and a variety of other growth factors,
5 any study that addressed the efficacy of Neupogen needs also
6 to address its safety in terms of its ability to stimulate
7 the disease or not, and that is what we set out to do.

8 [Slide.]

9 We conducted a large multicenter, double-blind,
10 multinational placebo-controlled, randomized Phase III study
11 of Filgrastim as an adjunct to induction and consolidation
12 chemotherapy for AML.

13 [Slide.]

14 These are the objectives of the study. We wanted
15 to determine the efficacy of Filgrastim by determining its
16 effects on the duration of neutropenia, the incidence and
17 duration of fever and antibiotic use, the incidence of
18 culture-confirmed infections, and the duration of
19 hospitalization.

20 We also wanted to determine its safety in terms of
21 its influence disease outcome as measured by complete
22 remission rate, event-free and overall survival.

23 [Slide.]

24 We wanted to study all adult patients with the
25 disease. We wanted to exclude patients whose AML had arisen

1 from underlying bone marrow disease like myeloid dysplasia
2 or as a result of prior chemotherapy. So we excluded
3 patients with a prior diagnosis of MDS or secondary AML.

4 All adult patients were eligible. In some
5 European countries, the age for giving legal informed
6 consent is 16, so all AML patients over the age of 16 were
7 eligible for our study.

8 [Slide.]

9 This shows the design of the study. We used a
10 well-established and widely-used chemotherapy regimen
11 comprising daunorubicin, Ara-C, and etoposide. All eligible
12 patients were registered into the study and started on
13 chemotherapy.

14 Randomization to Filgrastim or placebo was not
15 done until at least day 6 of chemotherapy, and this was done
16 deliberately to reduce the number of patients who were
17 withdrawn or who died early, who would be included in an
18 analysis of the growth factor. So patients weren't
19 randomized until day 6.

20 Thereafter, they received study medication,
21 Filgrastim, at 5mcg/kg subcutaneously or placebo, starting
22 24 hours after the last dose of chemotherapy and continuing
23 until neutrophil recovery.

24 Patients who went into complete remission after
25 one course went on to a consolidation course of similar

1 chemotherapy, and again received the same allocation of
2 study medication following that course until neutrophil
3 recovery.

4 Patients who didn't enter complete remission went
5 on to a second induction course of similar chemotherapy, and
6 again received the same allocation of study medication
7 following chemotherapy until neutrophil recovery.

8 Patients that were diagnosed as not having
9 remitted after the first course could start the second
10 induction course as soon as was considered clinically
11 feasible by their investigator. There was no time limit on
12 that.

13 At the time that we started this study in early
14 1992, there was no consensus as to the most appropriate
15 post-remission treatment for patients under the age of 50.
16 There was considerable interest in many parts of the world
17 in the use of high doses of Ara-C, and we thought it would
18 be important to investigate the utility of Filgrastim in
19 this very aggressive chemotherapy regimen.

20 So we introduced an optional second course of
21 consolidation, which comprised high-dose Ara-C. This was
22 only open to patients of 50 years and under, because that
23 was the upper age limit at that time for giving that
24 chemotherapy regimen.

25 Patients over the age of 50 could receive another

1 consolidation course of standard dose similar to the first
2 one. Again, the same allocation of study medication that
3 had been given from the outset was given after each course
4 until neutrophil recovery.

5 [Slide.]

6 The protocol specified some guidelines for
7 supportive care in this study, and I would like to review
8 those. Prophylactic oral quinolone antibiotics were given
9 to all patients in this study on every day at which they
10 were neutropenic.

11 This was the standard of care in Europe and
12 Australia and was based on a large number of published data
13 on the use of quinolones in prolonged durations of
14 neutropenia where they have been shown to reduce the
15 incidence of gram-negative bacteremias.

16 Intravenous antibiotics were required to be
17 commenced as soon as patient became febrile with a
18 temperature of 38 degrees or more or other signs of
19 infection.

20 The only criteria that the protocol specified for
21 stopping antibiotics were that if a patient had had a fever
22 of unknown origin and had become afebrile for 48 hours,
23 then, the antibiotics should stop provided there were no
24 other signs of infection.

25 Importantly, antibiotics use was not linked to

1 neutrophil recovery in the protocol, so this was done at the
2 discretion of the treating physician according to clinical
3 criteria.

4 All patients were hospitalized for most courses of
5 treatment. Discharge again was not mandated in the protocol
6 to be linked to neutrophil recovery, and it was according to
7 institutional policies. All that the protocol required was
8 that patients be afebrile and not receiving intravenous
9 antibiotics.

10 [Slide.]

11 My colleague, James Matcham, is now going to
12 review the principal efficacy and disease outcome data from
13 the study.

14 **Results and Discussion of Efficacy**

15 DR. MATCHAM: Good afternoon.

16 In my presentation, I will present data that
17 addresses the first two questions concerning the efficacy
18 and the safety of Filgrastim in induction and in
19 consolidation, but before I do this, I would just like to
20 describe the patient demography.

21 [Slide.]

22 A total of 521 patients were randomized into the
23 trial, making this the largest randomized trial of a growth
24 factor in AML. The patients were randomized into 31 centers
25 in Europe and in Australia.

1 The first patient was randomized during March of
2 1992 and the large patient came off study in May of 1995.

3 [Slide.]

4 This slide shows the summary of the patient
5 demography. The treatment groups were well balanced for
6 age, for sex, and for ECOG status. In comparison to other
7 published studies, this trial involved adult patients of all
8 ages ranging from 16 years of age to 89 years of age.

9 The groups were also well balanced for FAB subtype
10 and cytogenetic status.

11 [Slide.]

12 This slide shows the number of patients at each
13 stage in the trial. 259 patients were randomized to receive
14 Filgrastim and 262 were randomized to receive placebo. A
15 similar number of patients achieved complete remission in
16 both groups. Patients not achieving complete remission did
17 so because of persistent disease or death.

18 There were a similar number of withdrawals from
19 the study in each group, and a small number of patients
20 withdrew after achieving a complete remission. These were
21 due to the adverse events of chemotherapy.

22 A similar number of patients started the first
23 consolidation course in both groups, and a similar number of
24 patients started the optional second consolidation in both
25 groups.

1 [Slide.]

2 I would now like to address the first question
3 concerning the efficacy of Filgrastim in induction and in
4 consolidation chemotherapy.

5 The primary efficacy parameter was that of the
6 duration of neutropenia. The secondary efficacy parameters
7 were the infection-related endpoints of the incidence and
8 duration of fever, the incidence and duration of I.V.
9 antibiotic use, the incidence of culture-confirmed
10 infections, and the duration of hospitalization.

11 [Slide.]

12 In order to set the scene for discussing the
13 efficacy results in Induction Course 1, I would like to show
14 you this graph which shows the median neutrophil counts on
15 every day of Induction Course 1 for the patients in both
16 groups. I would like to draw your attention to the log
17 scale on the y axis on this graph.

18 The patients begin the course with low median
19 neutrophil counts, and there is an extensive duration of
20 neutropenia experienced in both groups. There is a sharp
21 rise in the median neutrophil counts which reaches
22 neutrophil counts of 500 five days earlier in the Filgrastim
23 group than in the placebo group.

24 In this course, the durations of the endpoints I
25 am going to show you are counted from day 6 of this course.

1 This was the earliest time that randomization could occur.

2 [Slide.]

3 This slide shows the analysis of the primary
4 efficacy endpoints of the duration of neutropenia. The
5 median duration of neutropenia in the placebo group was 19
6 days, and this has been significantly reduced by 5 days to a
7 median of 14 days in the Filgrastim group.

8 I would like to draw your attention to the upper
9 quartile. In the placebo group, 25 percent of patients had
10 durations of neutropenia of more than 29 days. This number
11 has been reduced to 20 days in the Filgrastim arm. This
12 shows a large effect of Filgrastim on the duration of
13 neutropenia with an increased benefit in the patients with
14 very long durations of neutropenia.

15 [Slide.]

16 Having demonstrated the large effects of
17 Filgrastim on the duration of neutropenia, this table shows
18 the effects of Filgrastim on the infection-related
19 endpoints. As we expected, with both groups experiencing
20 such long durations of neutropenia, more than 90 percent of
21 patients experienced fever in both groups, more than 95
22 percent of patients received an intravenous antibiotic in
23 both groups, and all patients are hospitalized.

24 We were able to document culture-confirmed
25 infections in 36 percent of the patients, however, the

1 durations of all these endpoints were impacted by the use of
2 Filgrastim.

3 The median days of fever in the placebo group was
4 8.5 days, and this has been significantly reduced to a
5 median of 7 days in the Filgrastim arm. The median duration
6 of intravenous antibiotic use in the placebo arm was 18.5
7 days, and this has been significantly reduced by 3.5 days to
8 a median of 15 days in the Filgrastim arm.

9 The median duration of hospitalization in the
10 placebo arm was 25 days, and this has been significantly
11 reduced by 5 days to a median of 20 days in the Filgrastim
12 group. So by reducing the duration of neutropenia, we have
13 produced a consistent reduction in the duration of all the
14 infection-related endpoints that could be measured.

15 [Slide.]

16 In patients with long durations of neutropenia,
17 intravenous anti-fungal agents are frequently used, and
18 these are generally very toxic. Since we reduced the
19 duration of neutropenia by such a large amount, we
20 hypothesized whether the requirement for intravenous anti-
21 fungal agents had been reduced.

22 In the placebo group, 47 percent of patients
23 required anti-fungal agents, and this has been significantly
24 reduced to 37 percent of patients in the Filgrastim arm.
25 This difference is mainly due to the reduction in the

1 requirement for amphotericin.

2 Although this was not stated as an endpoint in our
3 study, this represents an important clinical benefit for the
4 use of Filgrastim.

5 [Slide.]

6 I would now like to turn to the efficacy of
7 Filgrastim during consolidation. Only patients achieving
8 remission received consolidation. In our trial, 319
9 patients started the first consolidation course, 162
10 patients receiving Filgrastim and 157 patients receiving
11 placebo.

12 Unlike induction therapy, patients begin this
13 course with a normocellular bone marrow and normal
14 peripheral blood counts, and patients have no ongoing
15 infection. However, the chemotherapy is of a similar
16 intensity to that of induction.

17 [Slide.]

18 In order to set the scene for discussing the
19 efficacy results in this first consolidation course, this
20 slide again shows the median neutrophil counts on every day
21 of the first consolidation for patients in both groups.
22 Again, I would like to draw your attention to the log scale
23 on the y axis here.

24 Patients begin the course with normal peripheral
25 blood counts. As the use of Filgrastim starts, there is a

1 rise in the neutrophil count. The time at which the
2 neutropenia starts is the same in both arms, however, the
3 depth of the neutrophil nadir is not as deep with Filgrastim
4 with the majority of the patients in the Filgrastim group
5 not going lower than neutrophil counts of 200.

6 The median neutrophil count rises through
7 neutrophil counts of 500, approximately seven days earlier
8 in the Filgrastim group than in the placebo group.

9 In the slide I am going to show you, the durations
10 of the endpoints are counted from the first day of
11 chemotherapy in this course.

12 [Slide.]

13 This slide shows the summary for the incidence and
14 duration of neutropenia. The median duration of neutropenia
15 in the placebo group was 11 days, and this has been
16 significantly reduced by 7 days, to a median of 4 days in
17 the Filgrastim group. I would again like to draw your
18 attention to the quartiles.

19 In the placebo group, the middle 50 percent of
20 patients experienced a duration of neutropenia between 8 and
21 14 days. This range has been reduced to 2 and 6 days in the
22 Filgrastim group.

23 These ranges do not overlap, and this demonstrates
24 again the large effects of Filgrastim on the duration of
25 neutropenia in this first consolidation course. Unlike

1 induction, Filgrastim did have an effect on reducing the
2 incidence of neutropenia, with 10 percent of patients in the
3 Filgrastim group not even experiencing neutropenia during
4 this course.

5 [Slide.]

6 This slide shows the effects of Filgrastim on the
7 infection-related endpoints during first consolidation
8 course. In this course, Filgrastim significantly reduced
9 the incidence of fever and the duration of fever.

10 Filgrastim showed a trend of reducing the
11 incidence of intravenous antibiotic use and showed a
12 significant reduction in the duration of intravenous
13 antibiotic use.

14 [Slide.]

15 At the time the study was conducted, it was
16 practice in Europe and Australia to continue hospitalization
17 after chemotherapy for this course, and we showed that
18 Filgrastim significantly reduced the duration of
19 hospitalization.

20 There was a trend for fewer culture-confirmed
21 infections in the Filgrastim group. This shows that the
22 large reduction in the duration of neutropenia in this
23 course was paralleled by reductions in the durations of the
24 infection-related endpoints, and unlike induction, there
25 were either strong trends or significant reductions in the

1 incidence of fever, intravenous antibiotic use, and culture-
2 confirmed infections.

3 [Slide.]

4 This slide shows summaries of the durations of
5 neutropenia in all the courses that were studied during the
6 trial. There was significant reductions in the durations of
7 neutropenia in Induction Course 1 and Induction Course 2 in
8 first consolidation and in both options for the second
9 consolidation course.

10 This demonstrates the consistent effects of
11 Filgrastim on the duration on neutropenia in all courses.
12 These were paralleled by reductions in the infection-related
13 endpoints.

14 [Slide.]

15 In answer to the first question concerning the
16 efficacy of Filgrastim in induction and consolidation
17 chemotherapy for AML, we have shown that Filgrastim
18 significantly reduces the duration of neutropenia in
19 induction and in consolidation.

20 Filgrastim significantly reduces the duration of
21 fever, intravenous antibiotic use, and hospitalization in
22 induction and in consolidation, and Filgrastim significantly
23 reduced the incidence of neutropenia and fever in
24 consolidation.

25 We believe that we have clearly demonstrated the

1 efficacy of Filgrastim in both induction and consolidation
2 for chemotherapy in AML.

3 [Slide.]

4 I would like to address the second question
5 concerning the safety of Filgrastim in AML. The study was
6 designed around the primary safety endpoints of complete
7 remission rates. We anticipated that the complete remission
8 rates in the placebo group would be 65 percent, and the
9 study was designed to detect either a reduction in complete
10 remission rates of 15 percent or an increase of 15 percent.

11 This was to be detected with a power of 90 percent
12 at the 5 percent level of significance. Age is a well
13 documented prognostic factor for disease outcome in AML, and
14 since patients less than 50 years of age could receive the
15 high dose ara-C option in the second consolidation course,
16 we decided to stratify the randomization by age using the
17 age of 50 as a cutoff.

18 Interim analyses were planned to assess the
19 accumulating safety data and these were reviewed by an
20 independent data monitoring committee.

21 [Slide.]

22 This slide shows the results for the primary
23 safety endpoints of complete remission rates. The remission
24 rates in the placebo group was 68 percent, and the remission
25 rates in the Filgrastim group was 69 percent. These compare

1 favorably to the published literature.

2 The reasons for not achieving remission are
3 similar in both groups. One of the concerns of using a
4 myeloid growth factor in AML was the stimulation of leukemia
5 and therefore a possibly higher rate of persistent leukemia.
6 This was not observed in this study with 22 percent of
7 patients with persistent disease in the placebo group and 21
8 percent in the Filgrastim group. We conclude that
9 Filgrastim has no adverse impact on complete remission
10 rates.

11 [Slide.]

12 We were interested to look at the causes of death
13 for the patients who died during induction. Deaths during
14 induction are complex and multifactorial, and assigning a
15 single cause of death is very difficult. This slide shows
16 the causes that were assigned before unblinding the
17 treatment groups.

18 The number of deaths in induction was similar in
19 the two treatment groups, however, there were fewer
20 infection-related deaths in the Filgrastim group although
21 this is not statistically significant.

22 [Slide.]

23 This slide shows the event free survival for all
24 randomized patients. Event free survival is defined as the
25 time from randomization into either failure to achieve

1 remission, relapse, or death from any cause. Patients not
2 achieving remission are counted as having a survival of
3 zero. This is the same data and the same analysis referred
4 to in the FDA briefing document as time to progression.

5 The median event free survival in the placebo
6 group was 186 days and in the Filgrastim group was 165 days.
7 To represent the treatment difference while looking at the
8 difference in medians, which is only one point on this
9 curve, does not take into account the information contained
10 along the whole length of the curve.

11 A measure of treatment difference which does take
12 this into account is the hazard ratio. The hazard ratio of
13 1 indicates that there is no difference between the
14 treatment groups, and the hazard ratio observed here in this
15 data is almost exactly 1.

16 The log rank test, which compares the whole curve,
17 also shows no significant difference between the groups.
18 These curves are virtually superimposable and we conclude
19 that there is no adverse effect of Filgrastim on event free
20 survival.

21 [Slide.]

22 This slide shows the event free survival for
23 patients aged 50 years or over. Here, the hazard ratio is
24 again close to 1 and the log rank test indicates no
25 significant difference between the treatment groups.

1 [Slide.]

2 This slide shows the event free survival for the
3 patients less than 50 years of age. Again, the hazard ratio
4 is almost exactly 1 and the log rank test indicates no
5 significant difference between the treatment groups.

6 [Slide.]

7 This slide shows the relapse free survival for all
8 the patients that achieved a complete remission. In this
9 case, the hazard ratio is exactly equal to 1 and the log
10 rank test indicates no significant difference between the
11 treatment groups.

12 These curves are again virtually superimposable
13 and we conclude there is no adverse impacts of Filgrastim on
14 relapse free survival.

15 [Slide.]

16 This slide shows the overall survival for all the
17 randomized patients. The hazard ratio here is almost
18 exactly 1 and the log rank test indicates no significant
19 difference between the two treatment groups.

20 [Slide.]

21 This slide shows the overall survival for patients
22 age 50 or more. The hazard ratio here is again close to 1
23 and the log rank test indicates no significant difference
24 between the groups.

25 [Slide.]

1 This slide shows the overall survival for patients
2 less than 50 years of age. Again the hazard ratio is close
3 to 1 and the log rank test indicates no significant
4 difference.

5 We conclude that there is no evidence of an
6 adverse impact of Filgrastim on overall survival.

7 I would now like to hand back to Dr. Alan Barge
8 who will describe the adverse events reported during the
9 trial.

10 **Discussion of Results-Safety, Review of**
11 **Published Literature, Summary and Conclusion**

12 DR. BARGE: Thank you.

13 [Slide.]

14 We wanted in this study to determine whether or
15 note Filgrastim had any additional impact on other lineages.
16 We examined the time to platelet recovery for all patients
17 undergoing induction therapy.

18 This shows a Kaplan-Meier plot of the time to
19 platelet recovery for all 521 patients that received
20 induction therapy. As you can see, there is absolutely no
21 difference in the time to platelet recovery in the two
22 groups.

23 [Slide.]

24 We also looked at the requirement for platelet
25 transfusions in patients undergoing induction therapy and

1 again both patients had a median of 8 days of platelet
2 transfusions and there was no difference between the groups.

3 [Slide.]

4 We looked at the impact of treatment with
5 Filgrastim on hemoglobin recovery and again, as expected,
6 there was no difference in hemoglobin recovery between the
7 two groups during induction

8 [Slide.]

9 We also looked at platelet recovery during the
10 first consolidation course and again showed that there was
11 no difference whatsoever in the time to platelet recovery
12 between the two groups, and we conclude that Filgrastim has
13 had a lineage-specific effect in this disease and has not
14 affected hemoglobin or platelet recovery at all.

15 [Slide.]

16 We looked at the adverse events that were
17 reported. As expected in this population, adverse events
18 were reported very frequently. This slide summarizes the
19 severe, life threatening or fatal adverse events as
20 described by the participating investigators.

21 There was no difference in the frequency of these
22 events between the treatment groups, and most of the events
23 were those of gastrointestinal toxicities attributed to the
24 chemotherapy.

25 [Slide.]

1 In conclusion, we believe we have demonstrated
2 that Filgrastim is a safe and effective adjunct to
3 chemotherapy for AML resulting in significant clinical
4 benefits in terms of reductions in the duration of
5 neutropenia, fever, intravenous antibiotic use and
6 hospitalization in both induction and consolidation therapy.

7 We have seen no adverse effect on disease outcome
8 as measured by remission rate, relapse free and overall
9 survival.

10 [Slide.]

11 We were interested to compare the results of this
12 study with other randomized studies of hematopoietic growth
13 factors in induction for AML.

14 This slide summarizes the remission outcome
15 results for all of the published studies. There have been
16 seven randomized studies of GM-CSF and four of G-CSF. The
17 slide expresses the remission rates between the treatment
18 groups as an odds ratio.

19 An odds ratio to the right of the line indicates a
20 superior remission rate in the growth factor group, to the
21 left of the line, a superior remission rate in the placebo
22 group.

23 The wider the confidence interval, the smaller the
24 number of patients in the study. As you can see, the larger
25 studies of GM-CSF, those by Drs. Witz, Lowenberg, and Stone,

1 show no impact of the growth factor on remission rate.

2 The larger studies of G-CSF, that of Dr. Godwin,
3 and this study also show no difference in remission rate
4 between the treatment groups, and we conclude that neither
5 hematopoietic growth factor has any effect on remission rate
6 in this disease.

7 When the overall survivals of these studies are
8 compared, there is no difference between the treatment
9 groups in terms of overall survival in the larger studies.

10 [Slide.]

11 I would now like to turn to address some of the
12 specific issues that have been raised by the FDA for the
13 committee.

14 [Slide.]

15 They have asked whether or not it is reasonable to
16 extrapolate the results in adults with AML to children with
17 this disease. The company has conducted no randomized
18 studies of Filgrastim in children. However, the Children's
19 Cancer Group in the United States have conducted a study,
20 the analysis for which is still ongoing. This has been
21 reported in abstract form only by Dr. Woods two years ago,
22 but the Children's Cancer Group have generously supplied us
23 with some interim data from their ongoing analysis.

24 [Slide.]

25 Children's Cancer Group Study 2891 was designed

1 primarily to evaluate an intensively-timed versus a standard
2 timing induction regimen in children with AML. The
3 chemotherapy is a standard five drug - dexamethasone,
4 cytosine arabinoside, thioguanine, etoposide, and idarubicin
5 regimen administered usually every 21 days.

6 The intensively-timed arm is repeated every 10
7 days and is termed DCTER-DCTER, and is given regardless of
8 peripheral blood counts.

9 In mid-1992, because of the high incidence of
10 neutropenia-associated morbidity in the intensively-timed
11 arm, the study was modified to routinely incorporate
12 Filgrastim in all subsequently randomized patients, so the
13 comparison I am going to show you is between patients
14 enrolled in the study after 1992 who routinely received
15 Filgrastim with those entering the study before 1992 who did
16 not.

17 [Slide.]

18 541 patients have been randomized to the intensive
19 arm, 286 of which had not received Filgrastim, 255 of which
20 had.

21 Both groups were well balanced for age, sex, and
22 presenting white and platelet counts.

23 [Slide.]

24 This shows the disease outcome results. As
25 expected in children, the remission rate is high. The

1 remission rate in the Filgrastim-treated group is at least
2 as good as the remission rate in the previous group that
3 didn't receive Filgrastim, with 82.7 percent of the children
4 receiving Filgrastim going into remission.

5 The reasons for failing to enter remission are
6 similar in both groups. There were 30 deaths before G-CSF
7 was instituted in this study and only 20 afterwards.

8 The study wasn't designed primarily to study the
9 efficacy of Filgrastim, and so only weekly neutrophil counts
10 have been collected by the CCG. Nonetheless, they show that
11 the median neutrophil count is significantly higher at each
12 weekly interval timepoint after both courses of therapy in
13 the Filgrastim group.

14 [Slide.]

15 We conclude from this study that Filgrastim had
16 not adversely influenced the CR rate in children receiving
17 intensive induction therapy in comparison to the previous
18 cohort, and that it significantly elevated the ANC at the
19 end of each cycle and at the end of each course.

20 Therefore, we think that Filgrastim appears to
21 have a similar efficacy and safety profile in children with
22 AML to that, that we have demonstrated in adults.

23 [Slide.]

24 Another question raised by the FDA has been the
25 impact or otherwise of the use of prophylactic quinolone

1 antibiotics on the incidence of documented infection in our
2 study.

3 [Slide.]

4 Prophylactic quinolone antibiotics are routinely
5 used as the standard of care in many places in Europe,
6 Australia, and the United States. Their purpose, which is
7 just like the purpose of using empiric intravenous
8 antibiotics as soon as patients become febrile, is to reduce
9 the incidence of culture-confirmed infections, and large
10 randomized studies of quinolones have shown that they have
11 reduced the incidence of some gram-negative infections in
12 patients undergoing induction for leukemia or bone marrow
13 transplantation. They are therefore used on a widespread
14 basis worldwide.

15 Despite their use, in this study, over 95 percent
16 of patients in both treatment groups still required
17 intravenous antibiotics. The effects of Filgrastim on
18 reducing the duration of I.V. antibiotics and on other
19 infection related endpoints is clear despite their use.

20 [Slide.]

21 Another question that has been raised has been
22 about a label recommendation for bone marrow evaluations
23 prior to the first administration of Filgrastim. In this
24 study, Filgrastim was administered 24 hours after the last
25 dose of chemotherapy following induction and consolidation

1 regardless of bone marrow status. Some of the earlier
2 studies had delayed the administration of growth factor
3 until hypoplastic bone marrow had been documented.

4 In our study, we saw no increased need for a
5 second induction in patients receiving Filgrastim, so it
6 indicated there was no evidence that it was stimulating the
7 disease, and Filgrastim commenced 24 hours after the
8 completion of each course of chemotherapy from this study
9 has been shown to be safe and effective.

10 [Slide.]

11 Finally, a question has been asked in relation to
12 whether or not the results of this study can be extrapolated
13 to patients with secondary AML.

14 [Slide.]

15 Secondary AML, as you know, is a heterogeneous
16 disease. There are very limited data available and we have
17 conducted no prospectively randomized studies of our own.
18 There were some limited data available from Dr. Godwin in
19 the Southwest Oncology Group who included secondary AMLs in
20 a randomized study of Filgrastim that they did.

21 In our study, although we excluded secondary AMLs,
22 we looked at those patients who had an adverse cytogenetic
23 profile which is similar to that sometimes seen in secondary
24 AML.

25 [Slide.]

1 When we looked at patients with Monosomy 7,
2 Monosomy 5, 11q(2,3), and complex abnormalities, and
3 compared the remission rates between the treatment groups,
4 we saw no difference in the remission rate. We conclude
5 from this that at least in patients with adverse
6 cytogenetics, Filgrastim does not adversely affect the
7 outcome.

8 [Slide.]

9 In summary, we have shown that Filgrastim is a
10 safe and effective adjunct to chemotherapy for AML,
11 resulting in no effect on disease outcome in terms of
12 remission rate, event free and overall survival.

13 We have shown that it confers significant benefits
14 in terms of reductions in the duration of neutropenia and
15 infection related endpoints in both induction and
16 consolidation with chemotherapy.

17 I would be very happy to answer any of your
18 questions.

19 DR. VOSE: Thank you, Dr. Barge.

20 Let's proceed with questions from the committee
21 for the sponsor.

22 Dr. Anderson.

23 DR. ANDERSON: In your table on severe life
24 threatening or fatal adverse events, the only adverse event
25 which was only seen in the experimental, and not the

1 placebo, was hemorrhage.

2 Can you describe what those four events were?

3 DR. BARGE: Yes, I can. We have looked at
4 hemorrhage in some detail in this study. As I showed you,
5 the platelet count recovery was identical, as was the
6 requirement for platelet transfusions.

7 It is certainly true that more hemorrhagic events
8 were reported as severe events, as shown on that slide.
9 When you look at the overall hemorrhagic event rate, the
10 overall number of hemorrhagic events reported as adverse
11 events, they were similar to both groups. I can summarize
12 that on a slide.

13 [Slide.]

14 These are all the adverse events, all the
15 hemorrhagic adverse event reported. We saw similar
16 frequencies of all events in both groups, so the attribution
17 of severity, which is something that is done by the
18 investigator, was probably responsible for that.

19 DR. ANDERSON: But those four events, which of the
20 various types of hemorrhage was it, do you happen to
21 remember?

22 DR. BARGE: In the severe events --

23 DR. ANDERSON: Right, in the severe.

24 DR. BARGE: It is the next slide, I think.

25 [Slide.]

1 There were five cerebral hemorrhages reported in
2 the Filgrastim group and one in the placebo group. Now,
3 when we first saw this again, we took some interest in
4 looking at these, and I have summarized the characteristics
5 of the patients, the next slide.

6 [Slide.]

7 We saw six cerebral hemorrhages overall. Five of
8 them were in the Filgrastim group. They were all in
9 patients in the over 50 group. As you can see, they
10 occurred early. The day of death is the day of treatment,
11 so they all occurred early, before platelet recovery, and
12 they were all during induction.

13 Interestingly, most of those patients also had
14 significant concomitant ongoing pathologies, as well, such
15 as ongoing pulmonary hemorrhage, hepatic failure,
16 bacteremia, renal impairment, and a probable A-V
17 malformation, as well. So we conclude from this that these
18 events occurred before platelet recovery.

19 DR. ANDERSON: Now, how many of these classified
20 as severe?

21 DR. BARGE: I don't know. They were all
22 classified as severe, life threatening or fatal.

23 DR. ANDERSON: But there is only four in the
24 table, and if there is five of these, they can't all be --

25 DR. BARGE: I am sorry, they are all classified as

1 serious is what I mean. I think it is the distinction
2 between severe and serious that is confusing.

3 DR. VOSE: Does that answer your question, Dr.
4 Anderson?

5 DR. ANDERSON: No, but I think the exact details
6 of which of the four isn't immediately available, I would
7 guess.

8 DR. BARGE: That's right.

9 DR. VOSE: Dr. Berman.

10 DR. BERMAN: I have a question about the slide
11 entitled "Infection-Related Endpoints - Consolidation 1."
12 You alluded to it briefly in your discussion.

13 The median time for hospitalization was 19 days on
14 the G arm and 25 days on the placebo arm. Yet, on the G
15 arm, it looks like the median days of fever and I.V.
16 antibiotics was zero. So, are we to infer that patients are
17 hospitalized for 19 days without a fever and without I.V.
18 antibiotics?

19 DR. BARGE: It was certainly standard practice in
20 Europe and Australia when we did the study for all patients
21 to be hospitalized for the duration of consolidation
22 therapy.

23 DR. BERMAN: The chemotherapy itself only took
24 five days, so were people observed without fevers for
25 another 14 days, just observed only?

1 DR. BARGE: Put the slide up again.

2 [Slide.]

3 It is certainly true that the durations -- bear in
4 mind that the durations of fevers record every day of fever,
5 so the fevers can occur sporadically throughout the period
6 of hypoplasia before they recover.

7 DR. BERMAN: So again, patients were hospitalized
8 without any intervention for a median of 19 days on the G
9 arm?

10 DR. BARGE: Can I ask Dr. Heil to address the
11 question.

12 DR. HEIL: I think the question is correct. We
13 have a different practice in Europe and Australia than the
14 U.S. In fact, all our patients who receive induction or
15 consolidation chemotherapy are kept in hospital
16 irrespectively of there is some infectious complications or
17 not. We are bound to do this.

18 DR. BROUDY: What are your criteria for discharge
19 if that contributes to the difference between the 19 and 25
20 days?

21 DR. HEIL: Yes, that's right. We leave a patient
22 at home if he has completely recovered with his peripheral
23 blood count and if he has complete remission of his disease,
24 then, we send the patient home. Sorry for that. We must
25 change our practice now, but that was the practice during

1 this study.

2 DR. BROUDY: So the days of hospitalization really
3 reflect the days of neutropenia, is that what you are
4 telling me, or thrombocytopenia?

5 DR. HEIL: That is very difficult. It doesn't
6 depend on the neutrophil count, but it depends on how the
7 patient was, if he was well, without infections, no evidence
8 of residual leukemia, we sent him home.

9 DR. VOSE: Additional questions? Dr. Miller.

10 DR. MILLER: Were the placebo and G-CSF arms
11 balanced for cytogenetics?

12 DR. BARGE: Yes, they were. We were able to
13 document cytogenetic profiles in 73 percent of the patients
14 overall, and they had similar proportions of favorable
15 normal and unfavorable karyotypes.

16 DR. VOSE: Dr. Berman.

17 DR. BERMAN: I have another procedure question.
18 The protocol outline that a bone marrow would be done on day
19 3, after G-CSF was stopped, it seems a fairly short time.
20 While the peripheral white count may have come down to
21 normal or be dropping, the bone marrow probably still shows
22 an excessive neutrophilia at that time.

23 Was the rate of relapse between the two arms the
24 same?

25 DR. BARGE: The rate of relapse between the arms

1 was identical, yes. When we started the study, we were
2 concerned about the potentially confounding effects of
3 Filgrastim on bone marrow morphology because we had seen in
4 other studies occasionally that you do see a large number of
5 relatively immature myeloid cells in the marrow when
6 patients are receiving G-CSF. So we were concerned that
7 this didn't confound the diagnosis of remission.

8 So, we asked that the drug be stopped for a
9 minimum of three days after neutrophil recovery before
10 formally assessing the remission status. We also had the
11 remission status bone marrow essentially reviewed by an
12 independent hematologist.

13 As it turned out, it wasn't nearly so confounding
14 an issue as we had at first anticipated, and there is no
15 difference in early relapses.

16 DR. BERMAN: I have one more question, and I think
17 the answer is obvious, but did you do a cost analysis of the
18 money saved by use of G-CSF compared to the cost of the
19 drug?

20 DR. BARGE: Well, an analysis has been done. This
21 study was done in many different countries in Europe and
22 Australia, which have really rather different reimbursement
23 and funding mechanisms for inpatient medical care, but a
24 pharmacoeconomic group has tried to translate these data to
25 U.S.-based costs, and they have shown that there is a

1 significant cost saving, which is driven largely by the
2 hospitalization as you might expect in the Filgrastim group,
3 but I can't quote you the numbers.

4 DR. VOSE: Dr. Barge, as you mentioned, the
5 treatment for AML is really affected by age of the patient,
6 and you did a cutoff at age 50 because of the different
7 consolidation they received.

8 Did you also do an analysis of age of 60, which is
9 more traditional for AML?

10 DR. BARGE: No, we haven't done that. We have
11 looked at age as a continuous variable in multivariate
12 analysis for both survival and for the primary efficacy
13 endpoints. Age does not influence the effects of Filgrastim
14 in that regard, but we have reanalyzed the data at 60, no.

15 DR. VOSE: Additional questions?

16 DR. BROUDY: Could you comment on the paper by
17 Godwin, et al., in which a subset of the patients had
18 secondary AML, and the remission rate was 5 percent in the
19 patients treated with G-CSF and 33 percent in those treated
20 with placebo? This was not statistically different,
21 probably because of very small numbers involved, but the
22 trend is certainly impressive.

23 DR. BARGE: That's right. I am familiar with the
24 data. That is not a study that we have undertaken. It has
25 been done by the Southwest Oncology Group, and I am not

1 privy to the data, so I have only seen what was presented at
2 the American Society meeting a couple of years ago.

3 There are 50 patients with secondary AML
4 randomized into that study, and you are right, that there is
5 an apparently large difference in outcome between the
6 groups. I understand from the Southwest Oncology Group that
7 the groups are very imbalanced for prognostic factors of
8 cytogenetics and MDR expression, and when that is controlled
9 for, the difference is less.

10 DR. VOSE: Dr. O'Fallon.

11 DR. O'FALLON: This was a statistical tour de
12 force, so it would be almost mean of me to ask any
13 questions, but I must, of course. I think you just answered
14 one of them. In these many survival analyses that you
15 stratified by age in particular, I was going to ask if you
16 had done analyses with more variables in them, in other
17 words, multivariate Cox proportional hazards models. The
18 answer I take it is yes, at least you used age as a
19 continuous variable.

20 DR. BARGE: The answer is yes, but I can ask my
21 statistical colleague to answer it better.

22 DR. O'FALLON: What other variables did you
23 investigate in such a multivariate model?

24 DR. MATCHAM: For survival.

25 DR. O'FALLON: For any of the survivals, yes.

1 DR. MATCHAM: We looked at the effects of the
2 prognostic factors of age, ECOG status, FAB subtype, gender,
3 and center. The important prognostic factors that came
4 through were those that were generally accepted to be
5 prognostic factors in AML, so those of age, ECOG status, and
6 FAB subtype, so we found all of those in our data.

7 When you adjust for the effects of those in a Cox
8 proportional hazards model, there was still no effect of
9 Filgrastim on overall survival.

10 DR. O'FALLON: So your hazards ratios were the
11 same.

12 DR. MATCHAM: That's right, so either with or
13 without adjustment for those, we still see no effects of
14 Filgrastim on event-free or overall survival.

15 DR. O'FALLON: Now, when you investigated the
16 interaction of those adjusting variables with the indicator
17 variable, did you find any --

18 DR. MATCHAM: We found no significant interactions
19 between those and the effect of treatment.

20 DR. O'FALLON: How close to significance did you
21 get?

22 DR. MATCHAM: In one we did get a bit close, but
23 it didn't meet our criteria for statistical significance
24 that we had set.

25 DR. O'FALLON: It was stated early that interim

1 analyses were planned in this large study, but I didn't
2 hear, number one, what the results of any of them were.
3 Obviously, you didn't terminate the study. Number two, how
4 did you adjust the p values that you quoted to us here for
5 those analyses?

6 DR. MATCHAM: The interim analyses were planned to
7 take place when the results of each sequential group of 60
8 patients had their results, so we took the first 60
9 randomized patients, waited for their results to come in,
10 and then we did the first interim analysis, and so on,
11 through the trial.

12 The scheme that we used was a sequential trial
13 method called the double triangular test, and we set out the
14 framework for the interim analysis using this double
15 triangular test. These were presented to the Data
16 Monitoring Committee at the end of each interim analysis, and
17 this was their basis for the decision to either continue or
18 to stop the study.

19 At each interim analysis, there was no concern
20 about the safety of Filgrastim, and the study ended when the
21 Data Monitoring Committee said we are not going to be able
22 to demonstrate a difference in 15 percent with these data,
23 and we are confident that that conclusion will not change.

24 DR. O'FALLON: The adjusted hazards ratio of a
25 confidence interval on that extended how far?

1 DR. MATCHAM: The confidence interval for the
2 difference in proportions of the remission rates was
3 actually quite small. I don't have the numbers to hand, but
4 the difference in percent was 1 percent, and the confidence
5 interval -- I am trying to do this from memory, and I don't
6 have the numbers to hand.

7 DR. O'FALLON: You showed us some confidence
8 intervals, which after all are really the critical things
9 that we want to look at, and they are not much different.
10 Are they narrower in the overall adjusted model?

11 DR. MATCHAM: They are narrower, of course,
12 because you are adjusting for important prognostic factors.

13 DR. O'FALLON: Right. There was a plot where odds
14 ratios were quoted -- were they odds ratios or hazards
15 ratios just out of curiosity?

16 DR. MATCHAM: This was the plot of the different
17 randomized --

18 DR. O'FALLON: The different studies, right.

19 DR. MATCHAM: The different trials?

20 DR. O'FALLON: Right.

21 DR. MATCHAM: These plots were the plots of the
22 odds ratio, and they are associated 95 percent confidence
23 interval, and the odds ratio was based on the difference in
24 proportion of patients achieving complete remission in each
25 trial.

1 DR. O'FALLON: Thank you.

2 DR. VOSE: Additional questions?

3 I have one additional question about infection,
4 specifically, the use of oral quinolones in the transplant
5 literature has been associated with increased incidence of
6 alpha-hemolytic strep.

7 Is there any evidence in the G-CSF arm that you
8 could reduce that incidence or any difference or reduce the
9 use of I.V. vancomycin, for example?

10 DR. BARGE: We really haven't looked at that. I
11 mean the overall incidence of bacteremias and other culture
12 documented infections, which we looked at in some detail,
13 just wasn't different between the arms in terms of the
14 number of events occurring each group.

15 DR. VOSE: But you didn't specifically look at
16 that and report it.

17 DR. BARGE: No.

18 DR. VOSE: Other questions for the sponsor?

19 Okay. We are going to take a five-minute break to
20 change equipment and then we will go with the FDA
21 presentation. Thank you.

22 [Recess.]

23 **FDA Perspective**

24 DR. CHANG: I wish I had a British accent to make
25 my presentation sound better, but since I don't, and it's

1 Friday afternoon, I will just keep it as brief as possible.

2 [Slide.]

3 This is the review team for this BLA.

4 [Slide.]

5 I am just going to highlight the key information.

6 Dr. Barge already presented that this was a double-blind,
7 randomized, placebo-controlled, Phase III trial at 31
8 centers in Europe and Australia. There were a total of 521
9 patients enrolled with de novo AML, and they were all 16
10 years of age or older.

11 The G-CSF was started 24 hours after the induction
12 and consolidation courses.

13 [Slide.]

14 The primary endpoints for the study were safety,
15 the effect of G-CSF on remission rate. The sample size was
16 based on a 90 percent power to detect a 15 percent
17 difference from the placebo with an expected 65 percent
18 complete remission rate. There were seven blinded interim
19 analyses performed after each of 60 patients enrolled. The
20 efficacy endpoint at that time was the duration of
21 neutropenia.

22 [Slide.]

23 This is the results of the primary safety and
24 efficacy endpoints, as you have heard. The primary
25 endpoints were complete remission rate and the median

1 duration of neutropenia. This was the Filgrastim arm and
2 the placebo arm, and this is the treatment difference and
3 the p value.

4 As you have been told, there was no difference in
5 the complete remission rate between the Filgrastim and
6 placebo. In terms of the median duration of neutropenia,
7 there was a difference of five days. This represents a 95
8 percent confidence that the difference would be as little as
9 four days and could be as much as six days with a p value of
10 0.0001.

11 [Slide.]

12 These are the secondary endpoints, fever and
13 infections, and you can see that as far as the incidence of
14 fever goes, and the incidence of documented infection goes,
15 there is no difference between the two arms.

16 However, in terms of the median days of fever,
17 there was a 1.5 day difference, 8.5 days reduced to 7.0
18 days.

19 [Slide.]

20 The secondary endpoints of I.V. antibiotic
21 administration and hospitalization. One can see again that
22 there was no difference in the use of non-prophylactic I.V.
23 antibiotics, however, the median days of I.V. non-
24 prophylactic antibiotics was reduced from 18.5 days to 15
25 days, a difference of 3.5 days and a confidence interval of

1 minus 5 to minus 2 with a p value of 0.0001.

2 The median days of hospitalization also was
3 reduced from 25 to 20 with a five-day difference and a
4 significant p value.

5 [Slide.]

6 This was already presented as the secondary safety
7 endpoints here, the time to disease progression and the
8 survival time. The median time to disease progression
9 seemed to be lower in the Filgrastim arm compared to the
10 placebo, 186 compared to 165. This is a difference of minus
11 21 days.

12 Now, the sponsor presented these hazard ratios
13 which showed no significant difference, and Dr. Siegel
14 suggested that we perform something called confidence
15 intervals around the difference, and Dr. Tiwari perhaps can
16 explain this a little better, but it gives you a better idea
17 of the 95 percent confidence interval in terms of days, so
18 that the difference between the placebo and Filgrastim arm
19 could be as much as 77 days, slower for Filgrastim or 47
20 days faster than Filgrastim.

21 As far as the survival time goes, this was again
22 less for the Filgrastim arm versus placebo, and here there
23 was a greater difference of minus 45 days, being as much as
24 minus 107 days less with a 95 percent confidence interval.

25 [Slide.]

1 This is a chart of the serious non-fatal adverse
2 events. There were 41 patients in the Filgrastim arm with
3 45 events compared to 31 patients in the placebo arm with 36
4 events. Again, the hemorrhagic events here were as have
5 already been discussed.

6 As far as the respiratory events go, there seemed
7 to be a slight excess of pneumonias in the Filgrastim arm, 6
8 in this arm, compared to 2 in that arm. Two of those
9 pneumonias, however, were culture-negative. So, in addition
10 to some cases of respiratory failure and ARDS, we are not
11 quite sure exactly what that excess was due to.

12 There was a small number also of cardiac and
13 vascular events.

14 [Slide.]

15 Dr. Barge presented a possible -- trying to
16 explain why these hemorrhagic events occurred, and we looked
17 at the median days to platelet count greater than 20,000,
18 but the duration of thrombocytopenia, and he looked at
19 consolidation, but we also looked at induction, and we found
20 that the days of thrombocytopenia were the same basically in
21 both arms.

22 [Slide.]

23 Amgen had stratified the two age groups to less
24 than 50 and greater than 50 years of age, but we were
25 interested in using the 55 years of age cutoff because we

1 wanted to compare against other colony stimulating factors.

2 Basically, when we did the stratification of less
3 than 50, 55 or under and greater than 55, we found that the
4 difference basically persisted in terms of the duration of
5 neutropenia, the duration of antibiotic use, and
6 hospitalization. It was consistent with both the age
7 groups.

8 The difference in fever apparently was significant
9 for the younger age group, but was not for the older age
10 group, but again this difference is fairly small.

11 [Slide.]

12 I just want to point out an error, a copy error in
13 this slide, and that is the significance footnote down here.
14 We looked at the two age groups in terms of the safety
15 endpoints of complete remission rate after Induction 1, the
16 median time to progression and the medial overall survival.

17 The complete remission rate was basically the same
18 for both arms in both age groups. The difference in time to
19 progression was a little more pronounced in the younger age
20 groups, for example, 253 days versus 203 days compared to
21 154 days and 140 days here.

22 The same disparity persisted with regard to median
23 overall survival with 491 days in the placebo arm versus 405
24 days in the Filgrastim arm. For the older age group, there
25 was less of a difference, 349 days versus 345 days.

1 [Slide.]

2 One of the reasons why we were interested in using
3 the 55-year-old age cutoff was we wanted to just look at GM-
4 CSF because it has already been approved for use in AML in
5 the elderly. So we took the age 55, greater than age 55
6 group for G-CSF and just then reevaluated their complete
7 remission rate, which was comparable in both arms, and it
8 looked pretty similar to the GM-CSF arm.

9 The median overall survival actually was fairly
10 close between the two arms, and even closer to the CM-CSF
11 arm. There seemed to be for some reason, in the GM-CSF
12 study, there seemed to be fairly poor survival in the
13 placebo arm.

14 I just want to mention that there was a difference
15 between these two studies, at least one difference anyway,
16 in the sense that the patients who went on this trial, the
17 smaller trial of 99 patients, underwent bone marrow
18 examination right after their chemotherapy, before they were
19 given GM-CSF, whereas, the patients in this study were given
20 G-CSF right after chemotherapy without a bone marrow
21 examination.

22 [Slide.]

23 In summary, this is a single large, well-conducted
24 trial. Results were supported by smaller studies in the
25 published literature. I should mention that there have been

1 some anecdotal patients with stimulation of blast
2 production, and there has been some controversy in the
3 literature about the clinical benefit and the cost
4 effectiveness of some of these secondary endpoints, but in
5 any case, in this particular study, the primary safety and
6 efficacy endpoints were met. There was no change in the
7 complete remission rate for AML, and there was a decreased
8 duration of neutropenia.

9 [Slide.]

10 As far as the secondary endpoints are concerned,
11 there was a decreased duration of fever, I.V. antibiotics,
12 and hospitalization, and there was no effect on the
13 incidence of fever or infections.

14 In terms of survival, we should discuss why the
15 time to progression, overall survival might be a little bit
16 poorer for the G-CSF arm and why the effect might be
17 consistent over young and old age groups.

18 Thank you.

19 DR. VOSE: Thank you, Dr. Chang.

20 Questions for Dr. Chang?

21 MS. MEYERS: I have a question.

22 DR. VOSE: Abbey.

23 MS. MEYERS: It was my impression that FDA really
24 requires study in pediatric studies, as well as assuring
25 inclusion of minorities, et cetera, inclusion of women. I

1 thought that this has been happening over the last several
2 years, and I am wondering why this study was done without
3 children.

4 DR. VOSE: Dr. Weiss, would you like to address
5 that?

6 DR. WEISS: There is actually going to be some I
7 think more emphasis on this from now on in terms of earlier
8 discussions with all of our sponsors about providing us
9 data, but pediatric regulations, because of some of the
10 difficulties in oftentimes a smaller number of pediatric
11 patients similarly affected and the difficulty in conducting
12 randomized control trials, pediatric regulations
13 specifically -- excuse me -- regulations regarding pediatric
14 use specifically say that if -- and this is actually, I am
15 probably getting a little bit ahead because this is actually
16 a question, I think No. 5 or 6 over here -- but the
17 regulations allow us to extrapolate efficacy data from
18 randomized trials in adults to pediatric studied, basically
19 say if we have enough information on dosage and safety, and
20 enough knowledge about the disease and disease processes to
21 say they are similar, that one does not have to actually
22 require efficacy trials in pediatrics.

23 DR. KLEINERMAN: I really think that is a
24 dangerous precedent to start. Number one, the thing that
25 bothers me about this survival data is that it appears to be

1 worse in the younger age group, the under 55, and I would be
2 concerned that if you look at AML in children, that it may
3 be even worse.

4 So, I wouldn't want to extrapolate the results
5 from this. The second is, as we have seen with many agents,
6 maybe not this agent, but other agents, the pharmacokinetics
7 are not the same, and so I don't think you can extrapolate.

8 I think that is a very dangerous precedent.
9 Again, I want to support Abbey's statement that I think that
10 there needs to be from the start, studies that are required
11 in pediatric populations. I think in this pamphlet it was
12 said there are 400 cases of childhood AML, and certainly 400
13 cases is a significant amount of AML in this country, not
14 worldwide, so I don't think it is like we heard this
15 morning, only 200 cases, we are getting double the number of
16 cases. So, I think it is a significant --

17 MS. MEYERS: Even the 200 cases, those lives are
18 not disposable.

19 DR. WEISS: Right. We are not saying it is not
20 important to know about that. The question always is should
21 sponsors be required to do trials, if something is approved,
22 it is available for use in all ages as long as a physician
23 feels it is appropriate to use in that population.

24 It is more a question of whether or not efficacy
25 trials, randomized control trials are required or is it

1 adequate to say that course of the disease is similar, the
2 response, we know enough about the dosing and the safety of
3 this drug in pediatrics to safely extrapolate, and that is
4 not going to be the same for every single disease.

5 DR. KLEINERMAN: Again, I have to say I don't
6 think that that is acceptable. I think that sponsors need
7 to start early on, just when they are starting with the
8 adult population, have the pediatric population included,
9 and I don't believe it is hard to do trials.

10 In fact, pediatricians have a hard time getting
11 companies to do trials that we are interested in doing,
12 because we have smaller numbers of patients, and they just
13 don't think it is going to make a significant impact on the
14 total sales.

15 So, I think at some point you have to come forth
16 and make them do it, and so I think it is very dangerous to
17 extrapolate from data even if you think you know the
18 disease. Kids often fool you. They don't metabolize the
19 drugs the same. It could be more toxic. It could be less
20 effective. I don't think that you can make extrapolations.

21 DR. WEISS: Our regulations say we have to know
22 enough about genetics, about metabolism to know what dose to
23 recommend and to know whether or not there is different
24 safety issues.

25 MS. MEYERS: On the other hand, I would just like

1 to say that I have to salute the company for coming here
2 with what amounts to a supplemental approval, knowing that
3 this drug is being used all over the place anyway for many,
4 many different types of cancer, and I wish more
5 manufacturers would come in and get the supplemental
6 approval, because if it is approved, it means it will be
7 reimbursed, and if you don't have it on your label, patients
8 don't get reimbursed for it, so it is very important, and
9 you really deserve to be saluted for that.

10 DR. WEISS: Ms. Meyers, also, in the case of
11 myeloid growth factors, too, until this trial was done, it
12 is specifically not indicated for individuals with myeloid
13 malignancies because of the concern, and that is why we all
14 agree that we needed to see a randomized controlled trial to
15 assure us that it was safe and effective in this kind of
16 disease setting.

17 DR. VOSE: Dr. O'Fallon.

18 DR. O'FALLON: I would like to ask Dr. Chang why
19 this sort of emphasis on the median time to event, why not
20 the 75th percentile, in one of those examples, you would
21 have had a completely different picture than the one that
22 you showed. The hazards ratios are generally accepted as
23 the best way to summarize overall survival curves provided
24 you are satisfied with the proportionality issues, which I
25 presume our colleagues can tell us that they aren't

1 satisfied with.

2 DR. CHANG: Well, Dr. Tiwari is more equipped to
3 answer that.

4 DR. O'FALLON: Okay.

5 DR. TIWARI: Jawahar Tiwari, CBER. That is one
6 way to look at it, and we tried to put additional
7 information there.

8 DR. O'FALLON: Well, I accept the additional
9 information. There just seemed to be a special emphasis
10 that we should be looking at that rather than the hazards
11 ratio.

12 DR. TIWARI: Most frequently, people quote that
13 the median survival is this in placebo, and the median
14 survival is this for the confidence interval around the
15 difference to look at how --

16 DR. O'FALLON: And that is perfectly appropriate.

17 DR. SIEGEL: It is of note in these curves, in
18 looking at the curves that were put up, that for this
19 particular data set, the median does appear to perhaps give
20 a less favorable point of view of the data in terms of the
21 drug than earlier or later time points or higher or lower
22 percentiles, so it should be noted that that is not
23 representative of the curve.

24 I am not sure, you know, I don't know what the
25 statistical assessments show. I am not sure that one would

1 biologically assume proportionality as one might go in with
2 an estimate that the drug might, in fact, reduce early
3 infectious causes of death, and the concern is whether it
4 would increase late tumor causes of death, so that concern
5 might lead to lack of proportionality, although there is
6 nothing one views in the data that would make one think
7 that, in fact, proportionality wasn't there.

8 DR. O'FALLON: I presume that you all looked.

9 DR. VOSE: Additional questions for Dr. Chang or
10 the sponsor?

11 [No response.]

12 DR. VOSE: Thank you.

13 I am going to take the Chair's prerogative of
14 skipping the break and going on to the questions.

15 **Committee Discussion**

16 DR. VOSE: For informational purposes we are going
17 to be voting on the two parts of Question 1. We will go
18 ahead and discuss information in Question 1 first. That
19 basically gets to the basic area of what we are discussing
20 today, that among the endpoints, there were no differences
21 observed in the incidences of fever, documented infections,
22 or antibiotics, but the durations of fever, antibiotic use,
23 and hospitalization were significantly shorter in the G-CSF
24 arm.

25 We are going to discuss the two issues separately.

1 First, whether Neupogen has been demonstrated to be
2 effective following induction therapy for AML.

3 Who wants to start the discussion on that? Dr.
4 Berman.

5 DR. BERMAN: I think the data were very
6 straightforward and very clear and concisely presented, that
7 it is effective in shortening the period of neutropenia,
8 hospitalization, use of antibiotics including the
9 antifungals, which is important.

10 DR. VOSE: Dr. Miller, would you like to comment?

11 DR. MILLER: I agree that the data suggests that
12 it has met those endpoints. I would note there is no
13 survival advantage, but it does meet the efficacy endpoints
14 as defined in the protocol.

15 DR. BROUDY: I completely agree and I would just
16 like to add the comment that the other thing that impressed
17 me was the depth of neutropenia, not just the duration, but
18 the depth, that the neutrophils didn't go down nearly as far
19 in induction and particularly during Consolidation No. 1,
20 and we all know that it is the depth, as well as the
21 duration that is important. So I would completely agree
22 with that statement.

23 DR. VOSE: And I would also agree that was a very
24 well-designed trial and clearly demonstrated the endpoints.

25 Any different discussion during consolidation that

1 we would like to discuss? I think in particular during the
2 consolidation, that the depth was impressive, that it didn't
3 go down in depth and duration.

4 DR. BROUDY: The median didn't go below 200, and
5 we all know that if you are 200 to 300 neutrophils per
6 microliter, you are in much better shape than if you are
7 below 50 or down to zero. So I think this particular curve
8 in particular really impressed me in terms of the
9 neutropenia during consolidation.

10 DR. VOSE: Additional discussion?

11 [No response.]

12 DR. VOSE: Why don't we go ahead and take a vote.
13 We are going to take a vote on these two issues separately.

14 Has Neupogen been demonstrated to be effective
15 following induction, chemotherapy in AML?

16 Everyone who thinks that it has been demonstrated
17 to be effective, please signify by raising your hand.

18 [Show of hands.]

19 DR. FREAS: Fifteen votes demonstrating
20 effectiveness.

21 DR. VOSE: The second question. Has Neupogen been
22 demonstrated to be effective following consolidation therapy
23 in AML? Please signify by raising your hand if you think it
24 is effective.

25 [Show of hands.]

1 DR. FREAS: Fifteen votes.

2 DR. VOSE: Effectiveness and consolidation.

3 Let's move on to Question No. 2, which is the
4 discussion question.

5 Please discuss the extent to which prophylactic
6 oral antibiotics have reduced the incidence of documented
7 infections in this setting.

8 Just to start the discussion, there have been some
9 studies at M.D. Anderson where patients were randomized to
10 oral quinolones versus a growth factor, and, in fact, the
11 patients in the oral quinolones had less infections in the
12 G-CSF patients, so I think there are studies that
13 demonstrate that is an effective use of decreasing
14 infections, and I am sure it had to have some effect on what
15 we saw in this trial. Obviously, this patient population is
16 very suppressed and they do need additional support.

17 Does anyone else want to comment on that? Dr.
18 Berman.

19 DR. BERMAN: I just have a question for a
20 microbiologist really, and that is with the widespread use
21 of Ciprofloxacin, is there a concern about growing out
22 resistant organisms in the future? I mean this is not
23 typically something that a lot of the hospitals have done,
24 especially in view of some of the resistant organisms that
25 have come out.

1 DR. VOSE: As I talked about earlier in the
2 transplant literature, there is definite documentation of
3 alpha strep, for example, that patients have had sepsis and
4 even some deaths associated with that when it is used in the
5 transplant setting, and that is usually when patients have
6 high incidence of mucositis, so I think that is somewhat of
7 a concern.

8 DR. BERMAN: I was just wondering about resisting
9 gram-negative rods.

10 DR. VOSE: Dr. August.

11 DR. AUGUST: My comment will underline something
12 that Dr. Kleinerman said earlier. Because of the fear that
13 the quinolone antibiotics will affect cartilage growth in
14 children, they are routinely not used, and so a pediatric
15 study of this agent G-CSF would be, of necessity, different
16 than the study we have heard about today by virtue of the
17 fact that there would not be at least the quinolones used as
18 prophylactic antibiotics.

19 In fact, I am not aware, at least in the pediatric
20 oncology group, prophylactic antibiotics are used in
21 induction of AML at all, so that it makes relevant I think
22 the issue of doing the studies -- if you want to know about
23 children, doing the studies rather than extrapolating from
24 adult studies in general, and this one in particular.

25 DR. VOSE: Additional questions or concerns?

1 DR. BROUDY: I would just like to comment that
2 some patients with childhood leukemia have mutations in the
3 G-CSF receptor, as well, and there has been a question
4 raised at least as whether G-CSF treatment may even more
5 promote leukemogenesis in these children, so I would
6 completely agree with your statement that studies should be
7 done in the pediatric group.

8 DR. VOSE: Thank you.

9 Dr. Weiss, any additional comments or information
10 you need?

11 DR. WEISS: The other trial, the other GM-CSF that
12 was discussed before this committee, there was a significant
13 reduction in infections and in deaths from infection during
14 induction. I actually do not recall about prophylactic
15 quinolones and whether or not that was commonly used the,
16 but that is the reason why I think this question came up is
17 it was clear in the study, this was prospectively defined
18 and it was pretty much used in all patients, so it was just
19 more of an information question for us.

20 DR. VOSE: I don't believe in the other trial that
21 that was used routinely. That would be a difference between
22 the two trials.

23 Let's move on to Question No. 3. Are these data
24 on time to progression and overall survival sufficient to
25 support the use of Neupogen following induction and

1 consolidation therapy in AML?

2 DR. BROUDY: I guess I would say yes. I am
3 convinced by the curves shown by the sponsor that there
4 really was no difference if you look at the entire curve in
5 time to progression and overall survival in the placebo and
6 the G-CSF-treated group.

7 I don't know if our resident statistician would
8 like to comment, but those curves look very much overlapping
9 to me.

10 DR. O'FALLON: The curves are very much
11 overlapping the hazards ratios that they quoted and assured
12 us that they even have a more precise estimate given the
13 multivariate hazard ratio had a pretty tight confidence
14 interval, which is something we probably could have
15 concentrated on a little bit more, but I certainly felt very
16 comfortable that they were very nearly as identical as
17 anything I have observed in doing analyses, and they had
18 powered this study to detect differences of a pretty narrow
19 range anyway and don't even come close to getting anything
20 that looks like significance.

21 DR. VOSE: As we talked about before, I think it
22 is a very large, well-designed trial, and those issues
23 should have come out if they were going to be there.

24 Any other questions? Dr. Anderson.

25 DR. ANDERSON: I was just looking for some

1 appropriate place to make a point, and this is about the
2 only place I can see.

3 This is basically just a comment for the FDA
4 staff. My feeling that one of the roles of the advisory
5 committee besides doing the straightforward and obvious is
6 to look for potential tips of icebergs or potential hidden
7 problems that are not problems, and that is why I didn't
8 want to say anything until after the vote, but just might
9 be, and we did that this morning, and I would like to bring
10 it up here.

11 That is again what I brought up before, and that
12 is the issue of hemorrhage. It is probably not a relevant
13 issue, but a couple of things indicate this might be
14 something simply to keep an eye on.

15 In the first place, the only adverse reactions
16 that were listed as severe, that did not occur in the
17 control, were for hemorrhage. They appear to be, even
18 though we couldn't get the data for exactly which ones, they
19 were probably brain bleeds.

20 The question is whether or not it might be that
21 under some circumstances, G-CSF in the brain under certain
22 circumstances besides having a capillary leak, might have a
23 little bit of a vascular leak, not enough to affect the
24 risk-benefit at this point, not enough to even be concerned
25 about, but just as a flag that might this be something that

1 might drop up later.

2 DR. VOSE: Dr. Miller.

3 DR. MILLER: I would just like to make the comment
4 that this question of supporting the use of Neupogen
5 following induction, consolidation therapy, I think it
6 clearly answered the question that it is a safe drug and it
7 is efficacious at preventing neutropenia. I guess I am
8 somewhat disappointed with the fact that, especially the
9 consolidation arm, the degree of neutropenia is so much
10 improved, why are we not seeing a benefit in documented
11 infections or potentially any survival benefits.

12 Yes, it clearly appears to be safe and it is not
13 harming, but I think that we will just have to realize that
14 it also is not clear that except for decreasing
15 hospitalization, decreasing febrile days, that it affects
16 the overall survival of patients with acute leukemia, so
17 that clinicians need to keep that in mind when they decide
18 whether or not to use any drug in patients.

19 DR. BROUDY: I guess my only thought about that
20 would be that it does look like the patients during the
21 consolidation arm could be discharged much sooner than
22 perhaps the 19 days that was the practice in Europe at that
23 time.

24 If we look at these curves of duration of
25 neutropenia, it really looks like they could get in and out

1 of the hospital much faster, and I see that as a benefit
2 even though no decrease in infectious death was documented
3 in this study.

4 DR. VOSE: Of course, some of the practice in the
5 U.S. is again changing to the fact that we don't even keep
6 patients in the hospital if they are neutropenic, so that in
7 itself is going to change.

8 Any other issues?

9 Okay. Let's move on to the next question. If
10 approved, should the label recommend a bone marrow
11 evaluation prior to the first administration of Neupogen,
12 i.e., soon after completion of induction therapy as has been
13 the practice in other growth factor trials?

14 Dr. Berman.

15 DR. BERMAN: I think the data shown to us this
16 morning showed that while there may have been blasts still
17 present in the marrow, that it is safe to give and there was
18 difference in remission rate, so I would say no based on the
19 data, I don't think bone marrow is indicated.

20 DR. VOSE: Dr. Miller, do you have some thoughts
21 about that?

22 DR. MILLER: I agree.

23 DR. BROUDY: I would just like to say it looks
24 like the proportion of patients requiring a second induction
25 was no different in the G-CSF than in the placebo-treated

1 arms, so even if the theoretical concern is there, that
2 there is lots of blasts, it looks like there was no
3 difference in the proportion.

4 DR. VOSE: Any other discussion?

5 The next question gets to the use in the pediatric
6 population which I think we have already pretty much
7 discussed ad nauseam.

8 Any other issues regarding pediatric population?

9 Finally, Question No. 6. Can these results be
10 reasonably extrapolated to the setting of secondary AML?
11 Are there new or heightened safety concerns about Neupogen
12 in secondary AML?

13 Dr. Berman, do you have any comments on that?

14 DR. BERMAN: Well, we did see data, didn't we,
15 from not this trial, but it was another trial. It was a
16 randomized trial? My memory is beginning to fade. It did
17 not show any difference, but I think the numbers were still
18 small, less than 50 patients or around 50 patients in each
19 arm. So it is really based on one trial with relatively
20 small numbers of patients. It certainly didn't appear that
21 there was any difference, however.

22 DR. MILLER: I don't think there is data to
23 justify being a splitter instead of a lumpner, so I wouldn't
24 divide.

25 DR. VOSE: There is really not enough data for us

1 to say it is or isn't different compared to that. There
2 might be some theoretical concerns regarding complete
3 remission rate or something like that, but without data it
4 is hard to say.

5 DR. MILLER: I guess the other question may also
6 be not so much from an efficacy standpoint, from a safety,
7 remission aspect, a question that hasn't been answered, and
8 should be answered, is whether or not it works as well in
9 secondary leukemia with underlying bone marrow
10 myelodysplasia, I mean is it going to be as effective.

11 I think in the absence of knowing the data, I
12 think we should encourage further trials, but I don't think
13 it should be excluded.

14 DR. VOSE: Dr. Weiss, Dr. Siegel, is there any
15 additional information that you would like us to address?

16 DR. WEISS: I don't think so. I think everybody
17 has had a long day.

18 DR. VOSE: So we actually answered all your
19 questions then? Amazing.

20 Okay. Thank you very much.

21 DR. FREAS: I would like to ask the members to
22 remember this is confidential information we are responsible
23 for. Please leave it on your table and we will come by and
24 shred it.

25 Also, I would like to say this is my last meeting

1 here as an Exec. Sec., and I would like to thank you for
2 being so great. I am still going to be in the same office,
3 but you were a great group to work with and I really
4 appreciate it, and I feel very privileged to have had the
5 opportunity. Thank you.

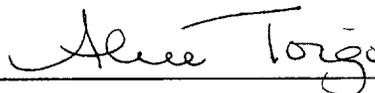
6 [Applause.]

7 [Whereupon, at 2:30 p.m., the meeting was
8 adjourned.]

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C E R T I F I C A T E

I, ALICE TOIGO, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.



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