DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

SIXTY-SIXTH MEETING

Wednesday, December 13, 2000

8:30 a.m.

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

Corrected pages + disk

PARTICIPANTS

Stacy R. Nerenstone, M.D., Chairperson
Karen M. Templeton-Somers, Ph.D.,Executive Secretary

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C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Introductions

DR. NERENSTONE: I would like to begin with the introduction of the people at the table, Dr. Berman, if you will begin?

DR. BERMAN: Dr. Ellin Berman, Memorial Sloan-Kettering Cancer Center.

MS. LACKRITZ: Barbara Lackritz, the Association of Cancer On-Line Resources, the Chronic Lymphocytic Leukemia Foundation and a cancer patient advocate.

DR. ALBAIN: Kathy Albain, medical oncologist, Loyola University Medical Center.

DR. CARPENTER: John Carpenter, University of Alabama at Birmingham, medical oncologist.

DR. PELUSI: Judy Pelusi, oncology nurse practitioner, Phoenix Indian Medical Center and the consumer rep.

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

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

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

DR. TAYLOR: Sarah Taylor, medical oncologist and Palliative Care at the University of Kansas.

DR. MILLER: Carole Miller, medical oncologist, hematologic malignancies, Johns Hopkins Oncology Center, Baltimore, Maryland.

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

DR. PRZEPIORKA: Donna Przepiorka, Baylor College of Medicine, Cell and Gene Therapy.

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

DR. LIPPMAN: Scott Lippman, medical oncology, M.D. Anderson Cancer Center.

DR. REDMAN: Bruce Redman, medical oncologist, University of Michigan Medical School.

DR. SCHECHTER: Genny Schechter, medical reviewer, Division of Clinical Trial and Design and Analysis in CBER.

DR. KEEGAN: Patricia Keegan, Division of Clinical Trials in CBER.

Conflict of Interest Statement

DR. TEMPLETON-SOMERS: The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made a part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug

Evaluation and Research present no potential for a conflict of interest at this meeting, with the following exceptions. In accordance with 18 USC Section 208(b)(3), full waivers have been granted to Barbara Lackritz, Drs. Blayney, Lippman, Santana and Sledge. A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building. In the event that the discussions involve any other products or firms not already in the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. Thank you, and thank you for coming out in the storm.

Open Public Hearing

DR. NERENSTONE: This is now the open public hearing part of the meeting, and I believe we have two video tapes in lieu of speakers. These two video tapes were provided by the sponsor.

DR. NERENSTONE: We do have one speaker who has asked to address the committee. Mr. Politis, if you would

like to come up?

MS. POLITIS: My father and I have been asked to come here by Dr. Rai to talk about my father's experience using Campath. They asked me to come because I was there and I was watching my father go through the cancer for the year before he had been treated with the Campath, and we wanted to come here to, I guess, give a positive endorsement of what this drug has done for his life and for the life of our family as well.

My father was probably diagnosed about three and a half years ago with CLL. He went through the standard chemotherapy treatments. To be honest, I don't really know what they had him on at first but they progressively stepped up the chemotherapy and I know that eventually he did get fludarabine, if that is not what he had in the beginning, and I saw that -- well, we knew that the chemotherapy wasn't working because they kept stepping up the dosage and he got progressively and progressively worse. He was probably diagnosed two weeks before Easter. About a year later, about a week before Easter he was in the hospital, in the ICU. He had fluid in his lungs, and his doctor was there telling me and the rest of our family that we would have to stop the chemotherapy. If they gave him the chemotherapy anymore he would die. If they didn't give him the chemotherapy anymore he would die, and they were going to start looking into an

experimental program for him.

About three weeks later we probably took him over to Long Island Jewish Hospital where he started receiving Campath. His doctor, at Staten Island University Hospital, said to us, you know, this is pretty much your best hope right now. If he doesn't do something, if he doesn't try this, we probably don't give him till the end of the summer. So, we started the treatments. About an hour away from the house, we drove every day for the first week and then three times a week after that.

At first, to be absolutely honest -- I was watching the speakers and, to be absolutely honest, it didn't even occur to us that we should be concerned about this drug because we knew that my father really didn't have any options, other than to try that. So, we were very hopeful. We approached it a little skeptically just because of the way my father was three weeks earlier, but we were very hopeful because this was not chemotherapy and, even though we didn't know what kind of side effects he might have, we knew that anything had to be better than the way he was when he was in the hospital three weeks earlier.

I guess after the first two or so weeks of the treatment, I think we started noticing a remarkable difference. After the first week, my father remembers having an improvement. I was still sort of holding my breath, I

guess, at the time. But within the first couple of weeks there was a marked difference in the level of white blood cells that he had in his system. By, I guess, three or four weeks it was down to a level that I had not seen it at in probably six or seven, maybe even eight, months. We kept doing the treatment. I think he did the treatment for the full twelve weeks just because he was in such bad shape when he had come in that we were hoping giving it a little longer might have a lasting effect. That was about two and a half years ago. He has probably been off the treatment since two years ago this past August, and he is doing quite well.

DR. NERENSTONE: Thank you. Does the committee have any questions?

[No response]

Thank you very much for your time. We would like to turn now to the sponsor presentation.

Sponsor Presentation

Introduction

DR. BRETTMAN: Good morning. My name is Lee Brettman, Senior Vice President of Medical Affairs of Millennium Pharmaceuticals. On behalf of Millennium and ILEX partners, I would like to thank the committee and the FDA for allowing us to be here today to discuss our BLA for Campath.

I would just like to start with a brief overview

of the agenda for this morning's presentation. I will give a brief introduction to Campath, following which Dr. Michael Keating will give you an overview of CLL. After Dr. Keating's presentation, I will present the clinical data from our BLA in support of the proposed indication.

We are also pleased to have with us a number of experts and investigators from Campath clinical trials: Dr. John Bennet, Dr. John Byrd and Dr. Kanti Rai. They would be happy to answer questions from the committee as well.

The proposed indication that we are here to discuss this morning for Campath is that Campath is indicated for the treatment of patients with CLL who have received alkylating agents and who have failed fludarabine therapy. This indication represents a group of patients for whom there are no approved therapies, and so represents a significant unmet need. In recognition of this fact, the agency has granted fast track approval status to Campath, and it has also been designated an orphan drug.

Campath is a humanized monoclonal antibody. As you can see in the company diagram, the murine CDRs have been grafted onto a human IgG-1 construct. The murine CDRs are in yellow, and these are essentially the only murine residues in the antibody. So, the murine residues are essentially limited to the CDRs. Campath is directed against an antigen called CD52 which is expressed on B and T lymphocytes, but

is not expressed on bone marrow progenitor cells.

The mechanism of action of Campath is based on complement mediated fixation and antibody dependent cell mediated cytotoxicity. Induction of apoptosis may also play a role. In this regard, Campath is different from cytotoxic chemotherapeutic agents for the treatment for CLL, and this may be important in its activity in treating refractory patients.

Let me just go over some of the key events in the historical time line of Campath. In 1978, Professors Harman Waldmann and Jeff Hale raised the original murine antibodies in the Department of Pathology at Cambridge University, and that is actually the origin of the name Campath, from Cambridge Pathology.

In 1990, Burroughs Wellcome licensed the technology and the antibody was humanized in collaboration with Professors Waldmann and Hale.

In 1997, Millennium and ILEX partners became the licensee, reviewed the Wellcome data, held a series of meetings with the FDA and initiated our pivotal trials in 1998. The BLA was filed in December of 1999 and during the course of this year we have submitted safety updates, as well as responses to FDA questions.

With that introduction, I would like to welcome Dr. Keating to the podium to give an overview of CLL and

outline the need for new therapeutic options for the treatment of patients with this disease.

Overview of CLL and Therapeutic Options

DR. KEATING: Thank you, Lee. I would like also to thank the committee and the agency for giving me the opportunity to present my view of the state-of-the-art of chronic lymphocytic leukemia.

CLL is the most common leukemia we see in the United States and, indeed, in the Western World. As you can see, it is a disease with a median age of 58 years at presentation, but both the incidence and prevalence of this disease is increasing because more and more patients are being diagnosed at a younger age on routine screening examinations, and this places a great stress on them as to what to do when the diagnosis is made at such a young age. And, as our population ages because of the exponential increase in the incidence of this disease with age, we are going to have more and more patients that are suffering from this condition.

Whereas some patients are blessed with having a non-progressive form of the disease, the majority of the patients do develop progressive CLL and, as documented in recent articles, the vast majority of these patients end up dying of complications of the disease, predominantly infection.

One of the major structural benefits of research in CLL was the development of staging systems, and the one which is most popular in the United States has been the Rai staging system which was developed in the late 1970's. Basically, this is a five-stage system which stratifies patients nicely both for previously treated and previously untreated patients, and the more benign stages are those where the patients only have lymphocytosis or enlargement lymph nodes or enlargement of the spleen and liver, in the Rai zero to II. But many patients actually develop or present with marrow compromised with anemia and thrombocytopenia, and even when they are first diagnosed, if they have these features the average life expectancy is only 1.5 to 3 years in different clinical trials.

What happens when the disease progresses is that a number of adverse events occur. After progression, the patients become at risk of developing a large cell lymphomatous transformation called Richter's syndrome, or they develop more and more prolymphocytes and, as the prolymphocytes increase in number the prognosis of these patients decreases. Dependent on the progression of the disease and the accumulated effects of chemotherapy and immunotherapy that is administered, they tend to develop progressive bone marrow failure and cumulative immunosuppression, with lowering of their gamma globulin

levels and a decrease in T-cell number and function. These two features contribute to the major concern that we have in CLL, which is the development of severe and life-threatening infection. As I mentioned already, once the patient develops progressive disease, probably 90 percent of them end up dying of complications of this disorder, not of incidental causes which is what I was taught when I was going through medical school.

The standard treatments of CLL are listed here. For first-line treatment there is no approved agent but grandfathered in have been chlorambucil or Leukeran and the cyclophosphamide regimens which have activity and have been explored with or without corticosteroids for a period of 50 years.

The only approved agent for the management of CLL is fludarabine, which was approved by the agency in the late 1980's, and this has now become the standard salvage therapy. Third-line treatment in patients that have been exposed to alkylating agents and have failed to respond, particularly to fludarabine, there is no such approved or even recommended treatment at the present time.

So, what do we try and achieve when we decide to treat someone with CLL? Well, obviously, we would like to decrease the total tumor burden of the disease because the tumor burden is what is causing the complications. Also, we

would like to get responses. For the patients, they really like getting responses. Doctors like getting responses, and patients who respond tend to live longer. There is always the statistical argument as to the relevance of that, but it is always better, in my experience, to get a response than not.

The clinical benefits are obvious to the patients. Many of the patients, as their disease advances, end up developing the B-symptoms we commonly attribute to lymphoma, with fever, night sweats, loss of weight, but also there tends to be a fairly incapacitating fatigue so that the patients can't continue their daily activities, and this tends to improve as the patients respond. Additionally, the risks to the patients are neutropenia from the cytopenia and the deleterious effects of anemia and, as the patients respond, these improve. These are some of the features of the NCI Working Group criteria in response to treatment of CLL. But many patients also have very enlarged lymph nodes and spleen, and these become tender and incapacitating in some circumstances, and resolution of this is obviously a major clinical benefit.

Since the approval of Fludara and, as you can see from the Fludara label, it was approved on the basis of 133 patients that were submitted. There has now been an extensive published experience so that we will now be

discussing the complications that occur in more than 1400 patients.

Unfortunately, many of these studies have not always used the NCI Working Group criteria for response, but the response rate varies from approximately 20 percent or approximately 50 percent, with probably a median of about 1 patient in 3.

You will notice that fludarabine as second-line treatment is not an innocuous therapy. There are very significant cytopenias that develop. A number of these patients, because of the accumulated myelosuppression and immunosuppression develop major infections and this contributes to the number of patients that die while they are being treated for salvage therapy with the approved drug. The median survival of all these publications has a medial survival expectancy of somewhere between 9 and 12.6 months.

So, if we begin to look at what is available in the literature for patients that have failed fludarabine, it doesn't take a long time to relate the publications. There are no publications of comparative studies from cooperative groups. There are some single agent publications from single centers on cladribine and one publication on a combination approach, and to try and get some expectations for this population we went and evaluated 147 patients at our

institution that have failed fludarabine.

So, when we look at the list of the four published manuscripts -- the Keating et al. is in press, the response rate varies from 0 percent up to 22 percent. So, the average expectation would be in the 15-20 percent range. You will also notice that the median life expectancy of patients going on these studies is consistently less than 12 months.

So, the conclusion that I can make about patients with Fludara refractory disease is that even after second-line therapy the median survival is not satisfactory and there is substantial morbidity that occurs. For third-line treatment the expectation for survival is consistently less than a year and, at the present time, we have no approved therapies and no chemotherapy approaches that we can even recommend to patients. So, on this basis I think it is obvious to me and most treating physicians that new approaches for the management of fludarabine refractory patients are urgently needed.

Thank you for your attention and I will pass it back to Dr. Brettman.

Clinical Data

DR. BRETTMAN: Thanks, Michael. I am going to start with a brief outline of what I will be discussing this morning. I will start with a presentation of the efficacy data which we believe supports the effectiveness of Campath

in treating a refractory group of patients for whom there are no approved therapies, and in addition, the responses to therapy are associated with meaningful clinical benefits for these patients. I will move on then to a presentation of the safety data which we believe supports that the safety profile of Campath in this advanced disease population is manageable. I will then conclude by focusing on the positive benefit/risk of Campath in this population of patients.

I will start with the Campath development in CLL which has two components to it. First, in 1992 Burroughs Wellcome began a series of three Phase I/II dose-ranging studies that looked at a number of different unit doses, ranging from 0.5 to 240 mg, and utilized different dosage frequencies, 1, 3 and 5 times a week. So, 175 patients were enrolled into these three dose-ranging studies.

Based on the data from these studies, Wellcome selected a dose of 30 mg 3 times a week to evaluate in Phase II. The two Phase II supportive studies, 005 and 009, were conducted with this dose of 30 mg 3 times a week.

Based on the encouraging data from those studies, Millennium and ILEX partners requested a meeting with the FDA and, through a series of discussions, the CAM211 pivotal trial design emerged. We initiated that trial in 1998, utilizing the dose of Campath 30 mg 3 times a week.

The core presentation I am going to make today

focuses on the two supportive and the pivotal CAM211 trial. Let me just go into a little bit of detail about these trials. The 005 was a multi-center European trial that enrolled both patients with CLL and NHL who had relapsed following or failed prior therapy. And, 32 of these patients had been previously treated and are included here. The 009 study enrolled patients exclusively with CLL who had received prior fludarabine therapy, and the CAM211 pivotal trial enrolled exclusively patients with CLL who were required to meet a strict definition of fludarabine failure that I will talk about in a moment. Together, 149 patients were enrolled into the three trials.

Let me start with the efficacy results from the two supportive studies, 005 and 009. I would like to point out that these studies were conducted by Wellcome between 1993 and 1995. In 1997, when Millennium and ILEX partners became the licensee, we performed additional follow up focusing on survival, verified the databases and, very importantly, organized an expert panel to assess responses.

The baseline characteristics of the patients enrolled in this study are shown on this slide, and there are two key points to make from this. First, the patients enrolled into these two studies had been intensively treated previously, having received a median of three prior distinct chemotherapeutic regimens. In addition, the majority of

these patients had advanced stage Rai III-IV disease.

The assessment, as I mentioned, was conducted by an independent panel according to the NCI Working Group 1996 criteria, and the members of that panel were Dr. Keating, Prof. Emilio Montserrat and Dr. Steve Johnson. Let me just go over the NCI criteria very briefly. The NCI criteria define a complete response as the elimination of all laboratory and clinical signs of disease. A partial response means that at least 50 percent reduction in all areas of disease involvement must be achieved, and there must be stabilization or improvement in hematopoiesis. These improvements must last for a minimum of two months to qualify as a response. Progressive disease is defined as a 50 percent increase in disease burden from the disease burden at baseline. Stable disease includes other patients who don't meet one of the three previous categories.

The responses assessed by the independent panel are shown on this slide, and it shows that in the 005 study the response rate was 28.1 percent and in the 009 study it was 33.3. I will note that these are all partial responses.

The time to event parameters associated with these responses are shown on this slide, and show that the median time to response was 3.8 and 3.9 months respectively and that these responses were durable, with a median of 7.1 and 15.4.

We obtained additional follow up concerning survival for the patients enrolled in these two studies, and that information is shown on this slide. The median was 25.9 in the 005 study and 27.5 in the 009 study. I don't want to overstate these because the 95 percent confidence intervals are very broad around these. Nonetheless, in the context of the information you just heard, where the median survival with second-line fludarabine therapy is in the range of 9-12.6 months, this was encouraging.

Based on this data, we requested a meeting with the FDA and, through a series of meetings, with the consensus and guidance of the FDA, we designed the CAM211 pivotal study. The key elements of the study design are shown on this slide. First, the study was designed as a single-arm, multi-center study. The protocol had a strict definition for fludarabine failure that all patients were required to meet for study entry. The primary endpoint was response rate as agreed to with the FDA, and the dose utilized was the same utilized in the two supportive studies, 30 mg 3 times a week.

I would like to spend a moment talking about some of the key design elements of this study, starting first with the rationale for a single-arm study design. First of all, this patient population represents a significant unmet need with no approved therapies that results in no consensus

on alternative salvage therapy or management of these patients. A placebo comparative trial was not considered acceptable in a population of patients with CLL which is progressively. I just want to mention also that we clearly recognized, and actually discussed with the FDA at the time, that ultimately a comparative trial would need to be conducted in a less advanced patient population, and we have submitted a concept sheet to the agency that I would be happy to discuss later.

The patients were also required to have received prior therapy as follows: They had to have received at least an alkylating agent and failed fludarabine therapy according to the definition that you see here. That is, they failed to achieve a CR or a PR with at least one fludarabine regimen where they had relapsed within 6 months of the last fludarabine dose. So, this means they had to have received a minimum of two prior treatment and the protocol allowed them to receive up to a maximum of five. So, by definition, this protocol selected a group of patients that were severely immunocompromised by virtue of the stage of their disease and their prior therapy, and were also immunosuppressed on that basis as well.

Patients were also required to have active disease as defined by the NCI Working Group criteria. That is, they had to have either Rai Stage III or IV disease or Rai Stage

0-II progressively disease, defined as being associated with one of the four prognostic factors that you see listed here: Rapid doubling of peripheral lymphocyte count; progressively lymphadenopathy and/or splenomegaly; B-symptoms, among others.

The primary endpoint agreed to with the FDA was the objective response rate according to the 1996 NCI Working Group criteria. Campath was required to achieve at least a threshold response rate of 20 percent. It had to be significantly better than 10 percent. This led to a sample size calculation of 75 patients.

The protocol also defined the number of key time-to-event parameters as secondary endpoints, including survival, duration of response and time to disease progression. A clinical benefit analysis was also prospectively planned, focusing on the types of signs and symptoms of disease that bother patients, including disease-related B-symptoms and fatigue or reduction or resolution in massive splenomegaly and other such benefits.

Campath was administered by intravenous infusion, and during the Wellcome Phase I/II studies it was observed that using gradual dose escalation during the first week of therapy was associated with a reduction in the incidence and severity of infusion-related events. So, the CAM211 protocol required that on the first day of therapy Campath be

administered at a dose of 3 mg. If that dose was well tolerated, on day 2 10 mg could be administered, and on day 3, 30. After that, Campath would be administered 3 times a week, typically on Monday, Wednesday and Friday. The duration of treatment was to be 4-12 weeks depending on response to therapy.

The protocol also required concomitant therapy to be given as follows: Premedication to reduce the incidence and severity of infusion-related events, consisting of diphenhydramine and acetaminophen, to be given before the first dose of Campath and before each dose escalation and, thereafter as clinically indicated. In addition, because all of the patients enrolled in this trial had previously been treated with fludarabine and would be immunocompromised and, in addition, Campath is an immunosuppressive agent, infectious prophylaxis directed against PCP and herpes was mandated in the protocol, consisting of trimethoprim and sulfamethoxazole or equivalent.

The baseline characteristics of the patients enrolled in this study are shown on this slide. Again, you can see that this is an intensively previously treated group of patients, having progressed through a median of three prior regimens and the majority, over three-quarters, of these patients had advanced stage, Rai Stage III/IV disease. In addition to having failed fludarabine, two-thirds of

these patients had also received salvage therapy after failing fludarabine, including 38 of the 61 patients receiving combination chemotherapy after failing fludarabine, who were now coming onto the CAM211 trial to receive Campath as a single agent.

The response was assessed by an independent panel. You can see the members listed here, Dr. John Bennett, Prof. Federico Caligaris-Cappio and Dr. Martin Tallman. In addition, after the BLA was submitted, the FDA reviewer, Dr. Schechter, conducted her own review. While there were minor disagreements between the assessment by the response panel and Dr. Schechter, the bottom line was that the objective response by both the panel and Dr. Schechter was 33.3 percent. I would point out that this not only significantly exceeds the 10 percent lower bound set out in the protocol but actually is significantly better than the threshold 20 percent that Campath was required to achieve in the protocol.

The key time to event parameters are shown on this slide, showing that the time to response was very rapid, with a median of 1.5 months, and that the responses were quite durable, with a median of 8.7 months.

You heard earlier that the survival in the 005 and the 009 studies was encouraging and on this slide, and particularly in the context, again, of the information you

heard earlier this morning that we are now looking at a third-line therapy and with second-line fludarabine repeatedly the median survival was 9-12.6 months. Obviously, I am not making any direct comparison but it does create a context for what to expect in patients that might go on to third-line therapy. The median survival was 16 months, and you can see the lower bound of the 95 percent confidence interval was 11.8 months.

Well, let me just sum up a couple of the key response parameters for the pivotal and the supportive studies. On this graph you can see the response rates with the 95 percent confidence interval around them for the CAM211, 005 and 009 studies. You can see also that this considerable overlap indicating that the response rates across the three studies are similar. In addition, for reference, the target lower bound of 10 percent, as indicated for the CAM211 study, shows that the response rate significantly exceeded this hurdle.

The median survival across the three studies was also comparable, ranging from 16 months to 27.5 months but with considerable overlap of the 95 percent confidence intervals.

As I mentioned, during the discussion of the study design we conducted a prospectively planned analysis of clinical benefit in all patients. In addition, after the BLA

was filed the FDA asked us to conduct a clinical benefit analysis specifically in responders, essentially to demonstrate why is a response to Campath of benefit to patients. So, we did that, focusing on the types of signs and symptoms of disease that are bothersome to patients, including disease-related B-symptoms, fatigue, massive splenomegaly which is noticeable to patients and uncomfortable, improvement in disease-related anemia and maintenance or improvement in performance status, which is clearly important to patients with a progressive disease like CLL.

I would like to start that discussion with the clinical benefit analysis conducted in responders. Overall, there were 31 responders of the 93 patients in the CAM211 trial, and 17 of these patients enrolled in the study with baseline B-symptoms of fatigue. All 17 of these patients experienced resolution of these symptoms on study and in follow up. Ten of the 31 enrolled in the study with massive splenomegaly, which was defined by the NCI Working Group as a spleen tip more than 5 cm below the left costal margin. Nine of these 10 experienced not only more than 50 percent improvement as required by the NCI Working Group criteria for response, but complete resolution of the splenomegaly. The remaining patient experienced more than 50 percent improvement in a spleen that was 10 cm below the costal

margin at study entry.

We also conducted an analysis of the impact of therapy on disease-related anemia. In several large studies it has been demonstrated that hemoglobin increases of greater than 2 g are associated with meaningful and measurable quality of life benefits, as well as improvement in Karnofsky status. In the responder group 15 of the patients enrolled in the study with hemoglobins less than 11, and 11 of these 15, or 33 percent, improved by greater than 2 g, with a range of improvement of 2 to 6.4 g. This improvement was not attributable to transfusions or erythropoietin administration.

In addition, with regard to performance statue, 8/20 patients enrolling with a performance status of 1 improved to 0. Overall, 23/31 maintained or improved their performance status. The remaining 8 patients either varied between performance status 0 and 1 or had insufficient follow up to determine the change in performance status.

I mentioned that we had conducted an analysis of clinical benefits in all patients. Just for completeness, I show a table here which shows the clinical benefit analysis in responders that I just discussed, but also shows that while the responders were the ones that predominantly benefited from therapy, some of the same types of clinical benefits were also seen in some patients who did not meet

the NCI Working Group criteria for response.

I will summarize the efficacy then for Campath in this patient population. Campath was effective in patients with CLL who had failed fludarabine. The objective response rate of 33.3 percent significantly exceeded both the lower bound of 10 percent that we were required to significantly exceed, but also significantly exceeded the threshold response rate of 20 percent. The survival that was observed in this trial was 16 months. The lower bound confidence interval associated with that is 11.8 months. In addition, these responses were associated with measurable and meaningful clinical benefits to patients, and the supportive studies were consistent with these results.

I would like to move on now and discuss the safety profile of Campath. First of all, I want to just remind you that the integrated safety database that I will be discussing includes all 149 patients enrolled into the pivotal and two supportive studies. These are patients with CLL, all of whom have been previously treated and all of whom received a dost of Campath 30 mg 3 times a week.

Before I do that though, I do want to characterize the population about which we will be discussing the safety profile. The demographics for this population are shown here, and there are a few things that I think deserve special emphasis. The first one is that this is an

intensively previously treated group. In fact, 86 percent of these patients had previously been treated with fludarabine. The only patients who did not previously receive fludarabine are a number of patients in the 005 European study because fludarabine was not yet approved in Europe at the time that study was initiated.

In addition, when you look at the baseline hematological parameters for patients enrolled in this study, 58 percent had hemoglobins less than 11; 26 percent ANCs less than 1500; and 61 platelet counts less than 100,000. In addition, in the CAM211 trial, where we had conducted flow cytometry to assess T-cell subsets over time, 46 percent of patients entered with CD4 counts less than 500. So, this was an intensively previously treated group of patients, very compromised bone marrow function and very immunosuppressed, and it is important to keep this profile in mind as we consider the safety profile of Campath.

I would like to start the safety discussion with an overview of the key adverse events that occur on study, and 15 patients of 149 died on study, and I will talk about that in more detail in a moment. In addition, 30 percent of patients discontinued due to adverse events which are the type and nature that I am going to talk about in detail when I discuss grade 3 or 4 adverse events, including grade 3 or 4 infections which occurred on study.

Let me go to the on-study deaths. Fifteen patients, or 10.1 percent of patients, died on study, which is defined as dying while being treated or within 30 days of the last dose of Campath. The most common causes of death in these patients were the typical causes one expects to see in a population of patients with CLL, including infection and disease progression and that was the case here.

We have also looked at the post-study period, more than 30 days after the last dose of Campath and out to 180 days. An additional 18.1 percent of patients died during this period of time but, again, due to the types of causes one would expect to see in patients with CLL, including disease progression as the most common one, as well as infections.

The graph that you can see on this slide is a truncated version of the complete table of adverse events occurring in more than 5 percent of patients that you will find on page 45 of your briefing document. What this graph shows, it illustrates the three key safety features of Campath which are infusion-related events, consisting of rigors, fever, nausea, etc., infections such as pneumonia and sepsis, and hematological toxicity. I will talk about all of these in more detail.

I would like to start with a discussion of the most common adverse events, acute infusion-related adverse

events. This graph shows the rate of adverse events occurring over time on study. You can see that during the first week of therapy these infusion-related adverse events are most common, after which there is a substantial decline in the rate. The second point is that grade 3, 4 events are uncommon at all time points.

I should mention before we move on that, as you heard from one of the testimonials this morning, investigators occasionally use other premedications, including steroids and Demerol, for patients who experience more severe or more persistent events, and these were helpful in reducing the incidence of events in those patients.

So, to characterize the acute infusion-related adverse events, these are events that occur with high frequency but are typically low grade. They decrease over time, but discontinuation due to these events are infrequent. Only 3.4 percent of patients discontinued due to an infusion-related adverse event.

Well, let me move now to the second key aspect of the safety profile of Campath, infections. As you heard earlier, infections are a major cause of morbidity and mortality in patients with CLL who have been previously treated, and 28.2 percent of the patients enrolled in these studies experienced a grade 3 or 4 infection on study. The

types of infection seen, again, were typical for the population of patients with CLL, including pneumonia, bacterial infections, such as line infections and sepsis or bacteremia, and viral infections, primarily CMV and herpes.

Pneumonias were the most common cause of infection, occurring in 15.4 percent of patients. Let me just go over some of the most common pathogens causing pneumonia in these patients. Bacterial pathogens were the most common, typically Klebsiella, Pseudomonas aeruginosa were the common pathogens seen. PCP was the next most common. I am going to talk about that in more detail in a moment. Also, infections due to fungi, such as Aspergillus and Cryptococcus were seen. There were two cases of interstitial pneumonia where no infectious pathogen could be identified and, in addition, five additional patients had pneumonias where no pathogen was identified.

I would like to discuss now opportunistic infections. This is clearly a topic of great interest in these studies because the vast majority of patients had previously been treated with fludarabine, an agent known to be associated with an increased risk of infection including those due to opportunistic pathogens and, in addition, Campath is an immunosuppressive agent as well.

So, we did an analysis of opportunistic infections utilizing the definition that you see here. That is,

infections caused by uncommon pathogens, such as Pneumocystis or cryptococcus, or unusually severe infections caused by common pathogens, such as CMV, Herpes zoster or candida.

This table gives an overview of the types of opportunistic infections seen on study. Overall, by the definition that you just saw, 13.4 percent of patients developed an opportunistic infection. Pneumonia due to Pneumocystis carinii was the most common, followed by CMV and Herpes zoster, although fungal infections were also represented in approximately 5 percent of patients, consisting of candida usually, esophagitis in 2 of those patients and cryptoccocal pneumonia and 3 cases of Aspergillus.

You can also see the number of opportunistic infections in the post-study period, where the incidence of opportunistic infections was lower during that 6-month period than it had been on study.

Now, one point I want to make before moving on is that in a large review by Anaissie et al., as well as others in the literature, it has been observed with second-line fludarabine therapy that opportunistic infections of exactly the same kind that you see here are observed in those studies, occurring with a similar frequency.

Well, obviously two of the more common

opportunistic infections, PCP and zoster, can be prevented and in the CAM211 protocol prophylaxis for these two pathogens was mandated. What you can see on this graph is, in blue, the incidence of PCP and zoster for the 005 and 009 patients and, in green, the incidence of these pathogens in patients enrolled in the CAM211 study. So, you can see there is a dramatic decline, which is not statistically significant but obviously it appears that the incidence of these infections was reduced with prophylaxis. In fact, we saw no zoster in the CAM211 study.

I mentioned in the discussion of the structure of Campath that it is directed against CD52, which is expressed not only on B-cells but also on T-cells. So, we were very interested in seeing what would happen to CD4 counts on therapy, and incorporated in the CAM211 study design flow cytometry assessment of T-cell subsets at baseline, at various times on study and during follow up.

The analysis that you see here represents a mutually exclusive cohort analysis of patients who had CD4 counts at baseline and at least at 2 months, at least at baseline and 4 months, and at least at baseline and 6 months.

You can see a couple of important things on this graph. The first one is that the patients enrolled in this study had a median CD4 count between 500 and 600, indicating

that they had markedly decreased levels of CD4 counts, in a large percentage of the patients.

The second important point is that CD4 counts dropped dramatically on therapy, bottoming out during the first few weeks of therapy and then there is a modest increase in CD4 counts on study, but after the drug is discontinued there is steady increase at 2 months, 4 months and 6 months respectively, and at the 6-month time point the median CD4 count had returned toward the median baseline count for those patients in whom we had baseline and at least 6-month follow up.

I would like to move on now and talk about the hematological toxicity associated with Campath therapy. I am going to start with a discussion of pancytopenia reported as an adverse event or the reason for discontinuation from the study. Pancytopenia was reported as an adverse event by the investigator in 10/149 patients, or 6.7 percent. This adverse event was not reported in patients enrolling in study with Rai Stage 0-II but exclusively in patients with Rai Stage III/IV disease. These patients for whom we have more than 3 weeks of follow up recovered and, in fact, ultimately experienced improvement in their platelet counts over their baseline study entry counts.

Since CLL is a disease of the bone marrow and this is an advanced refractory disease population we are talking

about, investigators frequently did not report hematological abnormalities as adverse events. So, I would just like to take you through a laboratory analysis of hematological abnormalities occurring on study. I want to start with this graph which shows the median count for hemoglobin, platelet count and ANC for all patients enrolled in the study. It shows the change over time in this median count and it makes a couple of important points.

The first one is that each one of these medians declines on treatment, typically during the first 2-6 weeks of therapy, after which they begin to recover. In the case of hemoglobin and platelet count, the median counts on study and post-study follow up actually exceed the median count at baseline, whereas the ANC recovery is slower and may take a month or two after therapy or longer in some patients to return to baseline ANC count.

With that in mind, the pattern of this decrease in counts which is very predictable with Campath after which recovery takes place, we wanted to try to dissect out the contribution of Campath to hematologic toxicity versus the stage of the underlying disease and the cumulative toxicity of previous chemotherapy. So, we looked at baseline median counts by Rai Stage, and the results are not surprising. It shows that patients with Rai Stage III/IV disease have abnormal hemoglobin and platelet counts which by definition

they must have. But the point I want to make here is that the median counts for hemoglobin and platelet are already CTC grade 2 at the time they enter study.

You can see this reflected in the types of changes that take place on study. So, patients with Rai Stage III/IV disease who start out lower are more likely to develop grade 3/4 toxicities on study. You can see the percents represented here for Rai Stage 0-II versus the Rai Stage III-IV. You will also note that grade 4 neutropenia was the most common hematologic abnormality occurring on study. It was seen in 12.5 percent of Rai Stage 0-II patients and 46 percent of Rai Stage III-IV patients who enrolled in study with a baseline grade of 0-2.

I mentioned in the median graph that counts go down and then they go back up. What this graph shows is the proportion of patients with grade 4 neutropenia over time on study. So, this is all patients who had grade 4 neutropenia at any time. It shows that at baseline about 8 percent of patients with Rai Stage 0-II had grade 4 neutropenia, and that approximately 13 percent of patients with Rai Stage III-IV already had grade 4 neutropenia at study entry. Over time on study there was an increase in the proportion of grade 4 neutropenia, after which it began to decline. In fact, in the post study follow-up period a lower proportion of patients had grade 4 neutropenia than had grade 4

neutropenia at baseline.

So, let me summarize then the hematological toxicity information that I just presented. Hemoglobin, platelet count and ANC do decline on treatment but then improve. ANC recovery, however, may be delayed in some patients. Grade 3/4 hematologic toxicity, not surprisingly, occurs predominantly in patients with severely compromised marrow.

I should mention that in the CAM211 study protocol there were discontinuation guidelines in the protocol that required investigators to temporarily discontinue Campath if the AND declined below 250 or the platelet count declines below 25,000. After recovery it could be reinstituted. You can see that temporary discontinuation of Campath was required in 16 percent of patients for this reason, after which it could be reinstituted, but only 4.7 percent discontinued therapy permanently because of this complication.

Another useful way to put into context the safety profile of Campath is to look at how the drug was delivered, as outlined in the study protocols. So, this table summarizes that information, and 98 percent of patients reached the target dose of 30 mg; 89 percent received more than 4 weeks of therapy, and the median duration of therapy was 9 weeks. This suggests that the safety profile of

Campath in this advanced refractory population of patients was manageable and that the drug could be delivered as planned to the majority of patients.

Before I leave the safety discussion, I would just like to provide an additional context in which to consider the safety results that I have just presented. I would like to do that by showing you some of the key safety parameters from the fludarabine package insert. Now, fludarabine, as you know, is approved for second-line therapy of CLL and the approval of fludarabine was based on two single-arm studies enrolling a total of 133 patients, and 22 percent of the patients died on study; 59 percent developed grade 4 neutropenia; and 16 and 22 percent respectively developed major pneumonias in the two studies; and the survival was 10 and 12 months in these two studies.

Now, I am not making any direct comparisons between this data and the Campath data, but I do want to make the point that it is reasonable to expect that patients failing second-line therapy and going on to third-line therapy, you would expect them to do worse, and that is perhaps not the here.

So, let me now move to my conclusions, starting with safety. The most common adverse events are acute infusion-related events which are most common during the first week of therapy and then decline substantially after

that. A small percentage of patients discontinue drug due to these events.

Severe infections are seen in 28 percent of patients including those due to opportunistic pathogens. These are the types of infections that would be expected in this population of patients and have been reported in fludarabine studies as well.

Hematologic toxicity, which can be severe, emerges on treatment in some patients. These are primarily patients that have substantial marrow compromise at the time they enter study, and these patients should be followed especially closely while receiving therapy with Campath. However, this represents a reasonable and manageable safety profile in this immunocompromised, refractory disease population.

Against this manageable safety profile is the efficacy profile of Campath. Campath is effective in a population of patients for whom no approved therapies are available and so represents a significant unmet medical need. The objective response rate of 33 percent seen in the pivotal trials significantly exceeded the hurdle set in the protocol, and the median survival associated with this was 16 months.

The supportive studies were consistent with these results with objective response rates of 28 and 33 percent

respectively, and comparable survivals overall. These responses were associated with meaningful clinical benefits that are very important to patients as well.

So, for the benefit/risk I would like to focus on the CAM211 study which enrolled exclusively patients with advanced refractory disease. The majority of these patients had received salvage therapy after failing fludarabine. So, they were immunocompromised at study entry. They had significantly compromised marrow at study entry and there were no approved or effective therapies for the treatment of these patients. In spite of that, Campath was effective and manageably safe in this patient population, and has the potential to address a significant unmet need in these patients.

We feel that this data strongly supports the use of Campath for the treatment of patients with CLL who have previously been treated with alkylating agents and have failed fludarabine therapy.

I would like to thank you for your attention, and I would be happy to answer any questions.

DR. NERENSTONE: Thank you very much. We will now open to the committee for questions of the sponsor. Dr. Przepiorka?

PRZEPIORKA: I will start with some questions for Dr. Keating, please. I have three questions. The first is,

can you tell us a little about your experience with use of anthracyclines as second-line and third-line therapy for ALL patients treated with F&D, CHOP or BED?

DR. KEATING: Yes, we have used a number of anthracyclines. It is of interest to note that there is no evidence that anthracyclines have any activity in CLL. There is no published paper that shows that doxorubicin, idarubicin or any other anthracycline is effective in CLL. We have looked at idarubicin and have found that there has been no significant response rate. I think we had 1 response out of 20 patients. The BED regimen we have used in a number of patients and, while it shrinks the lymph nodes, it doesn't really do very much in the way of improvement in hematological responses. Some patients do respond to the CHOP program, and I think the response rate is probably around 10-15 percent in patients that have never had exposure to alkylating agents before.

PRZEPIORKA: For patients treated with fludarabine, what is the survival for those who achieve a PR versus those who have no response whatsoever?

DR. KEATING: The median survival of patients that get PRs in salvage therapy is approximately two years, whereas those that survive the therapy and don't get an objective response, their median survival is around 9 months.

PRZEPIORKA: And for those who achieve some response but develop prolonged cytopenias, how long can those cytopenias last and do they resolve spontaneously later down the line?

DR. KEATING: The cytopenias that occur -- we have just analyzed that in particular in a group of patients that have had it as front line; it is more common in patients that receive it as second-line, many of these patients never recover normal red cell counts and normal platelet counts, normal neutrophil counts. There is a persistent low grade myelosuppression that occurs after fludarabine, predominantly in patients that are older than 70 years of age that start off with advanced stage and have other adverse characteristics like elevated beta-2 macroglobulin.

We haven't systematically looked at it in all patients that are receiving salvage treatment, but I know from our experience that it is significantly higher. I would imagine that in those who fail get a response and have persistent pancytopenia, it is probably about 15 percent or 20 percent of the patients that go through the trial and they usually don't recover.

PRZEPIORKA: Thank you.

DR. NERENSTONE: Dr. Blayney?

DR. BLAYNEY: Yes, thank you, Madam Chair. For Dr. Brettman, I was encouraged to hear you say that improving

and treating the underlying illness, the CLL, resulted in increase in performance status and hemoglobin improvement. Others in your industry, from reading the direct to consumer advertisement, seem to ignore treating the underlying illness as an important part of improving performance status and hemoglobin.

The adverse events that you describe seem to be infusion-related early on. Was there a correlation between the circulating lymphocyte count and the severity or onset of these infusion-related events? Is this seen in other monoclonal preparations?

DR. BRETTMAN: We did look at that and did not see any convincing association between the level of the circulating leukocyte count and the intensity of infusion-related events. However, certainly we have heard anecdotal experiences from some of the clinicians that patients with especially high lymphocyte counts -- and I think Dr. Rai had a patient with a white count of 700,000 who did experience a severe infusion-related event. I don't know whether you want to comment on that, Kanti.

DR. RAI: I agree with Lee --

DR. NERENSTONE: Could you please identify yourself?

DR. RAI: My name is Kanti Rai. I come from Long Island Jewish Medical Center, in New York. In answer to the

question about any relationship with adverse shaking chills and fever with Campath with height of leukocyte count, we have seen those reactions both with very low starting white count as well as with very high white count and, as Lee mentioned, the highest white count that we saw and treated was 750,000 and the level of reactions, infusion-related reactions were severe but no different from the low white count.

DR. BLAYNEY: In your briefing document you talk about pharmacokinetics being non-linear and I assume that that has to do with the disappearance of the compartment that may be absorbing the drug. Can you comment on that?

DR. BRETTMAN: Sure. First of all, there are two parts to it. The pharmacokinetics across unit doses ranging from 7.5 mg to 75 mg were actually dose proportional. So, if we could actually show slide 4, please?

This shows the PK parameters from the 002 Phase I study that administered Campath once a week. This is the study from which the most reliable pharmacokinetic information comes because of the sampling that was possible from a once weekly dosing regimen. You can see that the half-life across the doses from 7.5 to 75 are pretty comparable, as well as the C-max and the AUC being dose proportional in these doses.

But I think your question probably relates to what

is the impact of tumor burden on the pharmacokinetics of Campath.

DR. BLAYNEY: And repeated dosing as you outlined in your proposed package insert. Patients are going to get repeated dosing and apparently the pharmacokinetics with repeated dosing are somewhat different than the single dose you just showed.

DR. BRETTMAN: Let me see slide 12, please. This graph shows the data from the 005 study, the Phase II supportive study utilizing the dose of 30 mg 3 times a week. Now, in this study limited pharmacokinetic sampling was done, essentially limited to getting peak and trough levels over time in the patients enrolled in the study. This shows the analysis for the patients with CLL and you can see that the purple dotted line shows the median lymphocyte count rapidly coming down, reaching the nadir at approximately 4 weeks of therapy. You can see also over time that the peak and trough Campath levels gradually rise, approaching a plateau approximately around week 5 to 6 of therapy.

DR. BLAYNEY: When the lymphocyte count comes down, as you show, in week 4 is there any reason, other than protocol adherence, to continue Campath dosing?

DR. BRETTMAN: To continue dosing at all at that point?

DR. BLAYNEY: Yes.

DR. BRETTMAN: Yes, I think there is a very strong reason to continue dosing at that point. The lymphocyte count in the peripheral blood comes down very rapidly. Bone marrow also clears rapidly but not as rapidly as peripheral blood. Liver and spleen resolve less rapidly than that, and lymph nodes appear to resolve the most slowly. So, it has been observed in clinical trials that continued improvement on Campath can be seen up to 12 or 13 weeks of therapy in some patients, and so the duration of therapy should be tailored to the vigor of the response. If patients achieve a plateau and experience no further improvement then, as you are suggesting, therapy should be discontinued.

DR. BLAYNEY: My last question is what have you experienced we retreatments after a prolonged remission with either Campath or another monoclonal?

DR. BRETTMAN: We have data on 19 patients from the three studies who have gone on to be retreated with Campath, typically under a compassionate use protocol. If we could show that slide, please?

So, 9 patients from CAM211 and 10 patients from the two supportive studies -- 13 had responded to the initial treatment with Campath and 6 were non-responders. Ten of the 19 patients were reported by the investigators to have responded to therapy, including 2/6 patients who were prior non-responders.

DR. BLAYNEY: Thank you.

DR. NERENSTONE: Dr. Miller?

DR. MILLER: Thanks. I have some questions about the neutropenia. First, can you talk a little bit about the mechanism of the neutropenia proposed, and then the attempts to ameliorate the neutropenia by use of growth factors and whether there is any effect? Secondly, it appears that when you talk about managing the side effects of Campath, I think management of side effects suggests that we may be able, at least from the neutropenia standpoint, manage prolonged neutropenia or complications thereof.

DR. BRETTMAN: So, the first question is what is the putative mechanism of neutropenia.

DR. MILLER: Yes.

DR. BRETTMAN: The answer to that is we don't really know because CD52 is expressed on 5 percent of granulocytes, primarily eosinophils but not other granulocytes, and it is not expressed on myeloid precursors. So, from that basis it does not appear as if Campath is actually directly attacking progenitors of granulocytes. In addition, there is evidence from investigators, who have now extensively used Campath to <u>in vivo</u> purge patients prior to doing stem cell transplants, that Campath does not appear to impact the ability to get a good stem cell harvest.

However, I think there may be at least a partial

explanation. I don't think we can explain it entirely. If you look at the marrows of some of these patients, they are absolutely packed with disease, and there is rapid clearance over the first 3-4 weeks of therapy. These are patients who come in with very compromised marrow to begin with and I think at least one of the factors is release of cytokines injuring an already damaged marrow, and that at least may be one of the mechanisms at least early on. The prolonged recovery after Campath -- by the way, you see that pattern, they come down and they come back up in most patients. There is a subset of patients who take a longer time for the ANC to recover, out to several months after therapy, and we don't have a good explanation for that.

DR. MILLER: Can you comment on response to growth factors and what percent of the patients that have prolonged neutropenia fail to respond to growth factors?

DR. BRETTMAN: Yes. Give me a moment and I will find that slide for you. This shows the use of both G and GM-CSF and erythropoietin across the three studies. So, a quarter of the patients in the CAM211 study got growth factor support compared to 2.5 in the 005 study, primarily because it wasn't widely available at the time that study was done. The median duration of growth factor use in the CAM211 study was 14 days. Patients did respond to growth factor. You could see an increase in neutrophil count, not

surprisingly, after the initiation of growth factor therapy.

DR. MILLER: Particularly in the patients with the long neutropenia, is there any evidence that they responded? I mean, were those patients generally treated, and do you feel that growth factors can ameliorate at all the prolonged -- I mean, the real risk is not the going down to 500; it is the patients as we looked at in the toxicity data that had the prolonged neutropenia, lasting a month or two and didn't recover and, you know, had significant incidence of fungal infections. Were all those patients treated and, number two, did any of them respond?

DR. BRETTMAN: I am sorry, were all those patients treated --?

DR. MILLER: I suspect that growth factors, at least in 211, were allowed and clearly commercially available. The information on the patients with the prolonged neutropenia, the severe neutropenia -- do you have data on that group of patients and whether any of them responded to growth factor?

DR. BRETTMAN: I don't specifically have that information but we could certainly get it. It is a good thing to look at.

DR. MILLER: Do any of the investigators who are here have any experience with response in the prolonged neutropenia in patients with growth factor?

DR. BYRD: John Byrd, from Walter Reed, working in conjunction with Dr. Flynne at Hopkins, there were several patients treated that responded to growth factor, and we subsequently did a trial with Campath and GM-CSF where, in a proportion of patients, not all patients, the cytopenias that were seen initially with Campath were ameliorated by GM-CSF. I can't give you the exact number.

DR. BRETTMAN: I might add just for clarification that the recovery of ANC is defined as returning to their baseline level. So, you know, many of those patients get up above 1000 but don't get back to the baseline of 2000 that they had at study entry. There are some though, as you pointed out, that do have persistently low ANC counts after study.

DR. KEATING: Michael Keating, from M.D. Andersen. The patients that we saw on study -- I don't think there was a single patient that didn't have some response to growth factors. In some patients it was sluggish to respond but in those where we felt it necessary to give the growth factors, we didn't see anyone that didn't have some substantial response.

DR. MILLER: If you look at the sponsor's safety data or the actual patients who died of infection while on and off, those patients generally die with just the neutropenia and I suspect most of the patients got growth

factor. I am just trying to figure out, if you look specifically at those patients who had Aspergillus -- I assume that those patients were probably getting growth factor at the time, and I am just trying to figure out how reversible it is and if we have any understanding of that.

DR. BRETTMAN: Yes, it is a good question. We will look into it.

DR. MILLER: Secondly, in the toxicity there was some discussion of response and the toxic deaths or infusion-related death, and it would appear that many of the non-responders were the patients who had more toxicity. That may make sense. But is that a very clear correlation and do you have any data on the correlation between toxic or infusion-related death and response to treatment?

DR. BRETTMAN: Yes, we do. Let me show that to you. What this table shows is the incidence of some of the more significant adverse events, such as grade 3/4 infections, serious events and deaths within 30 days of the last dose. You can see that the rate of infection among non-responders is higher than in the responders, not surprisingly. For other events there does not appear to be a big difference between responders and non-responders, at least the ones you see listed here.

DR. MILLER: Just one last question, from other studies do you have data from other non-CLL, not very

heavily pretreated patients, do you have safety data about the risk of infections. From my standpoint, I am trying to determine the toxicity of the drug itself versus the severe immunocompromise of the patient population. While it is not apropos to the effective, it may be important to look at the toxicity and the risk of severe fungal infections and viral infections in other patient populations treated with Campath, and any further data supporting the safety and compassionate use over the last two years. Some of those patients may have been less heavily pretreated than your patients on the current study.

DR. KEATING: May I comment on that? Again, Michael Keating, from M.D. Andersen. We have looked at this in a number of our studies, and Dr. Anaissie did a multivariate analysis of the risk of infections in patients that were treated with fludarabine combinations, and in every subset of patients that we looked at we found that there was a higher risk of getting infections in patients that had a less effective response.

The second piece of information, which is interesting but I don't have a clear explanation for, is that in patients that finish therapy with front-line fludarabine you can correlate the risk of getting infection off treatment while they are still in remission according to the quality of response. So, those who have true complete

remissions have a low incidence. There is a higher incidence in those that have nodular partial responses, and a higher incidence in patients that have partial responses. These patients are not neutropenic. There is no correlation with the CD4 count. So, there seems to be some correlation between the responsiveness of the tumor and the risk of patients getting complications.

DR. BRETTMAN: Yes, an in answer to the second part of your question, we have not conducted studies of Campath front-line. There were a small number of patients in the 005 study who had CLL and were previously untreated. There were 9 such patients and the response rate, not surprisingly, was very high and 8/9 patients experienced a response. The absolute incidence of infections was lower, but with such a small sample not much can be said. In addition, earlier this year, at the European oncology meeting Anders Osterborg presented data that he has collected at the Karalinska. They have treated 25 patients front-line with Campath subcutaneously, and reported also that there was a lower incidence of infection and it seems that, particularly with hematological toxicities, grade 4 toxicities weren't seen at all in those patients but, again, it is a small sample and the methods for collecting data are very different from ones we would use, but I tell you that for what you can take from it.

DR. NERENSTONE: Dr. Berman?

DR. BERMAN: I have questions for Dr. Keating. Help us put this antibody into context with other compounds that are significant T-cell suppressing agents. Can you comment on the slide that showed the length of T-cell suppression with this compared to, for example, chlorodioxy adenosine in patients with hairy cell leukemia?

DR. KEATING: Yes, we have looked at the recovery time of patients that have received a single course of 2CDA, and we find that at the 6-month point, Dr. Brettman showed where there was recovery to approximately 500 to 600, we would still anticipate a median CD4 count in the 100 to 200 range. So that the purine analogs appear not to have as intense suppression of the CD4 count, but the suppression of the CD4 and CD8 counts is much more prolonged after the purine analogs than is after Campath.

DR. BERMAN: Another question is the small but noted incidence of autoimmune hemolytic anemia with fludarabine. Have there been any reported cases of autoimmune either hemolytic anemia or ITP that can be directly related to Campath and not to the underlying disease itself?

DR. BRETTMAN: Yes, in the CAM211 study there was one patient who developed ITP with an onset at about two weeks after the last dose of study drug, which we have

attributed to Campath. We have seen occasional patients who developed positive Coomb's tests on study but not associated with clinically apparent hemolysis.

DR. BERMAN: Was the patient who developed ITP responding to treatment?

DR. BRETTMAN: Yes, the patient did respond to treatment.

DR. BERMAN: A third question is the incidence of tumor lysis with this agent in patients who have a high white blood cell count.

DR. BRETTMAN: In the 005, 009 and CAM211 studies we did not see any cases compatible with tumor lysis syndrome. However, there were patients in the Phase I/II studies who appeared to have syndromes consistent with this. Now, remember, these were rising dose designs, and one patient received an 80 mg dose. This was a patient with NHL and had massive disease and received a single 80 mg dose as the first dose of Campath. That patient developed renal failure, high uric acid and other signs of tumor lysis syndrome. After that experience Wellcome actually modified their protocols to use a dose escalation strategy during the first week of therapy.

A second patient was reported by the investigator to have tumor lysis syndrome but the drug was never discontinued. The patient continued to receive therapy

although the investigator reported an adverse event of tumor lysis.

DR. BERMAN: Lastly, the mean age of the patients who died on study?

DR. BRETTMAN: Let me just show you that. It will take a moment.

DR. RAI: My name is Rai, from New York. While he is looking for that slide, I would like to address the question by Dr. Berman. Since 1992 or '93 that I have participated in various Campath trials, 009 and 211, I have always been concerned about causing tumor lysis, and we did not see any. We had 13 patients in 009 and 10 patients in 211 and all of the patients that started with very high leukocyte count, those patients were especially hydrated pre- and post-Campath and, as the protocol requires, the dose was started at 3 mg and then, 2 days later, was up to 10 mg and then 30 mg, and none of those patients had any biochemical or clinical evidence of tumor lysis syndrome, which surprised me.

DR. BRETTMAN: I am going to answer your question in two ways. We did an analysis of risk factors and age did not come out as a significant factor, and the death rate above and below the median of 63 years was not different. So, the second part of it is that in the multivariate analysis, as well as univariate analysis, age did not show

up as a significant factor.

DR. BERMAN: Were there any significant factors that did show up?

DR. BRETTMAN: Yes, and we can show that slide. This is the prognostic factor assessment for the CAM211 study, and the only factors that turned up in multivariate analysis as being significant were the degree of marrow infiltration greater than 90 percent and region, U.S. versus Europe, although there is a small number of patients; only 25 patients were enrolled in the CAM211 study from Europe.

DR. NERENSTONE: Dr. Sledge?

DR. SLEDGE: I have a couple of questions. First, I would like to get some better sense of the fate of the responding patients. Can you give us an event-free survival curve or an overall survival curve for the responding patients?

DR. BRETTMAN: Yes, we can. That is the survival curve for responders versus non-responders for the CAM211 trial.

DR. SLEDGE: Second question, could you give me a better sense of what the hypotensive events meant, and the severity of the hypotension that was observed, and was any of this anaphylactoid?

DR. BRETTMAN: No anaphylactic events were seen during the CAM211 trial. The hypotension events were most

commonly just a measurable drop in blood pressure without clinical symptoms. A small percent of patients did become symptomatic and responded quickly to fluids.

DR. SLEDGE: Going forward, is there something that you would recommend as part of the package that patients have their blood pressure monitored regularly while they are getting therapy?

DR. BRETTMAN: Certainly during the early stages of therapy, yes.

DR. NERENSTONE: Dr. Lippman?

DR. LIPPMAN: It was a very clear presentation of the primary data. My questions are really just trying to get a sense or a suggestion of which subgroups may do better or differently. Did you look at patients who had prior responses to fludarabine but had progressed within the 6-month eligibility? Did they do better on the subsequent Campath?

DR. BRETTMAN: Let me show that to you. Patients who had ever responded to fludarabine versus those that had not -- it will just take a moment.

DR. LIPPMAN: While they are looking for that, the other subgroup which you may not have data on because I know it is very rare, although we know that there is at least one patient that fit this category with T-cell CLL, was there a different response in that group, or did you look at that?

DR. BRETTMAN: Let me show you this and then we do have data from the 005 study on patients with T-PLL. This shows the response by prior fludarabine response. So, patients who were primarily refractory to fludarabine, had never responded, the response rate was 28.9 percent, and in those patients who had responded to at least one prior fludarabine-containing regimen the response rate was 37.5.

Let me show you the T-PLL. There was a total of 7 responders among 12 patients who were enrolled in the 005 study with a diagnosis of T-PLL, and these were also assessed by the independent response panel that I mentioned earlier. There was a total of 58.7 objective responses, with 25 and 33 CRs and PRs percentage respectively.

DR. NERENSTONE: Dr. Simon?

DR. SIMON: I feel that, because of the design that you used and the FDA approved, we are sort of placed in an inherently flawed and error prone situation, trying to assess whether the obvious activity represents clinical benefit, or to what extent it does, to what extent the negative effects represent effects of the treatment rather than effects of the disease, and we wind up using essentially all of the erroneous kinds of analyses, like comparing responders to non-responders and comparing survival of these patients to survival of patients from the literature, and making every mistake in the book essentially

and it all comes from the fact that we have used a design that doesn't really lead to very clear interpretation.

So, my question is why was it not possible to do a randomized trial using your monoclonal antibody and comparing it to essentially physician's choice of third-line treatment or supportive care?

DR. BRETTMAN: Well, that was actually one of the options that we discussed during our discussions with the FDA, and there was considerable opposition from the clinicians because, you know, if you want to assess safety in a comparative fashion it doesn't really help you a lot because you are going to be comparing it to a variety of different regimens. Secondly, there were very few choices that people were willing to recommend that could even be put forward as comparative regimens. That was essentially the major problem.

DR. SIMON: The patients with CLL who were not in your clinical trials are not getting your antibody so they are getting either something else or nothing else and, basically, you would compare it to that variety of approaches.

DR. KEEGAN: We did try and work out whether this could be done in a controlled fashion, and were told that they really didn't find that they could find investigators who would agree to randomize, in which case we recommended

that they start working on a second trial that was randomized to control during the conduct of this trial but, unfortunately, no such study was initiated but I think we fully agree with your comments.

DR. SIMON: Well, it is always easiest to do it this way but it leads to very error prone evaluations.

DR. KEEGAN: We agree with your comments.

DR. KEATING: Perhaps as one of the clinicians involved in the treatment of this subset of patients, I think it would be impossible in good spirit to actually ask patients to enter into a randomized comparison.

DR. SIMON: Well, you would have to find physicians who don't agree with you, of which I am sure there are very many.

[Laughter]

DR. KEATING: I would like to have a list of them provided.

[Laughter]

DR. NERENSTONE: Dr. Albain?

DR. RAI: Could I add to what Dr. Keating just said?

DR. NERENSTONE: Okay.

DR. RAI: I treat quite a few patients with CLL and see a large number of second and third opinions, and I find throughout the country that there is absolutely no

consensus about what is the third-line treatment for CLL patients who have failed fludarabine. People use all the drugs that we use in lymphoma but there is no general agreement. So, it would be very difficult if we tried to preempt and have a randomized trial at that moment.

DR. SIMON: You are misunderstanding. You don't have to agree on what the comparative treatment is. You can do the trial against a physician's treatment of choice.

DR. NERENSTONE: Dr. Albain?

DR. ALBAIN: Yes, I would like to go back to the biology a little bit. Given the ubiquitous presence of the antigen, any thoughts or have there been any studies done on mechanism of resistance to this compound?

DR. BRETTMAN: There have certainly been no detailed studies on the mechanism of resistance but we know some things. First of all, after treatment with Campath when patients subsequently relapse, the tumor cells still express CD52. There are occasional cases -- there have been two patients that I am aware of that have had emergence of a CD52-negative clone after treatment, but we didn't see it in any of our trials. This was reported by an investigator. There are patients who have clearly CD52-positive tumor -- they are rare -- that don't respond even in the peripheral blood, and it is just not clear whether that is an absence of sufficient effector mechanisms or other things of that

nature. So, we really don't know the answer to that question at this point.

DR. NERENSTONE: Dr. Przepiorka?

DR. PRZEPIORKA: There were reports in the literature on autoimmune thyroiditis in patients getting Campath in other settings prior to initiation of 211. Did you have the opportunity to review thyroid function tests in patients in CAM211, and were there any thyroid complications?

DR. BRETTMAN: No, we did not prospectively plan or retrospectively collect information concerning thyroid function, but we do know that in a population of over 400 oncology patients who received Campath during Phase I/II trials, Phase II trials etc., that autoimmune thyroiditis was reported in one patient so there is clinical evidence of it. The reports that you are referring to have been seen primarily in a population of patients with multiple sclerosis who have received Campath. In those patients there is a 30 percent incidence of autoimmune thyroiditis which seems to be, based on preliminary investigation, probably related to genetic factors specifically in that population although they haven't received a lot of cytotoxic or immunosuppressive therapy previously, and that may also be another reason why we don't see that in oncology patients.

DR. PRZEPIORKA: The second question is that your

adverse event listing clearly demonstrates infusion-related toxicities and clearly demonstrated the pulmonary infections, but I was intrigued by the category called interstitial pneumonitis which was not listed as infection or infusional. Can you talk about the non-infectious pulmonary toxicities?

DR. BRETTMAN: I am not sure exactly what number you are referring to but there were certainly patients for whom no pathogen could be identified. But specifically the patients who were diagnosed with interstitial pneumonitis, based on biopsies, no infectious pathogen was identified. One of the patients was treated with steroids and so was considered non-infectious, and with it is related to Campath or related to the multiple prior therapies those patients had received, it is not possible to say.

DR. PRZEPIORKA: My last question is how did you choose the dose of 30 mg 3 times a week?

DR. BRETTMAN: That dose was actually selected on the basis of the dose-ranging studies from Wellcome and I will just briefly show you that information. This shows the basic design element relative to the dosing unit and the dosing frequency of Campath for the three Phase I studies. So, one study was done with unit doses ranging from 2.5 to 80, administered 3 times a week. The second study is the doses you see there once a week, and study 003, the doses

you see there at 0.5 a week. These studies were designed so that the cumulative weekly dose was relatively comparable across the studies.

This shows the responses by regimen as assessed by the investigators involved in these studies. This is essentially the reason why Wellcome selected the dose of 30 mg 3 times a week, based on the activity seen essentially in the 3 times a week dosing regimen which was not seen in the once weekly -- there were no major responses as assessed by the investigator seen in the once weekly dosing regimen. In the 5 times weekly dosing regimen there were some responses but it clearly wasn't higher and 5 times a week isn't as convenient for patients. So, that is how Wellcome arrived at that dosing regimen, and the doses utilized in the study -- the 25 mg dose was actually the dose associated with the highest response rate; the 80 mg dose appeared to be associated with more toxicities. So, they selected a dose of 25-30 mg to utilize in the Phase II studies.

DR. PRZEPIORKA: Thank you.

DR. NERENSTONE: Dr. Berman and then Miss Lackritz, and then we are going to break.

DR. BERMAN: To expand a little bit on the meaningfulness of the partial responses, can you show us the data on patients whose response to Campath was, in fact, longer than their response to prior treatment on

fludarabine?

DR. BRETTMAN: Yes. It is difficult to do in the sense that all of the patients were required to have failed therapy coming in, but we did look at the median chemotherapy-free period for patients coming into the trial and we also looked at the duration -- sometimes you had to go back one or two regimens to find patients who had responded to fludarabine regimens. So, for those patients at least we can provide that information.

I am sorry, we don't have a slide on it, but the bottom line is that the duration of responses to the last regimen to which they had responded was from 2-6 months. You could at least compare for those patients the duration of the response to Campath, for what it is worth, and those patients did experience a longer duration of response.

DR. NERENSTONE: Miss Lackritz?

MS. LACKRITZ: My name is Barbara Lackritz. I have CLL and I speak for the patient population, and one of the concerns that we have had for a long time, a concern that is expressed by the members of the lists that I run which is 1750 people from 36 countries, indicates that when you fail fludarabine, when you fail purine analog therapy, there isn't anything out there that is available to really do the job. I have talked to patients who have been on CHOP, who have been on ESHAP, who have been on BEAM, who have been on

CVP, and these patients are very, very frustrated and eventually these are the patients who do not survive. Something is needed that will give us, as a patient body, the opportunity to live a little bit more of the kind of life that most people expect as a normal part of living.

DR. NERENSTONE: Thank you. I would like to break now and please be back by 10:15.

[Brief break]

DR. NERENSTONE: If we could, please, get everyone to sit down so we can get started here?

FDA Presentation

Introduction

DR. BRORSON: Good morning. My name is Kurt Brorson. I am in CBER's Division of Monoclonal Antibodies, and it is my pleasure this morning to introduce the FDA presentation on the Campath antibody. Campath-1H or alemtuzumab is an IgG-1 kappa humanized monoclonal antibody. It is humanized in the sense that the majority of the immunoacid sequence of this antibody is derived from human origin, the exception being the complementarity determining regions of the antibody which are derived from original rat hybrid monoclonal antibody.

The specificity of this antibody is against the CD52 antigen, and the presumed mechanism of action of this product is by lysis of CD52-positive cells via complement

activation, ADCC and possibly apoptosis.

The Campath BLA has been reviewed by an expert panel of CBER reviewers from a variety of disciplines, and I would like to acknowledge at this point the complete and thorough review that this panel has given to the BLA.

The CD52 antigen is a membrane-bound glycoprotein expressed at high levels on a variety of leukocytes, including B-cells, T-cells, monocytes, macrophages, and a minority fraction of granulocytes.

The sponsor of the BLA has performed a standard tissue screen for CD52 expression and has found it on some other cell types, including cells of the male reproductive tract. They found it in the skin. However, notably it was absent in other tissues, including erhythrocytes, platelets and hematopoietic stem cells.

The history of development of this antibody dates back to the 1970's. Two original precursor antibodies, Campath-1M and 1G were rat IgM and IgG2b antibodies which were tested in a variety of applications. The in vivo use of these antibodies, however, was limited by the development of human anti-rodent antibody responses. To overcome this problem, a humanized version of the antibody was produced by grafting the complementarity determining regions of the rat antibodies into human antibody expression constructs.

This concludes my introduction to the FDA

presentation, and I would like to turn over the podium to Dr. Genevive Schechter of the Division of Clinical Trials Design and Analysis.

DR. SCHECHTER: Before I begin, I wanted to acknowledge Dr. Patrician Keegan for her assistance and invaluable suggestions in analyzing this data. I want to thank Miss Paula Lincoln Smith for her administrative support, Linda Livingston and Rhonda Hill for their secretarial support, Mr. Kelly Tate and Miss Jackie Sincola from ILEX for their help in obtaining documentation and getting documents back and forth, and Lee Brettman for our fabulous, friendly agreements to disagree.

We are going to discuss Campath today, indications for the treatment of patients with CLL who have been treated with alkylating agents and who have failed or are refractory to fludarabine.

I would like to talk a little bit about the history of the submission which will help in understanding the questions. On September 12 of 1997 the sponsor approached the agency with a proposal for a BLS submission. I believe that the original proposal was based on studies 005 and 009, and it was realized that a confirmatory trial would have to be done. If they used a single-arm trial the response rate would be considered a surrogate endpoint for survival, and a commitment would have to be made to a post-

marketing randomized trial. The agency suggested Campath versus fludarabine, and we also recommended that that trial be ongoing at the time of approval.

The sponsor conducted their single-arm trial, study 211, in 1998 and came in for a pre-BLA filing meeting on March 25th of 1999. At that time a question was raised about the possibility of full approval. The sponsor was advised that a full or conventional approval would be possible if the response rate was so compelling, indicative of benefit, and the toxicities were so low that there would be no need for a confirmatory trial.

On December 23rd, 1999 the original submission was filed. On June 23rd of 2000 a completed review letter was issued to the sponsor, with request for further information, updated study reports and audit of some safety and efficacy information. This study was conducted very rapidly, with the accrual occurring actually in 211 in about four months, and in trying to catch up on all the data there was some incompleteness which is why we could not complete the review in that six-month period.

The sponsor resubmitted data on August 18, 2000 and the revised study reports and the data tables are the basis for the presentation today.

I want to talk a little bit about PK because we have a little different interpretation of the

pharmacokinetic data based on some work that was done by Dr. Martin Green of the Division of Clinical Trial Design and Analysis in looking at the 3 times per week dosing schedule of 30 mg. He noted that the PK is heavily influenced by the tumor burden. There was an increase in half-life as the tumor burden diminishes. The blood levels continue to increase with repeated dosing as receptors are saturated and as the tumor burden diminishes. He noticed that at the end of 4 weeks, in his calculation of the data that he was presented on CLL using this dosing schedule, that the half-life was about 100 hours, and at 12 weeks he estimates the half-life to be 400 to 900 hours. This is typical for monoclonal antibodies.

Let's move on to the clinical trials. I think we have pointed out that 211 was a clinical trial conducted in this country in 1998, enrolling 93 patients and the last follow-up for survival response was July 26, 2000. Data was censored on February 15, 2000 for the statistical analysis done during this review.

This mentions that study 009 was conducted by Burroughs Wellcome between 1993 and 1995 at 6 centers in the U.S., enrolling 24 patients. The last follow-up for survival was in March of 1997. There is some problem with possibly some safety data being missing from this study. I think this study was fairly well audited but in study 005 there is

concern about the study conducted in Europe about the possibility that some serious adverse event reports and other safety information may not be as complete as we would like. The company did go to Europe and audit and they were able to verify 50 percent of the source data.

Just going a little bit over the study design, the population is an intent-to-treat population, and I am going to emphasize 211. The other studies are included on these slides to offer you support and to show where there are consistencies and inconsistencies in the data.

The study design for 211 was to include patients with Rai Stage II-IV. They were fludarabine refractory. Lee has already given you the definition of fludarabine refractory. They had have had prior alkylator regimens. As you can see, there was a little difficult in the other studies.

The performance status could be a little bit inferior on 211. The life expectancy was similar in all studies, and the exclusion criteria were similar.

The route of administration on 211 is IV with the infusion over two hours. As Dr. Brettman has pointed out, patients begin initially with a dose of 3 mg and that dose is continued until they can tolerate it without serious infusional side effects. The dose is then escalated to 10 mg and that dose is continued till the patient can tolerate the

10 mg dose. Then they go to a maintenance dose of 30 mg per week. If a patient's dosing is interrupted for more than 7 days, it is recommended that the patient resume dosing at a lower dose level and be escalated back up to 30 mg to prevent reemergence of the acute infusion-related toxicities.

I want to make a point that on study 005 and 009 patients could be, with the permission of Burroughs Wellcome, escalated to 80 mg. This is a dosing of about 240 per week. This dose is associated with an increased incidence of hypoplasia and infection with suppression, and is not recommended. The maximal dose that would be recommended is 30 mg 3 times per week.

Turning to 005, 7 patients on this study received SQ Campath. Again, we don't have enough information on the difficult in the pharmacokinetics between the IV and SQ to really make any further comments about SQ dosing. Recommendation is for IV dosing.

The cycle duration was 4 weeks on 211 with a maximum of 3 cycles. Note that retreatment was not allowed on this study. On the other 2 studies patients could be retreated and the cycles were different. There was a maximum of 2 cycles on 005.

This is just a little bit of information about the premedication. On 211 diphenhydramine and acetaminophen were

required as premedications. Steroids and meperidine were optional. On the other 2 studies there was not a rigorous definition of premedication. On 005 there was a randomization for the first dose conducted by Burroughs Wellcome between an antihistamine and steroids. About two-thirds of the patients I think were randomized to steroid on this. Topical steroids are recommended st subcutaneous Campath because of local allergic reactions.

On 005 and 009 patients were prophylaxed optionally, while prophylaxis for PCP and viral infections was part of the protocol design on 211, and 82 percent of the patients received both viral and anti-PCP prophylaxis. There were 7 additional patients who were started but continue because it appeared they got allergic reactions. Two patients did not receive anti-PCP prophylaxis and one did not receive viral prophylaxis. Use of growth factors and gamma globulins were optional.

This gives you a breakdown of the median range in age, gender and the race, and I think we are all familiar with that and we can move on to the next slide.

This is Dr. Rai's stage and there is an error on this slide so let's go to the next one.

Rai Stage -- on 211 the majority of the patients or 77 percent were Stage III and IV. In reading the review, you probably figured out that I rigorously evaluated any

patient who had Stage II disease or less to make sure that they were really eligible for treatment, using the sponsor's criteria and the NCI criteria, and I think there was one patient who didn't pass muster but the rest did. So, we have an eligible group.

Looking at the disease state, there were 86 patients who had classical BCLL and there were 7 patients who had other diseases and 2 had an atypical flow cytometry pattern for BCLL. Fludarabine exposure -- all 93 patients were exposed and 88 were refractory by the definition. There were 3 patients who were treated with fludarabine and progressed, and this is an analog of fludarabine. There were 2 patients who relapsed at 6 months and 3 days, and there was 1 patient who developed thrombocytopenia with fludarabine and so technically these don't fit the definition but we agreed that all patients are refractory. All patients had prior alkylator therapy.

Completed therapy, disposition of patients 59 or 63 percent of the patients were reported to have completed therapy. That was based on whether you had a response or stable disease. You could receive between 4 and 12 weeks. You were assessed for disease every 4 weeks. Five patients were noted to have discontinued from study for progression. There were 3 deaths on study. There were 20 adverse events that resulted in discontinuation of therapy and there were 6

patients who refused. One of the patients who was "discontinued" for an adverse event was a patient -- well, I will discuss that later.

Efficacy information -- we agreed that there is a complete response rate of 2 percent and a partial response of 31 percent for an overall response rate of 33 percent, with confidence intervals between 23 and 43 percent, certainly meeting the primary objective of the protocol.

Our median time to response is 1.6 months, with a median duration of response of 6.9 months. For evaluation of response progression we used the NCI Working Group criteria, as published in the 1996 article in Blood by Chesson et al. as was proposed in the protocol and the amendment.

I wanted to look a little bit at responder characteristics, and one thing I didn't look at was response to prior fludarabine therapy but we did note that 2/5 patients with Stage I disease responded; 7/16 with Stage II disease; and 8/18 with Stage III disease, for a response rate in Stage I-III of 40-44 percent. We see a response rate of about 26 percent in the Stage IV disease. All 31 of the responders on 211 were refractory to fludarabine. The number of responders who had a response duration greater than 12 months was 7/31 or 23 percent.

Other efficacy parameters that we looked at were progression-free survival. At the time this analysis was

done, based on the revised data of February, 2000 censoring date, 92 patients had progressed and 1 was censored. The progression-free survival was 4 months with a 95 percent confidence interval of 32. to 4.7 months.

We looked at treatment failure and note the median time to treatment failure is shorter by one month due to the number of patients who were discontinued from treatment for reasons other than progression or completion of therapy and death.

Other efficacy parameters include a median survival of 15.9 months which, as you notice, is somewhat inferior to that on the other 2 studies. I want to point out on this slide that there were 5 patients on 005 -- 5 or 6 patients who did not have follow-up of any kind for more than 3-4 months after completion of therapy.

We tried to look for clinical benefit in responders and Lee has already sort of talked about this. We noted improvement in B-symptoms and fatigue and other things, just to demonstrate that there is some benefit.

I think the most important thing we have to talk about here today is the safety data. First of all, let's talk a little bit about dose delays. There were 20 patients on study 211 who had dose delays of less than 7 days, as indicated in your review. Seven of these patients also had dose delays greater than 7 days. In total then, there were

30 patients who had dose delays greater than 7 days on therapy, and 34 of these dose delays were related to adverse events. The median number of days of dose delays was 12, with a range from 7-53. For those patients who had a dose delay greater than 7 days, 56 percent of the time the reason was hematologic toxicity. In the others it was infection. There were 3 other dose delays for reasons not related to therapy.

We looked at mortality, and the reason why we have looked at mortality and all adverse events on study and for 6 months following study is because of the prolonged half-life of the antibody, the prolonged CD52 suppression and the prolonged neutropenia in some patients following completion of study therapy. We know that 28 deaths on study are within 180 days. You have 27 and there may be one patient that was slightly longer than 180 days but the patient had a treatment-related death so it was included in this count. Fourteen, or half of these were drug related and 14 were due to progression.

With regard to the drug related causes of death, we had infections with and without cytopenia. We know that about half are due to fungal, slightly more due to viral and there is one due to thrombocytopenia. Of interest in 005, there is a patient who developed progressive multi-focal encephalopathy and had virus isolated from the cerebral-

spinal fluid. It is not clear with this is related to Campath or to other therapy but the CD4 suppression is of concern.

We had 22 discontinuations for adverse events related to therapy. Five of these were infusional. Now, someone asked a question about hypotension and it appears that hypotension related to Campath improves over the course of therapy but there is one patient who developed severe hypotension after the 16th of 17th infusion. There was no interruption of therapy and he had to be discontinued from study. There was also one patient who was discontinued for grade 4 bronchospasm after receiving approximately 10 mg of Campath. The other types -- again, we see heme toxicity and infections. I tried to show the ones where there was also some myelosuppression associated with the infection. Three patients on study -- we originally reported that there were 6 patients who discontinued therapy. This is what was reported. On review of those cases, 3 of the patients actually discontinued therapy for drug-related adverse events. The other 3 of the patients just refused. There was 1 patient where the physician withdrew the patient from therapy because, quote, the patient was immunosuppressed because, quote, his lymphocyte had fallen. He was a PR, right? Yes. We went back and we looked and he was a PR.

Serious adverse events -- the serious adverse

event table is an attempt to obtain a comprehensive picture of the adverse events to allow you to look at those adverse events and decide if the assessment of relationship to drug therapy is correct. It also gives us an idea of everything that happened on study and for that period of six months after study. There is one patient who developed something and it was a little bit more than six months.

This table was devised from a table of hospitalization provided by the sponsor, the tables of adverse events pre- and post-study, a review of the serious adverse event narratives and case report forms. Based on all that information, I determined that there were 115 serious adverse events. There were 84 drug-related adverse events during this time period. Ten of these were judged to be infusional; 16 were judged to be infectious; 30 were infections with neutropenia. There were 16 episodes of febrile neutropenia and there were 12 episodes of just hematologic toxicity.

I tried to analyze this by stage of disease and the number of prior months of fludarabine therapy and alkylators because possibly more heavily treated patients would have problems. I looked at Stage I and Stage II patients and I note that there are fewer serious adverse events in Stage I/II patients and that the Stage I/II patients who had no serious adverse events did have somewhat

less therapy.

When I went to look at Stage III and IV, I couldn't find any difference. There are more serious adverse events in the Stage III/IV population. I couldn't find any difference in really the median number of cycles with fludarabine and, certainly, you would expect patients who had serious adverse events to have more months of alkylator therapy, not less months.

I looked at opportunistic infections. There were 27 patients, or 29 percent of the study population, who had opportunistic infections. There were 87, as I pointed out, patients who had prophylaxis, complete prophylaxis. There were 47 opportunistic infections. There were 29 opportunistic infections that were serious in nature, or about 62 percent of the opportunistic infections.

This is a detailed description of the types of opportunistic infections. This shows you that there is kind of a change in the pattern of opportunistic infections with prophylaxis for PCP. We don't really see any difference in the viral infections. In summary, there were 12 fungal infections on 211; 16 viral infections and 1 PCP infection.

I want to look a little bit at infusional toxicity, and 88 and 89 percent of the patients are going to get fever and rigors, especially with the first few infusions. Nausea and vomiting occur in between 30 and 50

percent. Hypotension occurs in about 15 percent and rash and urticaria occur in about 30 and 22 percent respectively. The rash and urticaria may well be related to the phenomenon or perivascular CD4 lymphocytes, CD52 antigen-bearing cells, and this may relate to this toxicity.

A number of grade 3/4 infusion-related toxicities were markedly less than the overall number of toxicities.

Premedications -- 38 patients or 41 percent of the patient population had steroids on study. I want to make a point that we looked at steroid therapy and disease response and I think it is noted in your review that it has nothing to do with objective disease response, the timing of steroid therapy.

Narcotic analgesics in 61 percent of the patients; antihistamines in all but one patient. There was one patient who had so much premedication that his physician would not give him an antihistamine. And, 43 percent of the patients received antiemetics. It appears that infusion-related reactions do diminish over time but I really can't be sure because of the premedication, until I analyze that data.

As Dr. Keating has pointed out, CLL has been associated with transformation to higher grade lymphomas, progression to PLL. The concerns, since we are suppressing CD4 counts, is with we may be inducing a potential new malignancy. We had one patient who developed a plasma cell

dyscrasia while CLL was in remission. We had one patient who had a prostatic nodule develop on therapy who had a Gleason stage 6 when they had an evaluation 6 months later.

On study 009 there were two higher grade lymphomas. On study 005 I didn't identify any but since the data is not complete on these two other studies, I am not sure.

Autoimmune phenomena -- I identified 3 patients who had autoimmune thrombocytopenia which was related to Campath therapy, and in one of these patients it was fatal and I think that case is well described in the review so you can see that patient, and it fits in with an estimated half-life of 400-900 hours. I did not identify in 005 and 009 any cases of autoimmune thrombocytopenia. In the 32 patients that we reviewed in study 005 it wasn't but in the other part of that study one of the patients died of Campath related autoimmune hemolytic anemia.

Pancytopenia -- in study 009 there were 8 patients who had pancytopenia and 3 patients died, one from cryptoccocal sepsis; one from pancytopenia with inundation with no proof of recovery. In 009 there were 3 patients and in 005 there was one patient.

With regard to recovery, it appears that there is recovery of the hemoglobin in about 2 months; recovery of the platelet count, return to the baseline grade in about 1-

2 months. The granulocytes -- some of the patients are suppressed for an extremely long time and one patient did not recover.

After I wrote the review, I relooked at the hematologic toxicity because I really wanted to give you a more complete feeling of the hematologic toxicity. We did some analysis to show you that we couldn't show a difference in toxicity between responders and non-responders and that patients who were transfused still had diminutions in their hemoglobin over the course of study, at least the first 8 weeks of study.

I went back and I looked at the number of patients pre-study on 211 who had grade 3 or 4 hemoglobin toxicity. At entry onto study there were 5 patients. I went back and looked through all the blood counts and I determined that there were 44 patients who had grade 3 or 4 anemia on study, or 47 percent of the population had one or more instance of grade 3/4 anemia. The median number of days of grade 3/4 anemia was 4, with a range from 1-40. This is because patients who got down to a hemoglobin of around 8 gm or less were immediately transfused. One of the 4 patients who had grade 3/4 at baseline is included because that patient's hemoglobin grade improved and then went down. The other 4 patients are excluded from those 44 patients.

I was kind of curious to see if the effect of

prior fludarabine and alkylators had any effect on development of the severity of the grade of anemia. So, I went and I looked at patients who came onto study with hemoglobin grade 0-2, and 88/93 patients came on study with grade 0-2. On study, 49/93 patients maintained grade 0-2. You can see down there that their median number of months of fludarabine therapy is 5 and the median months of alkylators is 10.

Then I looked at the patients who had grade 3 and 4 on study, those 44 patients. This includes all 5 of the patients with grade 3 at entry. No patients had grade 4 at entry. They had actually less fludarabine therapy and one month less of alkylator therapy. So, there doesn't seem to be much difference. That doesn't seem to influence the development of grade 3/4 anemia.

With regard to neutrophils, the pre-study neutrophil grade 3/4 was observed in 17/93 patients, or 18 percent. On study, 65/93, or 70 percent of the patients had a worsening of their grade 3/4 or developed grade 3/4 in one or more instance. I excluded 8 patients from that in this analysis who came onto study with grade 3/4 because their neutrophil grade didn't get any worse on study so it wouldn't be fair to count them when we are calculating the median number days. I determined from this that the median number of days of grade 3/4 neutropenia was 28 and that the

range was from 2-161.

I again looked at neutrophil toxicity on fludarabine and alkylator therapy and I split out the stages into 0-2, grade 3 and grade 4, and I couldn't find any difference in pretreatment.

I looked at platelet toxicity. Again, pre-study 18 patients had grade 3.4 thrombocytopenia; on study 52 percent of the patients had one or more instance of worsening grade 3/4 or of new grade 3/4 thrombocytopenia. Now, somebody could quibble with me that a more appropriate way to do this analysis would have been to look at platelet counts below 20,000 but that was impossible to do. Anyway, I calculated the median number of days of grade 3/4 platelet toxicity as 21, with a range from 2-165.

I think I pointed out in the review that the thrombocytopenia seems to be worsening thrombocytopenia as one progresses on study as maybe more related to progression of disease than it is to the treatment.

This is just to show you the fludarabine and the alkylators effect, and I couldn't determine any effect.

This is the 2-month follow-up and improvement in grade over baseline was noted in 49 percent of the patients. So, patients did benefit in improvement of their grade of their grade of hemoglobin over baseline, and 23 percent had neutrophil improvement over baseline and 31 percent of the

patients had improvement in platelets over baseline.

On the flip side, 13 percent of the patients had a worse hemoglobin than baseline; 38 percent had a neutrophil count at 2 months that was worse than baseline; and 12 percent had a platelet count that was worse than baseline.

I want to make a comment about use of growth factors and neutrophils. We know, I think, that 31 or 38 patients on 211 received growth factors. Looking at some of these, patients would be placed on growth factors and they would have an improvement of their counts. Some patients' counts would go up and the growth factor was stopped. In other cases, when the growth factor was stopped the neutrophil count went down and the growth factor had to be resumed. In some of the patients who were on growth factor who developed these prolonged neutropenias, they were on growth factor for a prolonged period of time after discontinuation of Campath therapy.

Blood product usage -- 19 percent of the study population on 211 required transfusion at entry onto the study. This is either/or red cells and/or platelets. Fifty of the 75 patients who did not have a pre-study requirement for transfusion developed a transfusion requirement on study. That is 66 percent of that group. I calculated a median range in the number of red cell transfusions of 6 units, and it is kind of interesting because it is

consistent across the studies. The median range of time that platelets were transfused of 3 times, with a range from 1-32 -- median number of 3, with a range from 1-32. There were more platelet transfusions on the other study. We used times with platelets because some patients got single-donor and other patients got multiple units. So, we had to use times rather than units of platelets.

Lastly, I just want to mention CD4 counts. I thought that the information that you really would be interested in is to know how many patients entered the study with a CD4 count at baseline less than 200. I think that we would agree that 200 is really the cut-off for infections. There was 12 percent of the population who had CD counts below 200 at baseline. I don't want to say a couple but there were a few patients who had a CD count of zero, and I didn't have time to go back to look and see how close to the time that they initiated their Campath therapy they had received their last dose of fludarabine. At 30 days on study 84/86 patients, or 98 percent of the patients had CD4 counts less than 200. I think the median CD4 count is between 1 and 3. At 2 months of follow-up still 23/55 patients in whom information was available, or 42 percent, still had CD4 counts less than 200. At 4 months 8/30 had CD counts less than 200, or 27 percent. At about 6 months it is about 12 or 13 percent. I didn't calculate that out rigorously.

Just to summarize, we have data from three single-arm studies. Before I go into this, there is other safety information but it is sketchy because we have relatively complete information on another group of patients from study 005. There is information from Phase I/II studies and we know that there have been other cases of hypoplasia and we know that there was one case of serum sickness.

We are looking at the data from three single-arm studies in 149 patients. We observed an objective response rate in these single-arm trials of 33 percent, with a complete response rate of 2 percent, with a median duration of response of about 7 months on 211. We know that there was some improvement or resolution in symptomatology in hematologic parameters. I didn't look at performance status because I found it very difficult to interpret. I found it was a lousy measure of benefit.

Campath-related mortality was observed in 13 to 15 percent of the study population on these three studies. Discontinuations for treatment-related events were observed at 21 to 25 percent. The incidence of serious adverse events was 66-80 percent of the study population who had one or more serious adverse event. Drug-related serious adverse events were observed in 73-88 percent of all of the adverse events. Opportunistic infections were seen in 28-42 percent of the study population and 50 percent these infections we

regarded as serious in nature.

Hematologic toxicity was observed at some point in greater than 50 percent of the study population. Pancytopenia and anaplasia were observed in 8 patients on 211 and in 3 it was fatal. Autoimmune toxicities were observed in 5 patients. Delayed recovery of neutrophils was 38 percent at 2 months of follow-up and 25 percent at 4 months. And increased or new need for transfusion requirements during therapy was documented in 68 percent of the patients on 211 and the percentage is similar in the other two studies. That information is in your review.

We had prolonged CD4 recovery, with 27 percent of the patients having CD4 counts less than 200/microliter at 4 months. Infusion-related toxicities are such that there is a need for premedication with at least acetaminophen and antihistamines and in some patients steroids. There is an absolute requirement for gradual dose escalation on initial treatment and post-dosing interruption. There is a maximal safe dose of 30 mg 3 times a week. We have no information at this time on the efficacy of the subcutaneous dosing regimen.

The questions that are unanswered are the potential for induction of a second malignancy, and the potential for a decrease in survival due to infections and hematologic toxicity related to Campath, and these can only

be demonstrated through a comparative trial.

Thank you very much for your attention. Questions?

DR. NERENSTONE: We will open the floor now for questions from the committee for the FDA. Dr. Miller?

DR. MILLER: Thank you for that excellent review. The hematologic toxicity -- I thought it was very nice the way you presented it with no difference in the grading of toxicity between patients -- the no difference in the amount of previous alkylator and fludarabine with the different gradings of hematologic toxicity. Did you look at the flip side as compared to looking at dividing patients up by less than 5 months of fludarabine, 5-10, greater than 10, to see if we can pick a group of patients, and whether that analysis gave any further information?

DR. SCHECHTER: No, I didn't because the medians were so similar.

DR. MILLER: Okay. The second thing, the delayed neutrophil recovery that you talked about at the end --

DR. SCHECHTER: Actually, if you really want to know I can do it for you but I would have to go back to do it but it is possible for me to give you a breakdown but I don't have my data set here.

DR. MILLER: That is fine. Secondly, you talked about the 27 percent delayed neutrophil recovery, was that to baseline or a neutrophil count greater than 500?

DR. SCHECHTER: That is to baseline. I think in your review I have a percentage and next to that is the number of patients who still had grade 4 neutropenia. I don't have my review here but if you look in that table, the first table for each one, it shows you the number of patients who still had grade 3/4 anemia, patients who had grade 4 neutropenia or grade 4 thrombocytopenia.

DR. NERENSTONE: I have a question. When a patient was being dose escalated and they had to stay at the 3 mg dose, did that count as a week of therapy, or did the week of therapy only count when the therapeutic 30 mg dose was started?

DR. SCHECHTER: No, therapy was counted from the first day, and the first week a patient might get 5 treatments but then they would go down to 3 times a week as they were gradually escalated up and, really, the way to analyze data is not by weeks of treatment but by number of doses because of the dosing interruptions -- the number of treatments, although that is a very interesting question.

DR. NERENSTONE: Dr. Albain?

DR. ALBAIN: The pharmacokinetic data you presented was interesting in terms of the changing half-life, lengthening of the half-life by decreasing tumor burden, and might that perhaps indicate that you could devise some more patient specific dosing that might

ameliorate this protracted neutropenia?

DR. SCHECHTER: I suspect that is probably true.

DR. NERENSTONE: We the sponsor also speculate about that at this time or later?

DR. SCHECHTER: Probably they want to speculate later.

DR. NERENSTONE: If the sponsor would like to respond to Dr. Albain's question, I think this would be the time.

DR. SCHECHTER: We don't have an agreement, I will tell you right now.

DR. NERENSTONE: Just identify yourself for the record.

DR. BRETTMAN: I am Lee Brettman from Millennium Pharmaceuticals. Our analysis of the data is very different and I think we need to try to resolve what the differences are coming from because we do not see that kind of increase in half-life. There is a very modest increase in half-life in the analysis that we have done in patients with previously treated CLL from the 005 study.

As to the question about whether dosing should be modified specifically for a patient, I think that you can see that there is a relationship between tumor burden and PK. We certainly agree on that point, and that suggests that that might be a viable option that should be investigated in

the future. However, I think it is only fair to say as well that the 30 mg dose 3 times a week that has been utilized appeared to be effective and, at least in our estimation of the PK, does not accumulate over time.

DR. SCHECHTER: Well, I think that your studies did show it went from 30.2 hours to over 80 hours and that is what I wrote in the introduction.

DR. BRETTMAN: Yes, that data was actually from a very limited number of patients with previously untreated CLL. So, the N at baseline was 1 and then there were only 3 or 4 patients that were evaluated. But we can straighten this out in discussions, I am sure.

DR. SCHECHTER: I think that is an excellent question and I think it may help very much to reduce toxicity.

DR. ALBAIN: What was the median time to maximum response?

DR. SCHECHTER: Oh dear, Lee, do you know the median time to maximum response? Well, yes, the median time to objective response was 1.6 months. Yes, we have just a little bit of difference. It was 1.6 months. It was longer on the other two studies and it was probably a function of the interval of assessment with the 6 week cycle and the 8 week cycle so that patients weren't assessed as often.

DR. NERENSTONE: Dr. Kelsen?

DR. KELSEN: There is a 10-15 percent treatment-related mortality with this agent in this population, and I know we don't have comparative data but could you give us a feel or could the experts on the committee give us a feel for what would the treatment-related mortality be expected with other therapies as third-line treatment? In other words, is this a striking thing to see in certain diseases. Is this unusually out of the range?

DR. KEEGAN: Actually, we did look at the data that supported approval of fludarabine for second-line therapy which was based on two single-arm studies. One was single center; one was multi-center and involved a total of 79 patients in those two single-arm studies. But there was data summarizing 133 patients with CLL and it was reported that there were 29 deaths on study. So, it is in a similar range but it is very hard to predict because these are obviously different studies at different times.

DR. KELSEN: I was going to ask about the fludarabine data and then I realized that this is a population that has already seen fludarabine so that 10-15 percent might not be so striking, and I am just trying to get a feel for how much that affected your overview on this.

DR. KEEGAN: I think any death on study affects --

DR. SCHECHTER: I think I was really, really concerned about deaths on study in patients who had no

evidence that they had progression of their disease but their marrow was really hypoplastic. While somebody may have assigned the progressive disease, I couldn't prove progressive disease and I began to realize that there was really a treatment-related mortality that is of concern, of grave concern. After all, it isn't saying that, you know, when you go from a single arm to a comparative study your response will drop in half. We have a response rate of 33 percent and we have a mortality rate of 15 percent in a single-arm study. I think that there is probably a reason for concern.

DR. SIEGEL: Let me just clarify a couple of numbers. The rate of death on this study was 28/93 or 30 percent. So, in terms of a comparison that you might make to somewhat different populations --

DR. SCHECHTER: We can --

DR. SIEGEL: in the fludarabine study, that rate was 29/133 or I get about 22 percent. This is 30 percent but --

DR. SCHECHTER: We can --

DR. SIEGEL: Let me finish please. The 15 percent is the proportion of deaths that the reviewer believes are more likely treatment related than disease progression related, and since many of the treatment-related deaths and disease-related deaths are going to be from the same cause,

you might say that those numbers have to be looked at with some question as to how precise or accurate they might be.

DR. NERENSTONE: Dr. Przepiorka?

DR. PRZEPIORKA: There is a statement in the review indicating that there was perhaps an association between toxicity and dose, cumulative dose. Could you speak to that a little bit, or PK?

DR. SCHECHTER: There was no formal PK done on this study. It did appear that toxicities do increase as patients continue on study. I did include the number of doses of Campath on the review sheet of serious adverse events to show you there was a distribution, and certainly there was an increased incidence of infections and adverse events right after discontinuation from study. Does that answer your question? I didn't have time to correlate -- it would be possible to look at the number of doses and serious adverse events but it is in there. I didn't do any formal analysis.

DR. NERENSTONE: Dr. Redman?

DR. REDMAN: I have a question and I guess I am going to direct this to Dr. Keating. It has to do with toxicity and relating the opportunistic infections. In a second-line treatment, if you want to choose fludarabine, what is the incidence of opportunistic infections on treatment?