DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

DAY ONE - MORNING SESSION

Wednesday, September 6, 2006

8:00 a.m.

Hilton Silver Spring
Silver Spring, Maryland

PARTICIPANTS

Maha H.A. Hussain, M.D., FACP, Acting Chair
Johanna M. Clifford, M.Sc., RN Executive Secretary

MEMBERS:

Ronald M. Bukowski, M.D.
James H. Doroshow, M.D.
S. Gail Eckhardt, M.D.
Michael C. Perry, M.D.
Maria Rodriguez, M.D.
David Harrington, Ph.D.

CONSUMER REPRESENTATIVE:

Pamela J. Haylock, RN

NON-VOTING INDUSTRY REPRESENTATIVE

Antonio J. Grillo-Lopez, M.D.

CONSULTANTS (VOTING):

Joao Ascensao, M.D., Ph.D.
Michael Link, M.D.
Gary Lyman, M.D.

PATIENT REPRESENTATIVE (VOTING):

Diane T. Mackinnon

FDA STAFF:

Richard Pazdur, M.D.
Robert Justice, M.D.
Ramzi Dagher, M.D.
Robert Kane, M.D.
Shenghui Tang, Ph.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. HUSSAIN: If I may ask you to take your seats, please? I am also going to ask you to please switch off your beepers and cell phones.

I want to welcome you this morning to this ODAC session. My name is Maha Hussain, from the University of Michigan. I will be the acting chair for the day. We have two separate presentations. This morning's presentation will be from Genta regarding Genasense in CLL.

Before I begin with the presentations I would like to ask the committee to introduce themselves and I will begin with Dr. Pazdur, on my left.

DR. PAZDUR: Richard Pazdur, Office Director.

DR. JUSTICE: Robert Justice, Division Director.

DR. DAGHER: Ramzi Dagher, medical team leader.

DR. KANE: Robert Kane, medical reviewer.

DR. TANG: Shenghui Tang, statistical reviewer.

DR. ASCENSAO: Joao Ascensao, consultant.

MS. MACKINNON: Diane Mackinnon, patient consultant.

MS. HAYLOCK: Pamela Haylock, consumer representative.

DR. LYMAN: Gary Layman, consultant.

DR. HUSSAIN: Maha Hussain, medical oncology.

MS. CLIFFORD: Johanna Clifford, designated federal official to the ODAC, FDA.

DR. HARRINGTON: David Harrington, statistician.

DR. LINK: I am Michael Link, pediatric oncologist.

DR. RODRIGUEZ: Maria Rodriguez, medical oncologist.

DR. BUKOWSKI: Ronald Bukowski, medical oncologist.

DR. PERRY: Michael Perry, medical oncologist, hematologist.

DR. GRILLO-LOPEZ: Antonio Grillo Lopez, I

am a medical oncologist and the industry representative on this committee. I do not receive any compensation from industry for my participation in these meetings.

DR. HUSSAIN: Thank you. I want to now invite Johanna Clifford, the executive secretary, to discuss the conflict of interest.

Conflict of Interest

MS. CLIFFORD: The following announcement addresses the issue of conflict of interest, and is made a part of the record to preclude even the appearance of such at this meeting:

Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest, with the following exceptions:

In accordance with 18 USC 208(b)3, a full waiver has been granted to Dr. Ronald Bukowski for his unrelated consulting for two competitors for

which he receives less than $5,001 per year per firm. Also, for his unrelated speakers bureau activities for a competitor he receives less than $5,001 per year.

Dr. Maha Hussain has been granted waivers in accordance with 18 USC 208(b)3 and 21 USC 355(n)4 for her stock ownership in three competing firms. Two are worth less than $5,001 per firm and a third is worth between $50,001 to $100,001.

In addition, in accordance with 21 USC 355(n)4, waivers have been granted to the following participants: Pamela Haylock for her spouse's ownership of stock in a competitor worth, $5,001 and $25,000. Because this stock interest falls below the de minimis exception allowed under 5CFR 2640.202(b)2, a waiver under 18 USC 208 is not required. Dr. Michael Perry for his ownership of stock in a competitor. This stock is valued between $5,001 and $25,000. Because this stock interest falls below the de minimis exception under 5CFR 2640.202(b)2, a waiver under 18 USC 208 is not required.

Waiver documents are available at FDA's dockets web page. Specific instructions as to how to access the web page are available outside today's meeting room, at the FDA's table. In addition, copies of all waivers can be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 in the Parklawn Building.

We would also like to note that Dr. Antonio Grillo-Lopez has been invited to participate in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Grillo-Lopez' role is to represent industry interests in general and not any one particular company. Dr. Grillo-Lopez is a retired employee of the Neoplastic Autoimmune Disease Research Institute.

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

exclusion will be noted for the record.

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

DR. HUSSAIN: I would like now to invite Dr. Pazdur, who is the Director of the Office of Oncology Drug Products, to give his opening remarks.

Opening Remarks

DR. PAZDUR: In chronic lymphocytic leukemia the FDA has used the overall response category, including complete responses, nodular partial responses and partial responses, to characterize the response rate for therapies currently available.

For the 1991 approval of Fludera two trials were conducted. Overall response rates were 32 percent and 48 percent, with durations of 1.25 and 1.75 years respectively. These responses were associated with improvement in hemoglobin and

platelet counts substantiating clinical benefit.

For the 2001 accelerated approval of CamPath, three trials were submitted and the overall response rates were 33, 21 and 29 percent, with durations of 7, 7 and 11 months respectively. Both Fludera and CamPath were tested as single agents and all of the response rates reflect the single agent activity.

For randomized trials conducted in CLL, the FDA has recommended to sponsors that either time-to-progression, TTP, or progression-free survival, PFS, be used as primary endpoints. The FDA believes that a statistically significant, clinically meaningful improvement in TTP would constitute clinical benefit leading to regular approval of a drug in CLL.

In contrast to the above approvals where activity was demonstrated in single-arm trials, the sponsor of the current submission has provided a randomized add-on trial, adding Genasense to Fludera plus cyclophosphamide. The trial randomized patients either to the two-drug

combination of Fludera plus cyclophosphamide or to the three-drug combination of fludarabine, cyclophosphamide plus Genasense. This randomized trial allows us to examine not only response rate analyses, but also allows analysis of TTP. A randomized trial provides a more accurate characterization of Genasense adverse event profile. Most importantly, the study design allows us to isolate the contribution of Genasense to the response rate of the three-drug combination.

The sponsor's protocol-defined endpoint was response rate, defined as complete response and nodular PR. The sample size calculation was based on the assumption of attaining a 44 percent response rate for the Genasense-containing three-drug treatment. A 20 percent improvement in this response rate by the addition of Genasense to the standard drug combination was projected.

The results of the trial demonstrated a 10 percent improvement in the protocol-defined response rate of complete response plus nodular PR with the addition of Genasense to the Fludera plus

cyclophosphamide. This finding was statistically significant. However, when response was defined as complete response plus nodular PR plus PR, the endpoint used in other CLL approvals, no improvement was demonstrated with the addition of Genasense to Fludera plus cyclophosphamide, 41 percent versus 45 percent. There was no improvement in overall response duration, TTP, survival or in any other planned secondary analyses.

The FDA considers the composite endpoint of symptom-free time presented by the sponsor in their briefing documents as exploratory. The clinical trial was not blinded, the analysis was not pre-specified, and the symptom-free time was calculated by adding discontinuous time. The addition of Genasense to Fludera plus cyclophosphamide regimen is associated with increased toxicities, including increased numbers of severe and serious AEs, and more nausea, vomiting, fever, fatigue, blood transfusions and bleeding.

Genasense administration requires an indwelling central venous access device for continuous intravenous infusion, and an external infusion pump or hospitalization for seven days monthly. Infusion catheter-related complications occurred in 16 percent of the Genasense patients, including catheter infections and venous thrombosis, compared to three percent in the control arm.

The sponsor has requested the agency to consider the current application under the accelerated approval regulations. Although endpoints may differ for these two types of approvals, regular and accelerated approvals, both should have substantial evidence of safety and efficacy demonstrated in adequate and well-controlled trials. The plurality of the word "trials" provides the basis for the FDA to request more than one trial to confirm safety and efficacy.

Prior to the demonstration of clinical benefit, the agency may grant approval on a surrogate endpoint under accelerated approval

regulations. This surrogate endpoint must be, quote, reasonably likely to predict clinical benefit. Hence, based on the mature data from the study, the FDA believes that accelerated approval in this situation is problematic since the protocol-defined response rate in this completed, randomized study did not predict an improvement in time-to-progression or other evidence of clinical benefit.

In accepting single trials for oncology approvals, the agency has relied on secondary endpoints to provide corroborating efficacy evidence. The addition of Genasense to fludarabine plus cyclophosphamide did not improve any secondary endpoints-overall response rates, defined as complete response, nodular PR, and partial responses, time-to-progression or any clinical benefit elements. Although the primary endpoint analysis was statistically significant, the clinical significance of this 10 percent improvement in complete plus nodular PR must be viewed both in the risk/benefit analysis of the

entire population exposed to the drug, and in the context of the totality of the evidence available. Thank you.

DR. HUSSAIN: Thanks. The way things will work out now is that the sponsor will have their presentation and at their conclusion the FDA will have their presentation. We will then follow that with questions from the committee. I would like to invite the sponsor for their presentation, Dr. Loretta Itri.

Sponsor Presentation

Introduction

DR. ITRI: Madam Chairman, members of ODAC, ladies and gentlemen, good morning.

[Slide]

On behalf of Genta, it is my pleasure to introduce today's proceedings regarding the use of Genasense for the treatment of patients with relapsed or refractory chronic lymphocytic leukemia.

[Slide]

Genasense is a novel, first in class,

therapeutic agent that augments the activity of chemotherapy by stimulating apoptosis through downregulation of Bcl-2.

[Slide]

Genasense is an 18-base strand of modified DNA. Sulphur is substituted for one of the oxygen atoms in each of the phosphate groups in the DNA backbone and renders the molecule more resistant to degradation. Genasense selectively targets Bcl-2 RNA to decrease the production of Bcl-2 protein. As partially summarized in our briefing document, Genasense has demonstrated downregulation of Bcl-2 in patients, and particularly in lymphoid cells.

[Slide]

The sponsor is seeking approval for the following indication: Genasense in combination with fludarabine and cyclophosphamide is indicated for the treatment of patients with relapsed/refractory CLL. Genasense has been granted both orphan drug and fast track designation by the FDA in recognition of the major unmet medical need in this life-threatening disease.

[Slide]

This is the agenda for today's sponsor presentation. Following my brief remarks, Dr. Michael Keating, from M.D. Anderson Cancer Center, who is one of the most widely published researchers in the field of CLL, will present an overview of the current management of relapsed/refractory CLL. Following Dr. Keating's presentation, I will return to present our data regarding the safety and efficacy of Genasense in this indication.

Then, Dr. Susan O'Brien, a well-known expert in the field of hematologic oncology, from M.D. Anderson Cancer Center, who has served as an advisor to ODAC in past deliberations on leukemia drugs and clinical trial endpoints, will present her assessment of the risks and benefits associated with the use of Genasense in CLL. Finally, I will return for brief concluding statements.

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In addition to our speakers, we have with us today a distinguished group of expert advisors, including Dr. Kanti Rai, Dr. Tony Tolcher, Dr. John

Bennett, Dr. John Reed, Dr. Richard Kay, Dr. Gary Koch and Miss Margaret Green, who are available to the committee to address any questions in their field of expertise.

[Slide]

ODAC is being asked for advice regarding the accelerated approval of Genasense in the CLL indication. Accelerated approval requires the identification of a surrogate endpoint from well-controlled clinical trials that are reasonably likely to predict for clinical benefit. At the ODAC meeting on accelerated approvals, in March, 2003, it was agreed that durable, complete response could serve as an appropriate surrogate in the situation of a life-threatening disease when a new drug provides benefit over existing therapy. Post-marketing studies should be conducted to verify the clinical benefit. Data will be presented today which we believe fulfill all of these criteria and provide compelling evidence for the clinical benefit associated with the use of Genasense.

I would like now to ask Dr. Michael Keating to come to the podium.

Relapsed/Refractory CLL

DR. KEATING: Thank you, Dr. Itri.

[Slide]

Members of the committee, members of the FDA, ladies and gentlemen, it is actually a pleasure to be with you today to share some of the insights that we have gained over the years into the situation of relapsed and refractory chronic lymphocytic leukemia.

[Slide]

Bcl-2 over-expression is almost a universal event in CLL, leading to the long-lived nature of the CLL lymphocytes. As you can see here, there are eight independent studies that demonstrate that almost all patients with CLL have over-expression of Bcl-2 protein. This makes it a very relevant target to see if we can inhibit the effect and lead to apoptosis occurring in the CLL cell population.

What I would like to emphasize with this

slide is that we are not talking about the kind of gentler form of CLL when patients are newly diagnosed and many of them have a very indolent course. These are patients who have already failed the "watch and wait" criterion or have had very advanced and progressive disease at the time of initial presentation. These are patients that have already been treated. They have progressed. Many of them have had two or three other attempts at induction therapy and have reached the point where investigational therapy is necessary.

The prognosis is about 30 months on average in most of the clinical trials that have been conducted. The patients are symptomatic with the B-symptoms commonly associated with poor prognosis lymphoma and, in addition, many of these patients have very bulky lymphadenopathy and splenomegaly. The major problems that occur as the disease progresses are that there is cumulative marrow damage from the treatment that is given, and also the presence of CLL per se. This is also the situation with impaired marrow function so that

most of the patients in this category will actually end up dying of complications of infection associated with active disease and not dying of coincidental causes which you commonly see in the initial therapy.

As you are aware, the alkylating agents were grand fathered in because they were in common usage in the drugs that have been through the ODAC committee and the FDA approval. They have been fludarabine, and repeating fludarabine over and over is a diminishing return situation. Alemtuzumab has been approved for fludarabine refractory disease, which is a very serious situation with a median survival of approximately 9-10 months at the time that alemtuzumab was approved. The most commonly used drug in the relapse/refractory CLL in the United States is rituximab, a drug which, as a single agent, had about a 10-15 percent partial response rate in CLL but it is widely used. Obviously, we need to explore investigational agents to improve the outcome of patients with relapsed or refractory

disease.

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There has been a change in emphasis in CLL over time. When we had agents such as chlorambucil doctors and patients were happy to get partial control of their disease, and in the recent comparative studies using the NCI working group criteria, Dr. Rai demonstrated that the complete remission rate was less than five percent, and this has been confirmed with a number of studies around the U.S. and Europe. So, it was quite nice to get some shrinkage in those and improvement in the white cell count, and occasionally there would be improvements in the hemoglobin and platelet count.

But now there is much more emphasis on the complete eradication of tumors so that patients can no longer be demonstrated to have enlargement of lymph nodes, spleen, etc. The symptoms tend to go away with this, as will be demonstrated in Dr. Itri's presentation, and suppression of normal blood counts actually returned to relatively normal ranges. From a patient's point of view, it is much

better to have long-lasting situations where their disease is inactive rather than a shorter remission duration, and this is true in all of oncology as you are aware.

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So, there have been two approvals, and Dr. Pazdur mentioned this in the introduction. I was able to be part of the presentation for fludarabine when there was a SWOG study, an M.D. Anderson study, and it was approved on two bases. One was that there was no other option after alkylating agent refractoriness was demonstrated. The second feature was that there were objective improvements in hemoglobin and platelet counts, which are features of development of complete or nodular partial remission when the counts returned to normal.

We can also see that this was a high risk treatment, and it is not a high risk treatment in previously untreated patients but, as the disease evolves, all treatments become higher risk and many of the patients either died on study or developed

serious life-threatening infections during that time.

Alemtuzumab, when it came up for evaluation, was again a non-comparative trial, non-randomized. Dr. Pazdur has rightly mentioned that there were three studies that were grouped together. The first study, the 93 patients, was the prospectively gathered data. The secondary data from studies that Glaxo-Wellcome developed were largely for safety and there was inadequate collection of data to establish objectively what the responses were. So, for more than half of the patients the response couldn't be evaluated. Indeed, this was again a serious, life-threatening situation and, as you can see, the response duration was actually very, very short overall. Partly it was a short response duration because almost all of the responses were partial responses. There were only two patients out of the 93 that actually got a complete remission of their disease.

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So, what are the criteria that have

evolved over time? The CR and nodular PRs have been grouped together because in the first iteration of the NIC working group guidelines the presence of these microscopic nodules in the bone marrow biopsy, which was the only demonstrable evidence of disease at that time, might have been considered normal lymphoid nodules which occur in elderly patients and there was no technology available at that time to demonstrate whether they were leukemic or not. But, as you can see, there is eradication in both CR and nodular PR of measurable tumor. The blood counts returned to relatively normal situations, and the only difference between the two is the presence of microscopic nodules in the bone marrow biopsy.

On the other hand, there is a much lower hurdle that has to be achieved to achieve partial response. There is a relatively modest decrease in the tumor volume. You only have to get 50 percent reduction in the lymphocyte count, which is relatively easy to achieve. And, the improvement in marrow function is very, very easily obtained

because you only have to have a 50 percent improvement in one parameter of the granulocytes, platelets and hemoglobin and there is no marrow evaluation that is described. So, in the second iteration CR and nodular PR were considered to be fairly similar and partial response was considered to be very different.

[Slide]

On the left you will see what happens to the marrow at the time that these patients are presenting with their symptoms. With progressive disease you actually have packing of the bone marrow with CLL lymphocytes. After treatment you can get to the point where, on the right-hand side, you can see that in the CR there is normal hematopoiesis that develops. This slide was developed by Dr. John Bennett as part of the evaluation of this study, and there are no clear nodules which are present. In the middle you will see that there is recovery of normal hematopoiesis but there is a well-defined nodule which is present, and that is the extent of tumor in

patients that have nodular partial response.

[Slide]

Now, what does this mean? Well, in the previously untreated group, in the graph on the left, you can see that the survival of the complete responders and nodular partial responders is very, very similar in a publication that we looked at for long-term follow-up of these patients. As you can see, the follow-up is now getting out to 10 years. And, there is a very significant difference between CR and nodular PR compared to the PR group, and a very modest improvement in PR over the patients that had stable disease or failed to respond.

Now, when we look at the relapsed/refractory group of patients, published by Dr. Weider, using the fludarabine/ cyclophosphamide/rituximab regimen, or F/C/R, the same event occurs. There is a very similar survival, not significantly different, and a very significant difference between either of these outcomes with the partial response group of

patients but in this situation partial responders are significantly superior to the patients that haven't achieved a PR.

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So, we are dealing with a life-threatening situation. Patients are aware, as time goes by and their disease keeps coming back with shorter intervals in between, that this is a very frightening situation for them. They are faced with a situation where they have persistent pancytopenia. They are at risk of infection. They are on a number of prophylactic antibiotics, etc. They are usually very symptomatic at the time, as will be demonstrated in the characteristics going onto this study. They have been refractory to conventional therapy in one or other situations commonly, and they are in search of something that will not only improve their outcome but improve their health for a reasonably long period of time.

Most of the problems that are occur are that you have this persistent pancytopenia or

cytopenia, and persistent immunosuppression which occurs, putting these patients chronically at risk of developing life-threatening infection.

So, based on this, it has been our experience that grouping of CRs and nodular partial response is the optimal outcome for patients because of its impact on probability of longer-term survival. Because we have 8,000 individuals in the United States that are in the relapsed/refractory situation, and almost all of these patients are going to die of complications of their CLL, this is certainly an unmet need and we are in a real situation where we need to develop new therapies which will improve the outcome of these patients. Thank you very much for your attention.

Clinical Efficacy/Safety

DR. ITRI: Thank you, Dr. Keating.

[Slide]

The Genasense program in CLL consisted of two studies. The first was a Phase 1-2 single-agent, dose-finding and efficacy study. The second was a randomized Phase 3 study. Both

studies were conducted in relapsed or refractory CLL patients. These disease specific findings are supported by a safety database of more than 1,000 patients who have received Genasense either in single-arm studies or in randomized trials in a variety of different types of cancer.

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In the Phase 1-2 study doses ranging from 3-7 mg/kg were evaluated using a 5-7 day continuous IV infusion. At doses higher than 3 mg/kg a dose-limiting first cycle reaction, consisting of fever, rigors, hypotension, as well as thrombocytopenia with or without tumor lysis was observed.

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At the established Phase 2 dose of 3 mg/kg single-agent Genasense demonstrated clear anti-tumor activity. In addition to the two patients who achieved a PR according to strict NCI working group criteria, approximately half of these very heavily pre-treated patients demonstrated a reduction in either circulating CLL cells, lymph

nodes or splenomegaly.

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Based upon the results obtained in the Phase 2 study, we conducted study GL303, the first randomized trial ever conducted in advanced CLL to be performed in support of a licensing application.

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This was a multicenter, multi-national trial in which 241 patients were randomly assigned on a 1:1 ratio to receive either flu/cy chemotherapy with Genasense or the same chemotherapy alone.

Before randomization patients were stratified on the basis of prior response to treatment, including refractoriness or relapse status after prior fludarabine therapy; the number of prior regimens, that is, one or two or greater than three; and whether the duration of response to the last therapy had lasted more or less than six months. As stated in the FDA briefing package, this protocol was amended six times. No patients were treated on the first version. The

majority of the remaining changes were to update the safety warnings, and the last revision was made to increase the follow-up from two to three years.

[Slide]

Definitions of responsiveness to prior fludarabine are outlined on this slide. Patients were required in this study to have received at least one prior fludarabine-containing regimen and at least two prior cycles of fludarabine. A patient was considered refractory if he failed to achieve at least a PR during the last fludarabine treatment or if a PR was achieved but lasted less than six months. A patient was called relapsed if, after the last treatment with fludarabine, they achieved at least a PR that lasted at least six months.

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Patients randomized to Genasense received the drug as an outpatient for seven consecutive days by continuous IV infusion using a portable ambulatory infusion pump. After four days of Genasense alone fludarabine and Cytoxin were given

together with Genasense for the following three days. Patients randomized to the chemotherapy alone received the same doses of fludarabine and Cytoxin on the same daily times three schedule. Cycles were repeated every 28 days. Patients were reevaluated for a response on a monthly basis while they were receiving therapy and every two months thereafter until time of progression, for up to a maximum of three years from the date of randomization.

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The prospectively defined primary objective of the study was to compare the relative proportion of patients on each arm who achieved a major response. Major response in this study was defined as a complete response or a nodular partial response.

Responses were classified using strict NCI working group criteria and were determined after blinded central review of both clinical parameters and bone marrow. In addition to standard criteria, in order to qualify as a CR or an nPR in this

study, the protocol also required normalization of any abnormality determined on baseline CT or ultrasound examinations. Secondary objectives included response duration, overall response, time-to-progression, overall survival, clinical benefit and, of course, safety.

The sponsor was blinded to study arm, patient identification and all results during the study. Additionally, the database was maintained off site by an external contract research organization.

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All patients were assessed for response and for progression of disease by central blinded review. Dr. Gregory Threatte, Chairman of the Department of Histopathology, SUNY Upstate Medical University, and national morphology reviewer for CALGB, performed all histopathologic reviews of bone marrow samples.

Dr. Kanti Rai, author of the Rai staging system for CLL, assessed all patient data for clinical response and disease progression according

to NCI working group criteria, as well as CT and ultrasound findings. Dr. Rai was also an investigator in the study.

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As observed by the FDA in their briefing document, most baseline variables were well balanced. There were no differences observed for age, gender or race. Baseline characteristics involving laboratory and physical examination factors were similarly well balanced. There were a few small imbalances and, although not shown on this slide, there were a greater number of patients more than age 75 on the Genasense arm. The median time from diagnosis was longer by approximately one year in the Genasense arm but this was not statistically significant. There was also a slight increase in the number of patients who had a prior splenectomy on the Genasense arm.

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Individual signs and symptoms characterizing active disease were prospectively captured on a case report form and were well

balanced between arms. Although the individual signs and symptoms were relatively evenly distributed, when taken together there were statistically significantly more patients on the Genasense arm with evidence of active or symptomatic disease.

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A presentation of patients according to the stratification factors reveals that the majority of patients, approximately 60 percent, were refractory to fludarabine at the time they entered the study. The average number of prior regimens received by these patients was three. More than half of the patients on study had a response to their last treatment that lasted less than six months in duration.

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When examining prior chemotherapy received by these patients, we can see that once again good balance was achieved. The primary efficacy endpoint of this study was achieved.

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The addition of Genasense to the standard regimen of fludarabine and cyclophosphamide resulted in a 17 percent rate of CR and nPR as compared to only seven percent for the control arm. This difference is statistically significant, with a p value of 0.025 by continuity-corrected chi-square test. This difference remains significant if one chooses just to look at the CRs, in which case the result is again significant, with a p value of 0.03 by Fisher's exact test. These results have been independently confirmed by the FDA.

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Importantly, in addition to a significantly greater number of major responses, there was also a significant difference noted in the durability of these responses. With two years of minimum follow-up, only 5/20 or 25 percent of patients on the Genasense arm had relapsed. This compares with 6/8 or 75 percent of patients on the control arm. The median duration in the F/C arm was 22 months but has not yet been reached in the

Genasense arm and is estimated to exceed three years. This difference is significant, with a p value of 0.031.

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The duration of response during and after completion of chemotherapy is shown here. Each bar represents a CR or nPR patient. The blue section on the bottom denotes the period of time from the start of remission while the patient was still receiving chemotherapy. The yellow designates the post-chemotherapy duration of remission. As you can see, the post-therapy durations of response are quite long. The median duration of remission post-chemotherapy in the Genasense arm has not yet been reached, but it is expected to exceed 31 months. This compares very favorably with a median of only 20 months in the control arm. Importantly, as you can see from the crosses on the top of the bars, most of the responses in the Genasense arm are ongoing as of the last evaluation.

[Slide]

Improvement in the incidence of major

response was distributed across all pre-specified strata and was numerically superior for patients who received Genasense in all subsets. In patients who had retained their sensitivity to chemotherapy as manifested by either their fludarabine relapse status, the number of prior regimens received, or the ability to retain a response to their last therapy for greater than six months, the benefit for the Genasense treatment population was more than four times that of the control.

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The overall response rate was similar between the two groups. Response duration overlapped initially but a separation between the curves becomes evident at 16 months, and there is then a trend that favors the Genasense group. This is being driven primarily by the CR and nPR population. [Slide]

At two years, time-to-progression was not statistically significant between arms. But although the overall time-to-progression curves were not different, the percentages of patients

with a progression-free duration of two years or more were remarkably greater for the CR and nPR population. Only a few patients with PR or less had not progressed by two years of follow-up.

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With three years of follow-up, overall survival for the ITT population was not different between the arms. But, like TTP, at three years survival correlated with best response. Only eight percent of patients with less than a PR survived for longer than three years, as did 37 percent of the PRs. In important contrast, 61 percent of the CR/nPR patients were still alive at three years of follow-up.

[Slide]

This is the first randomized trial in a salvage setting in which symptom data were routinely and prospectively collected. Although, as noted by FDA, there were no between arm differences for individual symptoms, it is, nevertheless, clear that major symptom benefit, as measured by the clearance of all of these

predefined symptoms for a period of at least six months in patients who had any of the symptoms on this slide at baseline is associated with the achievement of a CR or nPR. Almost all patients in this category, but virtually no patient with less than a PR, exhibited meaningful benefit. PRs are associated with an intermediate degree of benefit. That is clear. But they are not durable.

With additional follow-up, 83 percent of CR/nPR patients achieved at least a year of symptom-free status, whereas only 36 percent of PRs remained symptom-free for the same period of time. All of these findings are significant and support the appropriateness of CR and nPR as the primary endpoint in this study.

[Slide]

Turning now to safety, the most common grade 3 or grade 4 events that occurred during study are noted here. As a single agent, Genasense is known to produce flu-like symptoms as well as nausea. Therefore, it is not surprising that these events are occurring with greater frequency in the

Genasense arm. Please note that there was no meaningful increase in grade 4 events.

[Slide]

Neutropenia and anemia of a grade 3-4 nature were not different between arms. The incidence of opportunistic infection and the percentages of patients who received antibiotics and growth factors were similar across treatment arms. There was a higher incidence of grade 3-4, and mostly grade 3, thrombocytopenia in the Genasense arm with an increased incidence of platelet transfusions.

[Slide]

Platelet counts by cycle with median and inter-quartile ranges are shown here, and it is clear that the major difference in platelet count appears in cycle one. Recovery to baseline for all grade events of thrombocytopenia was similar between arms whether patients had baseline counts above or below 100,000. Recovery was equally longer between arms when patients entered the study already thrombocytopenic.

[Slide]

As previously stated, platelet transfusions were increased in the Genasense arm and occurred primarily in cycle one and in patients with lower baseline counts. There are more platelet transfusions given without associated bleeding in the Genasense arm, again, primarily in cycle one, which probably reflects a lower threshold for transfusion with a new drug. The number of platelet transfusions administered for low platelet counts associated with bleeding was very low and similar between groups.

[Slide]

Importantly for this significantly myelosuppressed population, neutrophil counts and hemoglobin were not adversely affected by the addition of Genasense. The curves for median neutrophil count and hemoglobin by cycle are shown on this slide and are virtually superimposable.

[Slide]

Overall, adverse events which occurred during study or within 30 days of the last dose on

study and led to discontinuation were balanced. Adverse events with an outcome of death were also balanced, with the exception of two deaths in the Genasense arm which were related to a first cycle infusion reaction in one patient and tumor lysis in another patient, both occurring in cycle one.

[Slide]

Infusion reactions are increasingly associated with active drugs that are commonly used for CLL. With Genasense these reactions are largely confined to the first treatment cycle and they can be ameliorated by vigilant observation and hydration. Timely intervention with antipyretics and antiemetics are warranted in order to prevent both sensible and insensible fluid loss.

[Slide]

Hospitalizations for grade 3-4 adverse events were increased in the Genasense arm, again primarily in cycle one. The specific adverse events leading to hospitalization with an increase greater than three percent are shown here. Febrile neutropenia was the most commonly cited reason for

admission, although documented infections such as sepsis and pneumonia were very well balanced. Since Genasense is known to cause fever, it is not unlikely that the higher incidence of febrile neutropenia is at least in part due to drug-related fever and not infection. Actual days in hospital support this hypothesis since approximately 25 percent of patients were hospitalized for less than three days and 50 percent for less than a week.

[Slide]

Because administration of Genasense requires an indwelling catheter related adverse events were increased. The two major complications associated with catheters are infection and thrombosis. No grade 4 events occurred for either complication. There were two more related hospitalizations due to infection but no increase in treatment interruptions. Two grade 3 thrombotic events, both involving the upper extremity, were noted in the Genasense arm.

[Slide]

Other complications commonly associated

with advanced CLL including opportunistic infection, autoimmune hemolytic anemia, autoimmune thrombocytopenia and second malignancies were not different between the arms of this study.

I would like now to ask Dr. Susan O'Brien to come to the podium for her summary of risk/benefit.

Risk/Benefit

DR. O'BRIEN: Good morning.

[Slide]

I would like to lead off by saying that I was the primary investigator and, in fact, treated many of the patients on the Phase 1 trial of Genasense. So, I am very familiar with this agent both in terms of its side effects and activity.

In my discussion I would like to try and put the data that you just heard into perspective in terms of how does it compare to data from other CLL trials, and to assess for you the risk/benefit ratio. So, from my discussion, the clinical significance of adding Genasense to chemotherapy will be established.

[Slide]

Let's start with some specific risks. As you just heard, thrombocytopenia was increased in the Genasense arm and this was associated with more platelet transfusions but no significant increase in bleeding. As noted on the cycle by cycle analysis, it was mostly confined to the first cycle of chemotherapy, and was also more common in patients entering the treatment with thrombocytopenia.

But I would like to point out that although the median with the Genasense is significantly lower, that median platelet count is 80,000 which I think would be a pretty acceptable platelet count to most oncologists.

[Slide]

As you heard, Genasense-induced tumor lysis was seen in two patients on this trial. Paradoxically, that is not that unattractive a side effect to a leukemia physician because that tells us that we have a very active agent, and most leukemia physicians are very well versed in

prophylaxing and treating tumor lysis.

Infusion reactions were dose-limiting on the Phase 1, but when we used the MTD that we established of 3 mg/kg/day on the current randomized trial the incidence was only two percent. These kind of infusion reactions are seen with other drugs that we frequently use in CLL, such as rituximab and alemtuzumab where, in fact, the incidence is markedly higher than this. Again, just like tumor lysis, the leukemia physicians are very well versed in prophylaxing and dealing with this type of side effect.

[Slide]

In contrast, a very important point is that Genasense did not worsen neutropenia. The reason that is important is that the major cause of morbidity and mortality in patients with CLL receiving chemotherapy are myelosuppression and infections. So, if we can add in an agent that increases the major response rate, without increasing myelosuppression and its concomitant risk for infection, this is very advantageous.

[Slide]

Let's look at the Genta randomized trial results here compared to the two other drugs that, as you have heard, have been approved for relapse/refractory CLL. Fludarabine approved in 1991 and alemtuzumab in 2001 were both based on single-arm trials with less than 100 patients. In contrast, in addition to the Phase 1-2 data with Genasense, we have the randomized trial which was 241 patients of whom 120 received Genasense. You have already heard about the stringency of the prospectively defined primary endpoint and the fact that that primary endpoint was met and was more durable than in the control arm. Also importantly, if you look at the lower half of the slide you see that of these three trials, the morbidity and the mortality was, in fact, the lowest on the current trial.

[Slide]

Now, the percentage of patients that achieved the primary endpoint of CR and nodular PR was significantly higher in the Genasense arm.

Since we are using this drug to enhance chemosensitivity, some patients with the ability to respond to chemo will have an improvement in the quality of their response. But you also heard that there was no improvement in overall response rates. I don't think that is that surprising. If we are using this drug to enhance chemosensitivity, the obvious implication is that the patient has to have some baseline sensitivity to the chemo in order to get an improvement. So, refractory patients would be very unlikely to be benefitted by such an approach, yet the magnitude of the improvement was significant because the CR/nPR rate was more than doubled.

[Slide]

As predicted, the CR/nPR remission durations were very durable and of a very similar quality on this trial. Note that they are significantly longer than the remission duration associated with partial remission.

[Slide]

I would like to address two points that

were brought up in the FDA briefing. The first is how does the pattern of response compare to that seen in other trials in relapse/refractory CLL? Very importantly, how does the magnitude of improvement with Genasense compare with other trials, and is it clinically important?

[Slide]

Well, we don't have any randomized trials in the relapse setting to look at this data so we are forced to look at single-arm trials that can give us some information. Let's take a look at this trial which is the M.D. Anderson data for flu/cy/rituximab compared to flu/cy, and this is sequential studies, not randomized. What you note is that when we added rituximab to flu/cy the CR/nPR rate increased by 14 percent, from 28 percent to 42 percent. Keep in mind, however, that this is single-center data with no requirement for CT confirmation.

However, if we now add partial responses into the mix we find that the overall response rate is the same and the time-to-progression is the

same. Well, this is exactly the kind of pattern that we are seeing in this trial with the addition of Genasense, namely, that the major responses are increased; that those responses are very durable; but we don't have any effect on overall response rate or time-to-progression. Again, I don't find that surprising because I think until we can get the majority of patients achieving a CR/nPR we are not likely to affect the entire curve.

[Slide]

The second question is about the magnitude of the response. Is it clinically relevant? Again, we have no randomized trials to compare to in the relapse/refractory setting. So, let's take a look at two recent multicenter trials that were published but in front line patients. Both of these trials compared flu/cy to fludarabine and in one trial, for the first time, confirmatory CT scanning was performed.

What we see is that the increase in CR rates in these trials is of a very similar magnitude as the increase that we see with the

addition of Genasense even though that is in the relapse/refractory setting. This is important. We are getting the same magnitude of improvement with Genasense in a relapse/refractory population that we get by adding another drug to fludarabine in a front line, much better population of patients.

[Slide]

The bottom line is that for patients who respond to Genasense the benefit is very clear. PRs are converted into better quality remissions, and that is reflected in the fact that post-chemotherapy remission durations are very long. The median post-chemotherapy remission duration, as indicated in the yellow in this trial, was 31 months in the Genasense arm, comparing very favorably to 20 months in the control arm.

The bottom line is that this shows that Genasense improved responses and improved response durations. The standard of care in CLL is myelosuppressive and immunosuppressive. If we can add in an agent that increases major responses without increasing infectious complications, this

is a genuine advance in the treatment of CLL. Thank you.

Conclusions

DR. ITRI: Thank you, Dr. O'Brien.

[Slide]

As required for accelerated approval, the sponsor has designed a confirmatory trial which is undergoing final special protocol assessment by the FDA. As already agreed with the FDA, this study will be performed in previously untreated patients who will be randomized to receive the combination of fludarabine and rituximab with or without a Genasense infusion. The primary endpoint, also already agreed, will be progression-free survival, with the stratifications as listed on this slide.

The sponsor had planned to initiate this trial prior to ODAC, however, there is still outstanding clarification regarding the methodology of blinded response review. More than 110 sites have already been qualified for this study and earliest results are expected to be available in about five years. Genta remains firmly committed

to the completion of this very important study.

[Slide]

Today you have heard a presentation of substantial evidence from our randomized, well-controlled study GL303 with Genasense combined with standard cytotoxic therapy in patients with relapsed/refractory chronic lymphocytic leukemia, a life-threatening disease with limited therapeutic options.

The Genasense plus flu/cy regimen was clearly superior to flu/cy alone as measured by a statistically significant increase in the centrally reviewed and independently confirmed primary endpoint of CR/nPR rate. In this study the achievement of a CR or nPR was also associated with a significant likelihood of a greater than two-year time-to-progression, a greater than two-year symptom-free duration, and a greater than three-year overall survival. Lastly, the sponsor has designed a large confirmatory trial, which is very near final in the FDA process and which will verify the clinical benefit observed in the current

study.

[Slide]

The FDA reiterated additional guidance on the acceptability of response as a surrogate endpoint at the alemtuzumab ODAC meeting. The association of response and clinical benefit is deemed to be stronger when first the tumor volume is undetectable. In our study, in which the primary endpoint of CR/nPR is associated with undetectable disease, the addition of Genasense significantly improved the number of major responders.

Second, when the reduction in tumor volume is durable. In this study the addition of Genasense was associated with a marked improvement in the durability of major responses.

Lastly, when the reduction extends beyond the period of chemotherapy administration. In this study the addition of Genasense was associated with a remarkable improvement in the duration of response after the completion of chemotherapy for the major responders. We believe that our data

have met all the criteria set forth by the FDA for accelerated approval, and hope that you will also be in agreement.

In closing, I would like to thank the patients, their families, the doctors, the nurses and research professionals, all of whom made this study possible. Thank you very much for your attention.

DR. HUSSAIN: Thank you, Dr. Itri. I would like to invite Dr. Robert Kane to make the case for the FDA presentation.

FDA Presentation

NDA 21-874

DR. KANE: You say "to make the case" but I am not an attorney but I do want to--

(Laughter)

DR. HUSSAIN: I meant to rebut what you heard!

DR. KANE: Thank you--but if called to testify, I shall!

[Slide]

Good morning. I am Robert Kane. I am a

formerly practicing hematologist/oncologist for too many years, and I am presenting the FDA analysis this morning of the NDA before you.

[Slide]

I would like first to recognize our entire review team for this NDA, and I have been asked to leave this slide on for quite some time!

[Style]

I will discuss the statutory requirements for marketing approval; the NCI working group response criteria for CLL; approved drugs, and if you didn't get it the first or second time I am giving you a third time to go over the approved drugs. I will discuss then the activity of the control arm in this study and the FDA analysis of this NDA. We will look at the design, the endpoints, efficacy results and, in particular, what does Genasense add to the chemotherapy all patients are receiving here? We will look at toxicities and present some conclusions.

[Slide]

The requirements for marketing approval

are substantial evidence provided by adequate and well-controlled investigations. These must demonstrate efficacy with acceptable safety, and the ability to generate product labeling. The point that you have heard is that these requirements apply equally for accelerated approval or for regular or full approval.

[Slide]

FDAMA amendments in 1997 provided that one adequate and well-controlled clinical trial and confirmatory evidence may suffice to fulfill this requirement. The FDA guidance on effectiveness, in 1998, indicated that if a single trial is the subject of the application it must be well conducted, internally consistent, and demonstrate a compelling result, statistically strong evidence of an important clinical benefit.

[Slide]

The guidance, in addition, went on to provide some specifics, to clarify: The study should be large and multicenter. There should be consistent efficacy across key study subsets.

Multiple studies, pair-wise comparisons within the study should be consistent in the positive result. Multiple endpoints within the study should also support the positive primary result. Statistically, the study should be very persuasive, a low p value. And, the results should be so compelling that an additional confirming study would be practically or ethically impossible to perform.

[Slide]

Let's turn for a moment to the criteria that have been published by the NCI working group. You have heard these once or twice before. The complete response category indicates patients who have achieved complete remission of their disease including normalization of blood counts and bone marrow, and this condition should persist for at least two months.

The partial response patients have to achieve at least a 50 percent reduction in blood lymphocyte counts and lymphadenopathy with some improvement and return to normalization of their

blood counts, also lasting at least two months.

An additional category, nodular partial response or partial remission, identifies those patients in whom all elements of the CR are present, except that there are persisting lymphoid aggregates in the marrow. I think the important point about this classification is that to some extent it is arbitrary. It was developed by a consensus panel initially in 1988, and was revised in 1996.

[Slide]

These represent very useful criteria to try to classify patients, but I think ultimately we have to remind ourselves that the goal is not just to get someone to a CR, our real goal would be if we could achieve a cure in this disease. These are, in a sense, all surrogate approximations of an outcome and we have to understand a little bit better what is the meaning of achieving a particular level of response as classified here.

[Slide]

The nPR category has remained problematic.

It indicates that there are persisting marrow lymphocytes, aggregates of lymphocytes, and these may represent residual disease, or reactive normal cells, or both. As you have seen and as is most likely, achieving the nPR status provides someone with an outcome that is intermediate between the CR and the PR category.

There are reasons to assert that achieving a PR is also a meaningful result in this disease process. This is not an acute leukemia; this is a chronic lymphoproliferative disorder. But I will ask again what are the clinical outcomes that are achieved by achieving a response category? It is not enough just to say that one has achieved a certain response category. We want to understand what is the meaning of that response. What are the clinical benefits associated with it? How should these be analyzed?

As of a week or so ago, I did not know that we would have the pleasure of Dr. Keating here so I have taken the liberty in my presentation of reminding us of some of the findings that Dr.

Keating has already informed us of.

[Slide]

This is a presentation published in 1998 and I think it already was shown earlier. This indicates the time-to-progression achieved by patients following fludarabine therapy. The conclusion from this paper and this analysis was that the nPR and PR patients appeared to have similar outcomes, as they are outline here. In fact, a statistical analysis was presented, indicating that PR and nodular PRs were not significantly different in outcome, in time to progression but were different from the CRs.

[Slide]

This is another graph, in this case time to treatment failure by response category after F/C/R therapy. As you have seen earlier, and we completely agree that the CR and nPR patients have time to treatment failure curves here, and here is the PR experience, but all of these are quite different than the patients who failed to achieve a response. These type of responder analyses, of

which you have seen several this morning, are not standard statistical presentations. They are not typically used by the FDA but we are flexible.

[Slide]

If we look at recent approvals, as you have also heard this morning, the approvals are based on the NCI working group criteria designating disease states that are achieved in response to treatment. The approvals have been based on overall response rate, and overall response rate consists of the CR plus the nPR plus the PR patients. I have presented some evidence that these should be combined in assessing a treatment effect in CLL, and we will look at additional evidence for that in a moment.

[Slide]

Again as a reminder, the alkylating agents have been with us for many, many years. It is hard to believe 50 hears for Leukeran, Fludera in 1991, alemtuzumab in 2001. As you heard before, the response information that was relevant to the approval of fludarabine in 1991 came from two

studies. Both were single agent and single arm in design. In each case the fludarabine was given after alkylating agent therapy, and the response criteria were all responders. In this case the overall response rate was 32 percent and 48 percent, and the responses were of long duration. In addition, hemoglobin and platelet counts increased in these patients, providing clinical correlation.

[Slide]

With alemtuzumab there were three independent studies, single agent, single arm in design, characterizing the single agent activity. The response criteria again involved all responders. I think it is notable here also that the great majority of responders were PR responders.

[Slide]

We have some information regarding the combination regimen used in the control arm of GL303, fludarabine plus cyclophosphamide. In this report patients were characterized as to whether

they had no prior therapy or alkylating agents or fludarabine and were either sensitive or refractory to the last fludarabine therapy. Response rates ranged from 88 percent to 39 percent depending on the effect of prior therapy. Note here too that the response was provided in terms of the overall response rate.

[Slide]

Turning then to NDA 21-874, one Phase 3 clinical trial was presented for this. You have heard that a Phase 1-2 study had been performed. I will point out to you that in the Phase 1-2 study the efficacy results were described. There were 2/26 patients who achieved a response in that study. Both responses were PRs.

In the Phase 3 study this consists of a two-arm, randomized, unblinded, multicenter, add-on design study of Genasense with fludarabine and cyclophosphamide. The population was patients with relapsed or refractory disease who were determined at that time to require therapy and who had previously received fludarabine. The sample size

calculation was based on the determination to demonstrate a 44 percent response rate and an absolute increment of 20 percent over the control arm response rate, 24 percent.

[Slide]

Central randomization was performed using a random block technique. There were three stratification factors, as you have already heard, whether patients were responsive versus refractory to prior fludarabine; whether they had received one to two or three or more prior regimens; and whether the response to the last therapy was greater than six months in duration or less.

[Slide]

In this study the response rate was defined as the CR plus the nPR responders. The primary statistical analysis was the continuity-corrected Pearson chi-square test using the intent-to-treat population. The response assessment was performed by a blinded clinical expert, in this case the study principal investigator.

[Slide]

The pre-specified secondary efficacy endpoints included the following: Overall response rate, that is, all responders, CR plus nPR plus PR; time to disease progression; overall survival; duration of response; and clinical benefit elements.

[Slide]

The pre-specified clinical benefit elements were resolution of B-symptoms; impaired mobility; impaired cosmesis; abdominal discomfort due to hepatosplenomegaly; early satiety; resolution or reduction in massive splenomegaly; relative improvement in performance status; improvement in disease-related anemia; and improvement in fatigue score. These were the individual elements identified.

[Slide]

I do want to point out that in the study there was no composite symptom endpoint or symptom-free time interval endpoint that was pre-specified. There were six protocol revisions,

with one additional statistical analysis plan submitted.

[Slide]

Those patients randomized to the Genasense-containing arm received their Genasense as a 3 mg/kg/day continuous infusion for seven days, requiring an indwelling IV access catheter and an infusion pump. All patients on both arms received the same chemotherapy, fludarabine plus cyclophosphamide given daily for three days. Cycles were repeated every 28 days and a total of six cycles were planned symmetrically for both patient groups.

[Slide]

To receive this therapy all patients also required G-CSF for at least seven days per cycle, sulfamethoxazole-trimethoprim during treatment and for six months after; acyclovir during treatment and for six months after. Erythropoietin for all symptomatic patients with hemoglobin values less than 10 was suggested; antiemetics and the central venous access catheter.

I might remind you at this point that since all patients in the study were receiving G-CSF and erythrocyte stimulating factors, it is not surprising that there was not much difference in the neutropenia or anemia as a consequence.

[Slide]

The first patient was enrolled in August, 2001 and the last one in June, 2003. Data cutoff for analysis was September, 2004, except for the survival data, enabling all patients to be followed up for a minimum of three years from the time of randomization.

[Slide]

The two arms appear well balanced for baseline disease and patient characteristics. Approximately 60 percent were judged to be fludarabine refractory at baseline in each arm. Average time from the diagnosis of CLL to study enrollment was six years, and chemotherapy drug exposure on study was similar on both arms. The median number of cycles was four. Thirty-seven percent of patients on the control arm completed

all six cycles, 30 percent on the Genasense arm.

[Slide]

The response information you have already seen. Shown here is the fact that 20 patients achieved the CR plus nPR response category, 16.7 percent versus 6.6 percent of those in the control arm. The difference, p equals 0.025 using the pre-specified test.

We talked about the study arms appearing well balanced in the baseline disease characteristics. I would just remind you that in this advanced treatment population less than half of the patients had splenomegaly or increased LDH or fever. About 50 percent had had one or two prior therapies. About one-half were Rai stage 1 or 2. I would also remind you that the patients had already a six-year time interval from their time of diagnosis.

[Slide]

Instead of looking at the response rate of CR plus nPR, if we look at the overall response rate and include the PR patients, which is a

protocol secondary endpoint, in fact there is a 45 percent response rate for the control arm compared to a 41 percent response rate for the Genasense-containing arm.

[Slide]

You have seen information from Genta a few moments ago looking at the response duration for the CR plus the nPR patients. This is a responder analysis showing response duration for all responders, which also is a secondary endpoint. There is no difference in duration of response between the two study arms if one looks at all responders.

[Slide]

Another secondary endpoint was time-to-progression and that is shown on the following curve. The lower curve, in red, is the Genasense-containing arm with median time-to-progression of six months. The upper curve, in blue, is the control arm with a median of nine months at this particular time point. By log-rank analysis no difference was demonstrated

between the two treatment groups.

[Slide]

This is the overall survival. Again, the lower curve is the Genasense-containing arm, in black. The upper is the control arm. Statistically no difference was demonstrated between the two curves for survival.

[Slide]

Looking at the pre-specified clinical benefit elements, which I have repeated here for you, the FDA analyzed each of these secondary clinical benefit elements separately as was pre-specified in the protocol. FDA agrees with Genta's stated conclusions in the briefing document. Analyses of clinical benefit endpoints show no statistically significant difference in findings between the treatment groups. We did note that more patients receiving Genasense required red cell transfusions, and more patients receiving Genasense required platelet transfusions.

These individual clinical benefit elements, none of which were statistically

significantly different individually, are the basis for the calculation of the composite endpoints of symptom relief, symptom-free time that you have seen. This endpoint was not a pre-specified endpoint and was calculated by adding discontinuous times.

[Slide]

Additional exploratory analyses by FDA noted no improvement in response with the addition of Genasense for patients greater than age 65, or for women, or for patients judged by Genta as fludarabine refractory at baseline. That is true either for the CR plus nPR responding subgroup or for all responders.

[Slide]

However, adding Genasense does increase toxicity. Now, there are many ways to show this. What I have provided graphically here is to indicate that overall AEs or AEs leading to drug discontinuation were not different. However, grade 3 or greater AEs, which are termed severe AEs or serious AEs or serious AEs considered relating to

study treatment, were all increased. The serious AEs considered related to study treatment indicates these are attributions made by the investigators treating the patients, and they felt that the serious AEs were doubled. AEs leading to death are noted also.

[Slide]

Another way of describing this with respect to specific symptoms is to point out, as noted here, that numerically there is an increase in nausea, fever, fatigue, vomiting, headache, dyspnea and dehydration on the Genasense-containing arm.

[Slide]

Looking at hematologic toxicity, as we noted earlier, there was not a great deal of difference in anemia or thrombocytopenia and one possible reason for this is that patients were receiving growth factor support. Thrombocytopenia, however, of all grades and grade 3-4 was more common with the Genasense-containing regimen and bleeding was more common.

[Slide]

Administration issues with respect to Genasense have to be commented on. It does involve a seven-day intravenous infusion every 28 days. This means an indwelling intravenous access catheter is necessary and an infusion pump is required. The infusion has to be maintained either with home health or clinic visits, and there are catheter-related complications.

[Slide]

In this table I have tried to summarize that the total catheter-related infusion complications on the Genasense-containing arm occurred in 16 percent of patients compared to 2.6 percent for the control arm. These did include catheter infections and venous thromboses and other symptoms such as pain, redness, swelling, bruising, oozing and infiltration, as described by the investigators.

I should note that the catheter complications were similar to toxicities which have been observed in the 2004 Genasense NDA, also

presented here to ODAC.

[Slide]

In reaching our conclusions, I again would like to remind you of the single-study characteristics that should be available to support effectiveness: A large study; consistent efficacy; multiple pair-wise comparisons; multiple endpoints; high level of statistical significance; and very compelling results.

[Slide]

In single-arm, single-agent studies in advanced and previously treated diseases response rates can provide preliminary evidence of drug activity, and may be of regulatory interest if they are persuasive in magnitude and duration. In parallel group Phase 3 trials meaningful treatment effects are better assessed and quantitated by comparisons of TTP, PFS and overall survival reflecting treatment effects on the entire study population.

[Slide]

Genasense is described as a targeted

therapy designed to inhibit the Bcl-2 pathway. However, in this presentation no evidence was provided that Genasense inhibits Bcl-2 in these CLL patients, or that altering Bcl-2 is beneficial for any group of CLL patients.

[Slide]

Study GL303 is a two-arm, Phase 3, unblinded, add-on design to demonstrate the effect of adding Genasense to the chemotherapy. The study is complete and it provides mature data on response, time-to-progression and overall survival.

[Slide]

With regard to response, we agree that the CR plus nPR rate was increased by 10 percent to a total of 17 percent with the addition of Genasense. The overall response rate, however, was slightly lower with the addition of Genasense, 41 percent compared with 45 percent for the control arm. We have to ask ourselves what is the meaning, what is conveyed by these response rates. With regard to duration of response for all responders, there is no improvement in the duration of response with the

addition of Genasense.

[Slide]

The addition of Genasense to the chemotherapy regimen provided no improvement in time-to-progression and no improvement in overall survival.

[Slide]

All of the other pre-specified analyses, as performed by Genta and confirmed by FDA, show no improvements with the addition of Genasense for any of the secondary clinical benefit endpoints, resolution of B- symptoms, resolution or reduction of massive splenomegaly, improvement in performance status, improvement in disease-related anemia or red cell transfusions, or changes in fatigue.

[Slide]

The symptom-free time analysis, a composite of the individual clinical benefit elements just listed, was not a pre-specified analysis. It is composed of discontinuous time intervals and may be considered exploratory. Although not pre-specified, we did an analysis of

symptom-free time for all responders, CR plus nPR plus PR, and showed no difference between the two study arms.

[Slide]

Toxicity is increased by the addition of Genasense to the control drug regimen, and Genasense administration requires a continuous intravenous infusion, central venous catheter and maintenance with an external infusion pump for seven days monthly.

I would agree with Dr. Keating's earlier remarks that treatment of CLL today remains inadequate and it remains palliative. Therefore, we must judge the higher responses for the CR and nPR patients in light of the increased toxicity and price that is paid for these responses. Thank you for your attention.

Questions from the Committee

DR. HUSSAIN: Thank you, Dr. Kane. I want to thank both the FDA and the sponsor for sticking to time which gives the committee a fair amount of discussion time. Just as a point of order, I am

sure you all have quite a bit of questions and, in order that we make sure that we accommodate all the questions, I am going to ask that you either indicate to me or to Miss Clifford that you have a question. We will acknowledge you and then you can ask your question to either the FDA or to the presenters. And, I am going to ask FDA and the sponsor to stick to the point and be brief in their response so we can accommodate as many questions as possible.

Does anyone from the committee have a question? Dr. Harrington?

DR. HARRINGTON: Thank you. I have a question and I hope the answer will shed some light on the apparent discrepancies between the survival and duration of response among the responders, and the lack of those differences among the entire population. So, this is for the sponsor at first but the FDA can certainly help with the answer.

I apologize for the length of this question. You all know that statisticians tend to be long-winded so in that population I will try to

be short-winded. If the sponsor could show either slide 37, which is the time-to-progression curve or the survival curve--either one will work.

[Slide]

Great! We have seen these curves which showed no overall difference in time-to-progression between the two arms. I think the curve just prior to this showed a difference in time-to-progression in the responders. So, could we see that curve as well, the one that is from your primary analyses which is the CRs plus the nPRs? Slide 38?

[Slide]

This one shows the difference in response rates between the CRs plus nPRs between the two groups. So, the basic inference here is that the addition of the Genasense has caused the more durable responses in those groups and I think you made a compelling case for some of that case, that there was a causal relationship here.

Let me give another side of that argument and then I would like the sponsor to address why the causal interpretation is the one that they feel

is the stronger one. So, let's go back to the curves that I asked for initially.

[Slide]

Thank you very much. Another interpretation, of course, is that there are people who have durable responses on both arms and what the Genasense may be doing is helping you identify the patients who are going to have the durable response. So, in fact, the Genasense is a marker for patients who are going to do well, and by having picked them out, by analyzing the responders plus the nodular PRs you are analyzing people who are far to the right, on the yellow curve, versus people who are little more to the left, on the orange curve.

So, I think the issue here to sort out the analysis of the responses is what the evidence is that Genasense has caused the increased duration of response, that is, has pushed people to the right on that curve, versus simply marked the people who are to the right on that curve already and helped to pick them out.

DR. ITRI: I am going to ask Dr. Gary Koch, our statistical expert consultant, to address this.

DR. KOCH: Yes, Gary Koch, biostatistics, University of North Carolina.

I don't think the sponsor intends to make a causal argument on this. I think that what is being displayed is simply that the people who achieved a CR/nPR were people who did, indeed, attain at least a two-year time-to-progression to a large extent and a three-year survival to a large extent. But the extent to which that is concomitant versus causal is not something that we have any kind of analysis to address.

DR. HARRINGTON: Thank you. So, I guess the conundrum for this committee then is, is the strength of the evidence--it is difficult to interpret--for Genasense improving a response versus marking patients who are going to get an improved response? That would be the crux of the decision about whether to approve the drug, I would think.

DR. KOCH: Well, the crux of the argument

is that I think there is agreement between the FDA and the sponsor that in the Genasense arm there is a significantly larger number of people who achieve a response that is CR/nPR. The dilemma that has been identified is that when you look at time-to-progression or survival you do not see a statistical difference. The other part of the dilemma is what does achieving a CR/nPR mean? What does it translate into?

The sponsor has provided some analyses that indicate that people who do achieve a CR/nPR have very long duration of response, and they have very long time-to-progression, and they have relatively long survival because those are the people that are still around at the end of the time to event, whether it is two years for time-to-progression or three years for survival.

But exactly why they are around is more of a clinical answer which others could address better than me, but there is no statistical causal argument here. It is simply that they are part of the people that are on the far right-hand side.

Maybe Dr. O'Brien could comment further.

DR. O'BRIEN: Well, I think that is the point, that if it were a single-arm study and you were comparing it to historical control you would, of course, have the issues of is the drug really doing anything. I think the whole point here is that it was randomized and so how do you account for a significant difference in improvement in the CR/nPR? We have the other arm to compare it to and the only difference between the two treatments was the addition of the Genasense.

DR. HARRINGTON: I think there is no question that there was an improvement in the response rates measured by CR plus nPR in the two groups. The question is whether that, in fact, is leading to more durable responses or has simply picked up the patients who would have had durable responses even without the Genasense.

DR. O'BRIEN: But also remember the durability of the responses. You know, if you compare the same type of response, CR/nPR, the ones with the Genasense were significantly more durable.

DR. HUSSAIN: Dr. Rodriguez?

DR. RODRIGUEZ: This is a question for the clinicians from the pharmaceutical study. We have looked at some historical evidence from other trials conducted at M.D. Anderson where clearly the addition of rituximab changed very much the same endpoint that we are discussing here, which is the CR/nPR, and the difference between the F/C/R and the F/C, again as pointed out by Dr. O'Brien, not a head-to-head comparison and not randomized, just a historical comparison. Nevertheless, was very dramatic, the percentage of individuals who did achieve the CR/nPR, such that I think today, as a clinician, I would have a great conflict on ethical grounds between determining whether the addition of Genasense to F/C if I were facing a patient and I had to advise them about how they should be treated today. I would ethically have to say the data from F/C/R look far more compelling than this data presented today. So, where do Dr. Keating and Dr. O'Brien see that, as a clinician facing a patient, I would advise them about the use of Genasense?

DR. O'BRIEN: Can we have the slide up, please?

[Slide]

As I showed you in the salvage setting, we did increase the CR/nPR rate with the addition of rituximab of a similar magnitude to what you saw in this trial. But, just like you saw in this trial, there was no difference in time-to-progression and, as I specified, I think the reason is that the CR/nPR patients are still the minority so they don't really affect the whole curve.

Now, you might be alluding to the fact that the CR/nPR rates appear to be better here than were seen in either arm of the current trial. I think there are some explanations for that. Slide up, please.

[Slide]

Our data, of course, is single-arm trials compared to historicals and we all know the issues with that. This was a randomized trial. It was a multicenter trial. It had blinded histopathologic review. It had blinded clinical review. They were

more heavily pre-treated; more fludarabine refractory; and, very importantly, and I hope this point was clear, the NCI guidelines do not require confirmatory CT or ultrasound scanning. So, our data does not use that.

[Slide]

The other point, which is not on this slide actually, is that the flu/cy doses in our trial were 300 and 30 of fludarabine and in this trial were 250 and 25. So, I think there are a lot of reasons why the absolute numbers might be higher from our single-center experience than you saw in this trial.

DR. HUSSAIN: I have a question to the sponsor. When you designed your trial you designed it looking for a 20 percent difference in what you viewed as a relevant endpoint. I would imagine the reason you did that is because you felt that that would have been clinically meaningful. You have failed to show that you have that much of a difference.

So, the question would be if you were to

design a trial that has a ten percent difference with the same numbers that you have, what would be really the power of that trial? I am sitting here, looking at your statistical design--and I am not a statistician, but you have an 80 percent power to detect a 20 percent difference. You have only a ten percent difference in a small trial. How confident can one be with these numbers? That would be my first question.

The second question is that as I sit here I can't help but think of the story of IRESSA in lung cancer where, again, there was no question that there was a small but real benefit to a small number of patients, and it turns out that there are reasons why some patients may respond. And, it seems to me that you have not demonstrated, or have failed to take an advantage, unless we didn't hear the data, of who actually is benefitting. Because as you sit here and look at it, to treat 100 patients you are getting a benefit in only 10 and you are subjecting 90 to arguably cost, both physical and monetary. So, that would be my second

question.

DR. ITRI: Dr. Koch is going to address your first question.

DR. KOCH: In terms of what was observed, yes, the observed difference was 10 percent rather than 20 percent, although the ratio of response rates was comparable because initially they were thinking of something like 40 percent versus 20 percent, which is a 2:1 ratio, and they got something like 17 percent versus 7 percent, which is about a 2:1 ratio.

From the point of view of statistical power, the sponsor has advised me that the sample size they had for the event rates they had would have had about 65 percent power. The reason why the power is that large is because when event rates are lower the standard deviation is also lower. So, that does improve your ability to detect a somewhat smaller difference. Although the power was somewhat below 80 percent, it was still a good power of 65 percent.

DR. ITRI: I guess to paraphrase your

second question which compares us to the IRESSA study, I think there are a couple of important points there. First of all, the IRESSA study was a single-arm study, open-label. This was a randomized trial in which, everyone agrees, there was good control and good comparisons between the two arms of the study. So, we are comparing apples with apples and we can be pretty comfortable that we have identified a real event.

Secondly, in IRESSA the responses were partial remissions which are clearly, at least if we are going to cross-compare with our study, not related with prolonged clinical benefit.

DR. HUSSAIN: Let me clarify my question. I am not asking you to compare IRESSA to your drug. What I am saying is that what is clear, like the IRESSA story, the number of patients who benefitted is very small. Therefore, it would have been wise and advisable for you to look at who actually might benefit so that one can spare the majority of patients toxic treatment that is futile. That really is my question. I am not comparing the

studies. I am just bringing an example of an agent that was approved based on, at best, very modest evidence of activity in a very dismal disease that has a much lower median survival and, yet, we came later to find out that, in fact, there are only certain subsets of patients that are likely to benefit. So, my question is in that regard.

DR. ITRI: Let me see if I can do a better job a second time around. Can we have the slide up?

[Slide]

This is the slide shown by Dr. O'Brien. First, I just want to contextualize your comments about the importance of the magnitude of the difference we are seeing. I think Dr. O'Brien has presented this previously, and the point that Dr. O'Brien made is that magnitude of improvement of this degree in the up-front setting in previously untreated patients has been sufficient to drive the standard of care.

We have shown the same level of improvement in an infinitely more difficult

population of relapsed/refractory patients. So, this is not an insignificant finding that we have and I think that is the first contextualization I want to make. Slide up.

[Slide]

Obviously, we could not know when we designed the study who would be the patients who achieved the greatest benefit, but there is a clear pattern emerging which we believe is consistent mechanistically with how Genasense works. When I showed this slide I tried to make the point, and probably I was going fast, but it is pretty clear to us that patients who retain their ability to respond to the the combination chemotherapy--because Bcl-2 downregulation and Genasense work to enhance the activity of chemotherapy so it makes sense that the patients who still are able to respond to the chemotherapy are going to be the ones who benefit most.

And, we have a clear story emerging that patients who have relapsed and are not refractory to the combination therapy, and patients who have

received relatively less chemotherapy and patients who are able to respond to their last treatment are the ones most likely to benefit. That is why we are designing the confirmatory study in the up-front population because it would make sense that in that population there are response rate differences. If we can translate this ten percent difference that we are seeing in this incredibly heavily pre-treated population who are so refractory, if we can translate that into the up-front setting then we have the possibility of affecting endpoints like progression-free survival. That is why we have agreed to that endpoint. Does that help?

DR. HUSSAIN: Thank you. I think Dr. O'Brien would like to add something.

DR. O'BRIEN: I would like to address the toxicity part. It is true that when you add Genasense to flu/cy there is more toxicity. In my mind, it is not that major. Why do I say that? Well, first of all, because most of it is grade 1-2 we can deal with nausea, headaches, those kinds of

things. If I try and add another drug onto flu/cy, and we have done it--let's say rituximab, 80 percent of those patients have infusion reactions. They are severe in about five to ten percent, way more than on this trial. If I try and add any other chemotherapy agent onto flu/cy I am going to get way more myelosuppression and infections.

So, I just want to put that sort of in the perspective of adding anything onto this two-drug regimen. Yes, we add another drug and we buy some more toxicity. But relative to what we might get adding any other drug, I think in fact it is not very much.

DR. HUSSAIN: Dr. Perry?

DR. PERRY: Since this drug works by downregulating Bcl-2, I wonder if we could see the Bcl-2 levels before and after treatment I both arms.

DR. ITRI: We did not obtain Bcl-2 levels in this study.

DR. PERRY: It is my understanding that is an easily obtainable blood test, is it not?

DR. ITRI: I am going to ask Dr. Bob Brown to address your issue.

DR. BROWN: Bcl-2 levels were not measured in this Phase 3 study, but they have been measured in studies where it is appropriate to demonstrate before and after treatment levels of Bcl-2. Slide MA-9, please.

[Slide]

Dr. Keating showed this slide in his introduction. I would like to bring your attention to the right-hand bar, here, the most recent study published in The Journal of Pathology. Five hundred and eight tumor biopsy samples from lymphoid tumor patients were analyzed in this paper. Fifty-seven of them were from CLL patients, and not only were 100 percent of those samples positive for Bcl-2, in fact, there were quantitative methods used and they were, far and away, the highest Bcl-2 expressors of all the lymphoid tumor types. So, you can see that analyzing Bcl-2 levels, for example for study entry, would not have excluded any patients from

the study.

DR. PERRY: That was not my point.

DR. BROWN: Sorry.

DR. PERRY: My point was you have an easily measurable test of whether or not your drug is having its purported biological effect.

DR. BROWN: And it has been measured in a surrogate cell population, peripheral blood mononuclear cells or bone marrow cells from patients in appropriate Phase 1 and 2 studies. I would like to show the slide that was in the briefing document. Slide 24, please.

[Slide]

The reason that this was in the briefing document is that this is the most recent study. However, seven other studies have been published that analyze Bcl-2 expression levels before and after treatment at doses ranging from 3, 5 and 7 mg/kg/day. You can see in this analysis that the majority of the patients treated did show a downregulation of Bcl-2. In fact, the majority of patients treated at three mg/kg/day showed

downregulation of Bcl-2. Dr. Tolcher has done the same analysis in other patients as well at the same doses.

Now, for CLL cells in particular we have a technical issue. You have seen evidence that the drug is directly effective. It has single-agent activity on CLL cells and what happens is that as those cells have downregulation of Blc-2 and they go into apoptosis, they die and they take a molecular marker with them. That is why that target cell population is problematic to analyze. So, this surrogate cell population has been analyzed. Dr. Tolcher?

DR. TOLCHER: Just to address this, I have been involved in three studies of Genasense involved with irinotecan, with FOLFOX and dositaxel and in those Phase 1Bs and Phase 2 studies we did actually measure Bcl-2 downregulation in both tumor specimens as well as peripheral blood mononuclear cells. The peripheral blood mononuclear cells are actually the best surrogate, you might say, to see a change since it is normally expressed in PBMCs.

In a larger series, which was from a multicenter Phase 2 study in patients with hormone refractory prostate cancer where PBMCs were collected before treatment with Genasense and day six, before the addition of dositaxel, and 19/28 patients had marked reductions in their Bcl-2 content as measured by Western Blots, with a median reduction of 49 percent.

So, a total of 69 percent of patients that entered onto the Genasense study had a significant reduction in their Bcl-2 content. Two patients had no change whatsoever and seven patients, in terms of their lymphocytes, really actually rose paradoxically. Nonetheless, we published this in Clinical Cancer Research in 2005. It seems that the majority of patients can have a marked reduction. With that median of 49 percent, that actually took the entire population, the entire 28, with many patients in their peripheral blood mononuclear cells having undetectable levels of Bcl-2 protein.

Now, this has been confirmed in other

studies, the Rheingold which is a pediatric paper as well as others, so it is a very relevant tissue surrogate, although a normal tissue surrogate. So, I think on the basis of that, on the tumor biopsies that have been presented by Brackard Jensen, by the prostate cancer biopsies we have done and published, and also by Dr. Marcucci's bone marrow aspirates, I think there is convincing evidence that Genasense alone does lead to Bcl-2 protein downregulation.

DR. HUSSAIN: Dr. Perry, did you hear an answer to your question?

DR. PERRY: I heard a lot of very interesting science; I didn't hear an answer to my question.

DR. HUSSAIN: So, we gather that actually Bcl-2 was not assessed in the study.

DR. ITRI: Yes, Bcl-2 was not assessed in this study. Because all patients express it we did not think it would be helpful in trying to identify a target population. In the study that we are doing now, enriched by the data that we have here,

in the confirmatory study we will be doing routine Bcl-2 measurements.

DR. HUSSAIN: Dr. Ascensao?

DR. ASCENSAO: Good morning. It is a question for the sponsors. I understand these are small numbers of patients but CLL is really a disease of the old individual. What percentage of the patients in the nodular PR and CR were over the age of 65 and over the age of 75?

DR. ITRI: It is going to take us a minute to retrieve that information but we have it.

DR. ASCENSAO: When one looks at the overall data in the patients who are over the age of 65 and 75, do we know whether there was a benefit of adding Genasense to the fludarabine/cyclophosphamide combination in terms of response, not just CR or not just nPR but PR?

DR. ITRI: Slide up, please.

[Slide]

These are the data we have available regarding age. You can see that greater than 75 years of age did have a degree of response. Next

slide up, please.

[Slide]

This should help address your question. This is broken down by age greater than 75 or less than 75. What you can see is that across both age subsets there is, for the CR/nPR, a benefit seen with the addition of Genasense.

DR. ASCENSAO: The other question I had is, you know, I happen to work in an institution that treats a number of individuals of African American descent. Do you have any data on individuals in the minority population?

DR. ITRI: One moment, please. Yes, unfortunately, most of our patients were Caucasian so we have very limited data.

DR. HUSSAIN: Dr. Bukowski?

DR. BUKOWSKI: Let me take you back to the Bcl-2 story because I think it is critical that we understand what Genasense is doing in this disease. Is it your hypothesis that Genasense has a direct effect on CLL cells, or is it a drug that in some way sensitizes these cells to the effects of

chemotherapy?

Number two, do you have any data in a preclinical model or clinical data in lymphoid malignancies that reflect on this issue?

DR. ITRI: Dr. Brown will address that.

DR. BROWN: Could you repeat your question for me, please?

DR. BUKOWSKI: I asked what the mechanisms of Genasense effects are in this disease because we are getting two stories. One is that it has a direct effect, the other that it sensitizes. Number two, do you have data that bear on that with either preclinical or clinical lymphoid malignancies?

DR. BROWN: Yes, thank you. Slide up, please.

[Slide]

When the study that we are presenting began an assay did not exist that was sensitive enough to determine Genasense in treated cells taken from patients, but now here it is showing measured levels at day zero and after five days of

treatment of Genasense in treated patient cells. So, we see an association of Genasense with the lymphoid cell type. This was published by Dai et al. In Clinical Cancer Research. The direct link between the intracellular level of Genasense and downregulation of Bcl-2 is shown in the next slide. Slide 22, please.

[Slide]

On the left-hand axis we see Bcl-2 expression levels in the white line and you see a decrease. On the right-hand side we see intracellular concentrations of Genasense measured by this assay, and you see the yellow line increasing. The critical thing to note here is that at very low concentrations of Genasense, in the range of what you saw measured in treated patient samples, we see an extremely sharp decrease in the level of Bcl-2 expression levels. Slide MA-23, please.

[Slide]

Now, in an individual patient you can see day zero levels of Bcl-2 protein expressed as a

ratio to actin, and at five days of treatment you can see the drop plotted quantitatively based on this Western Blot. Then, after day five there was additional therapy of this patient so the thing to focus on is the drop between day zero and five. So, we have measurement again in a marrow mononuclear cell population showing this decrease in Bcl-2 expression. Does that answer your question?

DR. HUSSAIN: Just perhaps a follow-up on Dr. Bukowski's question, and it is probably relevant to what you are talking about, Dr. Tolcher pointed out that in other tumors and measurements of Bcl-2 in the clinical setting in any of your clinical trials, whenever you measured Bcl-2 either surrogacy or otherwise--have you ever demonstrated that downregulation of that Bcl-2 translated into a response or increased response rates in any setting clinically?

DR. BROWN: Well, that is a clinical question. Preclinically, yes. We haven't measured the decreases in Bcl-2 expression in this study.

Dr. Tolcher?

DR. TOLCHER: Let me try to define, if I can for you, the question that I think you and Ron are trying to address. First and foremost, the solid tumor studies have only limited biopsies so we can't link that necessarily to response.

The second thing is I guess a broad view of agents that target the apoptotic pathway. There would be ultimately, you know, theoretically three populations. There are those cells that are pro-apoptotic and essentially they are restrained by Bcl-2 so you take away Bcl-2 and you end up with cell death and apoptosis. There are those cells that are viable. Bcl-2 is there that restricts the effects of chemotherapy and then you have that sensitization process occurring. Of course, there are those cells where, for whatever reason, are resistant to chemotherapy drugs. They don't engage the apoptotic pathway and changing Bcl-2 won't have a role.

Now, the question I think specifically in the CLL data is that there is no biopsy data that

confirms downregulation in this particular study. However, at the time that this study was being constructed investigators like us and many other investigators had demonstrated already, at least in peripheral blood mononuclear cells as well as a limited number of tumor biopsies, that the target, Bcl-2, was downregulated.

So, I think what we are doing is we are looking at study design but at the time there was I think a fair amount of convincing data to suggest that that was the case. Since CLL expressed Bcl-2 I over 100 percent of all cells, it didn't seem necessarily a logical place to go at that point.

DR. ITRI: I am going to ask Dr. Brown to come back one more time and present data from an AML study which I think will address more directly some of your issues.

I also want to say that, from a clinical perspective, we do believe that at least for CLL there is some direct relationship. Probably Bcl-2 is preventing apoptosis. So, that would explain why, when we treat with Genasense as a single

agent, we are seeing this clear low level of clinical responsiveness. It is also our hypothesis that it is working through downregulation of Bcl-2 in combination with chemotherapy to augment apoptosis. But you present the AML data. I think they will like that.

DR. BROWN: We don't have the slide of this in AML but there is emerging data where downregulation of both the protein and the messenger RNA is being measured and there is, as I say, emerging data showing an increase in chemosensitivity. Dr. Reed?

DR. REED: John Reed. I just wanted to add the point that I hope will clarify this issue about the relative benefit, or lack thereof, of measuring Bcl-2 in this trial for getting an insight into why some patients respond and others don't.

The comment I want to make is that Bcl-2 is a member of a multi-gene family. There are six members of this family that are essentially interchangeable with Bcl-2. So, the cellular context in which Bcl-2 becomes a regulating step

for dictating survival is highly important. So, I think what we are seeing from the data that came before this in the Phase 1-Phase 2 trials is that we don't have a sense that there is a lot of variation in whether this drug will downregulate Bcl-2 from patient to patient. We think that in most patients that will happen.

What is different though is whether that makes a difference for that patient. Possibly, because there are five other members in the family, in some patients it may be active in preventing the downregulation of Bcl-2 from having a response. Even though it is downregulated there are other members of the family that step in and do the job for Bcl-2.

To that effect, for example, there correlative studies that showed one of the other family members, called Mcl-1, can correlate with poor responses to fludarabine, for example, in patients with CLL. We don't know what the levels of Mcl-1 were in this patient population and whether those patients that perhaps didn't benefit

from Genasense may have had high Mcl-1. These are the kind of things that can be explored, of course, in future studies but I think there is a very good rationale for why not every patient is benefitted from the drug even though in the vast majority, I am confident, the drug worked and downregulated Bcl-2.

DR. HUSSAIN: Thank you. Dr. Lyman?

DR. LYMAN: Just a request and a brief question. The request is that when presenting time-to-event data it would help us greatly, who are trying to interpret the trends and comparisons of these groups, if you simultaneously presented the number of patients at risk over time, which frequently diminish quite dramatically, making the tails on those curves very unstable and hard to interpret.

The question is if one looks at some of the Phase 2 data of previously treated patients with CLL with the F/C regimen, one often sees higher response rates even when limited to CR and nodular PR. How would you interpret your seven

percent response rate in the control arm? Is this just the luck of the draw on the patients or do you think your criteria and external review was so tight that it really led to that fairly low-ball response rate in the control arm?

DR. ITRI: We are very confident of our response assessment but one can never completely get away from luck of the draw. So, I think we did have a sick population of patients but on top of that we really did have very stringent criteria. The simple addition of including CT and ultrasound normalization results--we know now from a careful randomized study and we have recapitulated this--in a 30 percent reduction in what we will call a CR or an nPR. I don't think we need a slide to prove that. But that is published data from the ICORT study from the German consortium. So, the addition of CT scanning, which I believe is important because we have been calling CRs routinely in the face of large residual CT findings. So for me at least, we know that that was all cleared in these patients but that itself is a 30 percent reduction.

Then when we add on other elements such as central blinded review, centralized review of bone marrow, multicenter trial and I find no difficulty in believing that strict criteria will reduce the response rate to the level we have seen. So, I have no difficulty believing this.

DR. HUSSAIN: Thank you. Miss Mackinnon?

MS. MACKINNON: It looks to me like we haven't hit the fludarabine refractory patient. I mean, that is just not in the cards here. It doesn't mean that you aren't helping other people but for those people F/C in itself may not be of much value either. So, in a sense, it is confirming why would put these people in such a study in a sense. But for the real salvage of fludarabine refractory patients, would you all agree that there really is no particular benefit for Genasense?

DR. ITRI: Can you put the slide up?

[Slide]

I think for the truly refractory patient there is limited benefit from giving fludarabine in

combination with anything. We did see a numerical benefit even in that subset of populations. But I will editorialize here, if I may, for a moment. I think there is a huge amount of confusion in the community about what a refractory patient really looks like. So, you know, if these patients were truly refractory I think those numbers should be zero. Six months is an arbitrary thing so it would be very hard.

In my view, if a patient is being considered by the physician for a fludarabine-containing regimen, that means that there must be some reasonable postulate for why the doc thinks that the patient is going to respond to fludarabine. If he thinks he is going to respond to fludarabine he should get Genasense combined with it because he has a much greater chance of getting a meaningful response.

MS. MACKINNON: If he is sensitive.

DR. ITRI: If he is sensitive, yes.

DR. HUSSAIN: Miss Haylock?

MS. HAYLOCK: There has been mention

several times about the cost, both financial but also emotional and in time in clinics or facilities, hospitals, with these patients in relation to the port, etc. So, I wonder if someone could speak to the drug administration issues as that relates to adding Genasense to the protocol.

DR. ITRI: We are very fortunate to have Peggy to more than Green with us who has administered Genasense to more than 40 patients on a variety of different trials at the University of Chicago, and I think she is probably the best person to address your question in a real-world frame.

DR. GREEN: Can I have the question again?

MS. HAYLOCK: Could you just speak a little bit to your perception of the issues when you add Genasense to a protocol? What does it really mean to the patient and what does it mean to the facilities which are doing this protocol?

DR. GREEN: Well, I think that with the addition of a central line and the addition of the pump that has to be carried by the patient,

education for the nursing staff and good patient education as well is helpful.

MS. HAYLOCK: Could you relate that to perhaps how the patients react to carrying the pump for that designated time, and what that might mean to quality of life as it regards using this particular drug?

DR. GREEN: The patients that I had contact with adapted to carrying the pump and didn't find that it affected their quality of life terribly. The patients that I had contact with also did not have an enormous amount of toxicities from the addition of Genasense.

MS. HAYLOCK: Thanks.

DR. HUSSAIN: The final question will go to Dr. Grillo-Lopez.

DR. GRILLO-LOPEZ: I have two questions, one for Dr. Keating and one for Dr. O'Brien. In my mind, the approval of this agent hinges on two important efficacy issues. The first one is, is nPR truly similar to CR and is it different from PR and non-response in terms of the benefit that it

provides to the patient? I am asking that question of Dr. Keating because Dr. Kane came to a different interpretation of Dr. Keating's data, in fact. So, if Dr. Keating could shed some more light on that, that would be useful.

Secondly, a question of Dr. O'Brien in terms of if nPR is truly similar to CR, then what is in it for the patient? Could she please also repeat some of the patient benefit that she sees in terms of obtaining a CR and nPR, not just in terms of the response itself but in terms of duration? The reason for that question is that the FDA bases some of their conclusions on their belief that it is better to analyze the patient population as a whole. However, the sponsor believes that the patients that are benefitting are those that achieve a CR and nPR and, therefore, it is more appropriate to analyze those patients for TTP, PFS, etc.

DR. KEATING: Yes, Antonio, consistently over time we have found that the survival of CR and nPR is very, very similar. The slide that was

shown earlier demonstrated that there was a shortening of the time-to-progression, but the survival in every study that we have looked at has similarity and no significant difference between CR and nPR, which may be a different biology of subsets of patients that get nPRs versus CRs. We analyzed the data before the study started with fludarabine plus prednisone and the F/C data by itself in relapsed patients, and found that there was no significant difference in survival between the CRs and the nPRs. Then prospectively in the next study of F/C/R we found that there was again a survival similarity between the CRs and the nPRs.

You have to realize that there is this entire spectrum of PRs. People always say the patient got a good PR. I have never seen a good PR. There are some less bad PRs but some people just get one little improvement in one parameter and they are classified as a PR. Whereas, to get a nodular PR you have to have restoration of normal counts as well as disappearance of disease. So, intuitively, it suggests that there is more

similarity than dissimilarity. Susan?

DR. O'BRIEN: Just to put that a little bit more graphically, if you examine an nPR patient, their exam is normal. If you check their blood counts, they are normal. There is no way you would know that patient had leukemia unless you did a bone marrow. You could examine a PR patient, they could have palpable adenopathy. They could have palpable splenomegaly. They could be anemic. They could have a packed marrow because there is no marrow requirement, and they could be thrombopenic, and that is a PR. So, I think it is a very dramatically different response.

The other thing that is very interesting is that nodular PR actually appears to be evolving. The reason I say that is that in the days when we had single-agent fludarabine what we called nodular PR was very often obvious disease in the bone marrow biopsy--plenty of nodules; sometimes even interstitial disease. Now what we often are calling nodular PR with our newer therapies is where the pathologist reads one isolated small

lymphoid aggregate. In fact, we and others have begun to do things like immunostaining on those nodules and sometimes they are residual disease and sometimes they come back polyclonal or T-cells.

So, I think, if anything, nodular PRs with combination therapy actually are, in some cases, not always, closer to CRs but sometimes they represent residual disease. But, again, I think there is a big chasm between PR and nodular PR.

Then, the question you asked me, Antonio, was in terms of why--could you rephrase the one you wanted to ask me or restate it?

DR. GRILLO-LOPEZ: Having heard all of that, is then the appropriate analysis in this study, in terms of duration, to do the nPR plus CR versus other patients rather than to do the entire study population?

DR. O'BRIEN: You know, I think that we would all like to have a B-vac for the diseases that we treat but we don't. I mean, so far we don't. None of us have been that lucky outside of the CML people. The bottom line is that the way we

have historically improved the outcome for our patients is by doing it in increments. We can get PRs in CLL. I could give these patients CHOP and probably get not a bad PR rate but with catheters, and alopecia, and more nausea and vomiting, and significantly more myelosuppression and infections. We can get people with CLL into PR. It is not easy and there is a lot of morbidity associated with it but we can do it.

But if you keep pushing that chemo you don't necessarily get anything more than a PR. So, the real benefit is obviously to get to the point where we have a CR and nodular PR and build on that, and that is how we are going to improve the outcome of this disease because there is no question, as you saw, that that subset had very durable remissions and improved survival.

DR. HUSSAIN: Thank you very much for all the discussants. We have one announcement to make and then we are going to break and come back promptly at 10:30 when we will start the next part of the discussion. Johanna?

MS. CLIFFORD: If you are speaking in the open public hearing session and you have not registered either at the front desk or checked in with me, if you could please do that? We will take about a 15-minute break. Thank you.

DR. HUSSAIN: So, at 10:30 back here, please.

[Brief recess]

Open Public Hearing

DR. HUSSAIN: We are going to be beginning with the public hearing. Please take your seats. In advance of the public hearing, I will read a statement:

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral

statement to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement it will not preclude you from speaking. Thank you. Johanna?

MS. CLIFFORD: Our first speaker is Mr. Andrew Schorr.

MR. SCHORR: My name is Andrew Schorr. I am from Seattle and I am speaking as a private citizen. Ten years ago, through a routine blood test, I was diagnosed with chronic lymphocytic leukemia, a disease I had never heard of. I was 46 years old and, coincidentally, co-founder of a

growing website, healthtalk.com, for patients with serious illnesses. Now I was a patient as well.

Hearing the word "leukemia" had my wife and I thinking my life was over. Fortunately, it did not work out that way. In the months that followed I used the internet to connect with CLL patients around the world and, with their help, I was directed to Dr. Michael Keating, as you know, a renowned CLL sub-specialist, who, I was delighted to see, is here today. After four and a half years of watchful waiting as my white count rose to 253,000 and my lymph nodes and spleen enlarged, eventually I participated in a Phase 2 trial at M.D. Anderson under Dr. Keating's care.

Fortunately, the combination therapy in this trial, fludarabine, cyclophosphamide and rituximab, worked for me and, five years after beginning therapy, I remain PCR negative in color flow cytometry remission. I am very grateful and pray it remains a durable remission.

However, while in treatment and since I have met many people for whom F/C/R did not work or

did not last. I am a poster child, admittedly, for F/C/R but know that not everyone has the same good fortune. Hence, the need for more options.

When I was diagnosed, I immediately sought educational funding to produce webcasts for patients like me and their families with experts, including many here today, Drs. Keating, Rai, O'Brien and many other CLL specialists. Since 1996 I have hosted probably 30 hours of such "ask the expert" programs and have interacted with hundreds, if not thousands, of CLL patients. Many even respond to my blog and 25,000 CLL patients and family members receive the biweekly online newsletter from healthtalk.com. I have heard many, many stories and recognize that my CLL story is at one end of the spectrum, just short of the few who need no treatment at all.

Last year I began talking with patients in a new way through a weekly radio show, "Patient Power," airing in Seattle and also heard in several other cities and online. It is the only weekly commercial radio show for people with chronic

illnesses and cancer and from the patient's perspective. It has further allowed me to hear calls and read emails from many other patients, and a number of them with CLL.

I am here today to make a plea for a broader range of effective therapies for CLL even if the additional therapy appears to only make a modest difference. I have seen how what statistically may seem like a modest difference to a broader population can be a huge difference to any one patient.

As I continue, please note that my appearance here today is not with any connection or endorsement from healthtalk, the CLL education network, nor the Leukemia Lymphoma Society for whom I have hosted educational programs. It is very much connected to the patient advocacy mission of "Patient Power," and Genta has made an unrestricted grant to that educational venture. That grant has enabled me to travel from Seattle to see you today, as well as allowed a member of another CLL family and other patients to be also here to testify

before you.

My message is a simple one. As we know, with many cancers today there are multiple genetic subtypes. That is certainly true for CLL. While F/C/R combination therapy has worked for me, it does not work for everyone or for many in a lasting way.

That is why having additional effective and approved agents is so important. It gives us hope that our oncologist toolbox is growing and in it there may be an effective therapy for us even when older medicines used alone or in combination don't pan out. CLL, unlike what you may have learned in medical school, is not just a disease of older people and, of course, people of any age deserve the best medicine has to offer.

I hope to lead a long life. Should I need treatment again, or for others who have not responded like me, it will be of vital importance that there is new agents like Genasense to offer hope. While I am not a scientist nor an oncologist, I have met a number of people who feel

Genasense has made a huge difference for them.

If the studies confirm its impact for you, I hope you will recommend it for approval. Give our doctors, give us in these days of increasingly individualized cancer care, the expanded treatment options we need and deserve. I know we are at a crossroads in cancer care. People are living meaningful lives with cancer, even advanced cancer, and that cancer can become chronic.

Yes, the "C" in CLL means chronic. It is true that for many the diseases is a worry and a nuisance over many years but not an immediate death sentence. New tests are beginning to tell us who has more aggressive disease; who needs treatment sooner. But treatment is what is still emerging. While we pray for a cure, if you judge Genasense to have notable activity in CLL even for some patients, please give it the chance to be an additional option to make CLL truly chronic for more of us than it is today, and give us all the chance to have expanded options whenever in our CLL journey we may need them. Thank you for your

attention on behalf of CLL patients across the U.S. and I wish you well with your deliberations.

DR. HUSSAIN: Thank you, Mr. Schorr.

MS. CLIFFORD: Our next speaker is Mr. Bernstein.

[No response]

Our next speaker is Chris Laudenslager.

MR. LAUDENSLAGER: Good morning. I have no affiliation with anybody here today. My name is Chris Laudenslager. I am a 39-year old and have lived in Morrisville, Pennsylvania where I own an upholstery shop. I have a wonderful wife and a son now aged 12.

I was first diagnosed with CLL in 1997, at the age of 30. My son was two at the time. My first treatment was with fludarabine. My disease was barely under control for about a year and then my lymph nodes started growing very rapidly. They treated me with fludarabine and Cytoxin, with a really good response for about a year then I relapsed. After that they treated me with Rituxan and that worked pretty well for about two years but

then I relapsed again. In April of 2002 they treated me with Novantrone and fludarabine and it did nothing at all. I was 35 years old and I was desperate.

Let me tell you what it was like. My lymph nodes in my neck stuck out further than my ears. My armpits were so swollen that I couldn't rest my arms at my side, and my liver and spleen were so big I literally couldn't stand up straight or eat anything substantial. I was anemic and my platelets were so low they were talking about transfusing me with platelets.

The nurse in Dr. Molke's office, Jennifer Klein, is my hero. She was the one who figured out how to get me into this study. I was so happy to even have the chance to get this drug I broke down. You have no idea how desperate I was for the chance to find something that might work. I started my treatment with Genasense in June of 2002 and took six cycles without any major problems. My lymph nodes, spleen and liver started shrinking dramatically after the first cycle. My platelets

were the last thing to recover but I have been completely free of disease for more than three years and have been living a completely normal life.

I am here on my own because I want to give back just a little of what was given to me. I got my life back. I am getting to see my son grow up and I am able to provide for my family and lead a happy life. I wanted you to hear my story so you understand what the drug means from a patient's point of view. I was lucky to be able to get on the protocol but there are many other patients who deserve the same chance and won't have it if you don't approve it today.

I also have a selfish reason. This is the only drug that offered me the hope for the future. If I ever come out of remission, I need this drug. Without your approval, it is like signing my death sentence, as well as the death sentence of thousands of other CLL patients who could have the same results I did.

One more thing just for the record, after

listening to today's presentation I am an nPR. I didn't know what that means until now but it feels all right to me. Thank you.

DR. HUSSAIN: Thank you, Mr. Laudenslager.

MS. CLIFFORD: Our next speaker is Laura Singer.

MS. SINGER: Good morning. I am still suffering from a bout of shingles but I came here today, over 200 miles, because I thought it was really important. I can't give you shingles; it isn't catching. But if you haven't had chickenpox don't shake my hand.

I will begin. My name is Laura Singer. I feel like I am 68 years young. I have a husband and three children and six grandchildren and one great-grandchild. I lived in New York for some 40 years but I presently live in an over-55 community in Delaware. No one paid me anything to come here today. I came on my own.

I was consulting with Dr. Rai, my oncologist, last week about this bout of shingles and he told me about this meeting and said it might

be useful to you if I came and told you about my experience with Genasense.

I was diagnosed with CLL in 1996, when I was 58, by chance after an auto accident required an MRI of my shoulder and it showed some abnormalities in my lymph nodes in my armpit. I was in "watch and wait" and worry also for about four and a half years. I was in treatment in a major cancer center in New York City. Although my white blood count went to 350,000 I was not eligible for this treatment because my hemoglobin had not reached a level of under 11 for three months straight.

I consulted with several other physicians. One wanted to, and I quote, cure me with chlorambucil and another consortium doctor wanted to put me into heavy chemotherapy and CamPath immediately. This was quite a while ago; not today. Then I met with a group of people who had CLL, at a meeting, and they recommended that I go to LIJ. I went to LIJ and met Dr. Rai in 2001. I have an 11-Q deletion which, I understand, is an

indicator of a very aggressive form of CLL.

Dr. Rai decided on six cycles of fludarabine and Rituxan but after three cycles Dr. Rai noted that the drugs were not working adequately and I was not going to get a good remission. So, he added Cytoxin for the last three cycles. I had a pretty good response then but I was a little sick with the addition of the Cytoxin and it took four months instead of three to complete the entire treatment.

By then my response was good. My numbers were very low but my lymph nodes really never fully went away. Nevertheless, I was comfortable and I lived a pretty normal life for about a year and a half. Of course, you have to exclude the doctor's visits, the blood tests, the anxiety. Then the disease started growing back again in March of 2004. It was obvious I was going to need additional treatment.

I have done a great deal of research about CamPath, about transplants, and I was looking at the leukemia and lymphoma website for clinical

trials. I read about Genasense, that it was being used at LIJ, and I read some very small articles without too much information. I came to Dr. Rai and asked him for more information, if he knew about the trial and if I was eligible to be a candidate.

My disease was mostly manifested by very large lymph nodes. My face and my neck were so swollen I looked like a chipmunk. Every time I looked in the mirror I was reminded I had cancer. My armpits were sore and I felt full and bloated no matter what size meal I ate. My internal lymph nodes were so large they pushed against my stomach. Probably the worst manifestation were the lymph nodes in my groin which prevented me from hiking, from exercising and from walking in general. That all became painful or impossible. I was also getting anemic and I was tired a good deal of the time.

Dr. Rai started me on the experimental combination of Genasense, fludarabine and Rituxan in April of 2004. I had a port implanted to

accommodate the eight-day infusion by pump, thus getting the Genasense was no problem. I wore a very small pack on my waist and it worked for the eight days without having to do anything about it. Getting the fludarabine and the Rituxan, on the other hand, was a lot more difficult because by then my veins were really difficult to access. I got six full cycles as an outpatient. I had some nausea on the fludarabine and Rituxan days. My Genasense pump was started on Friday and I felt a strong tingling sensation in my lymph nodes, especially the first four days, not painful but I was aware of the sensation and I noted it to Dr. Rai. I returned to the hospital on the following Tuesday, Wednesday, Thursday and Friday for my fludarabine and Rituxan.

My lymph nodes started to shrink very gradually and finally resolved to nothing after six months. I have remained in remission since then and I am celebrating my two-year remission anniversary this month. I feel like my life is normal. I can walk as much as I like. I exercise,

especially water aerobics. I just returned from a four-week walking tour of Italy and England. I visit my children and my grandchildren. I do my own housework. I participate in lots of activities offered by my community. I am enjoying life to the fullest and I am here to tell you that this drug needs to be available for other patients like myself who need it.

I hope my CLL health history was really complete enough for you and that this information will be beneficial to you to make a decision for Genasense. Thanks very much for listening.

DR. HUSSAIN: Thank you, Mrs. Singer.

MS. CLIFFORD: Miss Ruth Greenberg?

MS. GREENBERG: My name is Ruth Greenberg. I have nothing to gain or lose by this. My fare here and my room where paid for after I spoke to Andy Schorr that you heard from before, but I took a day off from work and got a babysitter so it is basically a net loss.

I am 50. I am a widow. I have two teenage kids. My husband was a doctor. He was

diagnosed at 46, he was dead by 51. He started out on "watch and wait." He was on "watch and wait" about eight months. At that point he was really not breathing from tumor in the lungs. He had Cytoxin, fludarabine and Rituxan. We thought he was done then. He was good. He tested PCR negative. He looked good. He had what they told us was a CamPath mop-up. But the Rituxan had been hard on him. It was a hard drug for him to tolerate and then the CamPath was really hard and he didn't finish it. He got whacking CMV and he was pretty sick. They took him off the CamPath halfway through because he was PCR negative anyway.

That was in April. We had a party. By June he had lymph nodes again. By July, Richter's transformation. This is familiar to you. And, pretty much that is how it went for us. The reason that I come to talk to you is that after he was diagnosed with Richter's he decided to be on the bone marrow transplant list. There was a wait for the bone marrow transplant. During this time he had Genasense as a compassionate use medication.

There was a lady that asked about the pump and the administration. The Genasense was terrific in that way. The pump was no problem. The kids loved it. It was easy to tolerate. You know, I want to sort of bring a breath of reality into this. You are talked about stage 4 and stage 2 adverse response. I mean, he had a little nausea; he had a backpack. It was nothing compared to CamPath and hanging the IV bags at home two hours a day with the CMV. It was nothing compared to staying at the hospital or next-door in the hotel, waiting for the Rituxan to cause the fever and the flush. The Genasense was nothing. You know, if you are a dying person a little nausea--it was terrific.

What I want to say to the committee is, you know, he went ahead, he had the bone marrow transplant. He was very sick. He got a lung infection and he died. So, why am I here? The thing that I want to say is we had the 12 weeks with the Genasense. It was terrific. He felt really good. He had 12 good weeks. So, the drug,

when you evaluate it, it is not only for the endpoint where you see a little thing, one squib on the screen for reduced fatigue. You have no idea what it means to people. He stood up. He went with the kids to Walden. They read Thoreau. They played Nintendo. He took them to see "Pirates of the Caribbean." They walked on the beach. Twelve weeks on the Genasense he wasn't sick. It doesn't sound like a lot. Other people got more. but even for the 12 weeks.

But even for the 12 weeks, it seems to me, when you say indolent disease and I know you have a duty of care to the public to protect them from drugs that can hurt them and I understand that, but I also want to bring out to you with some force--I spoke to the person that asked about the pump--to speak about ethical choices and what you can recommend to a patient.

When you are looking at CLL you are really looking at a devastating disease in a young person, and you are looking at a person who basically in some cases is not looking at a log of alternatives.

My husband was an educated man. He was a medical doctor. He was an endocrinologist. He had the finest treatment in the world. He was cared for by John Gribbin at Harvard. He consulted with Kanti Rai. He spoke to the people at M.D. Anderson. He was a research fiend. He looked at his own printouts every day until the day he died. It was important to him to have this available to him.

Even if it is true that there is only a small percentage of the population that it helped, and you don't know who they are, he was part of that percentage of the population that gained 12 weeks with his family. It was huge. And, the pump was not a problem and everybody has a port. I mean, these people are sick. They have a port; they get infections. The Genasense, it didn't make him sicker; it made him better. It was huge. And, even if he didn't get ten years from it, I think it is important that you make available to people who really have no other options this possibility if they want to do it, and that is what I cam here to say to you.

DR. HUSSAIN: Thank you, Mrs. Greenberg. On behalf of the committee, I really want to specifically thank the members of the public who came in to share their experiences with us. We really appreciate your coming here and we value your input.

Questions to the ODAC and ODAC Discussion

For the committee, we have about an hour to discuss the subject before us and there is room to ask each other and, certainly, there are experts who are invited specifically as part of the members of the committee. If you have any other questions to the sponsor or to the FDA, I am going to ask you to try to address it to them.

In front of you, on the second page, is the question that the FDA would like us to address. I want to begin by pointing out a couple of things. Our job is advisory to the FDA. We are not here to vote on approving or not on approving Genasense and I want to make that clear. Just so there is no misunderstanding about what we are voting on, the vote is strictly on the question.

The FDA chooses to approve or disapprove; we are advisory. So, I just want to restate that for the public and for the committee members.

I want to begin with a question to Dr. Harrington. In the break one of the attendees, who was an ex-University of Michigan "Go Blue" member, came to comment on my question about the power issue. When I asked it, I put in a disclaimer that I am not a statistician but when you look at the numbers, if you were to take only two responders out of the superior arm your p values may turn out not to be relevant. That really was my point.

Also, to my inexperienced eye, the confidence intervals appear to overlap. So, I wanted to have Dr. Harrington clarify for us his interpretation of the confidence intervals and the analysis there.

DR. HARRINGTON: I think that Dr. Hussain is referring to what is on slide 26 from the FDA's presentation, for people who have a copy of the handout.

DR. HUSSAIN: Could we have that slide up, by any chance, or not?

[Slide]

DR. HARRINGTON: I think what Dr. Hussain has noticed is that studies with small numbers of people or small numbers of responders can be very sensitive to the way in which calculations are done, or very sensitive to changes in the data. So, it is true that if a small number of responders were to be removed from one of the arms here, from the Genasense arm, the p value would change. But it is a hypothetical question that I think is not answerable. I have full confidence after the FDA review that these are verified responses, that they are confirmed responses and that we don't have any non-responders mixed in which could cloud the difference here.

The issue of the confidence intervals overlapping but the p values being significant is also I think related to the smallish sample size here and the small number of responders. These calculations can be somewhat sensitive to the way

in which they are done numerically when there are small numbers of responders. I suspect, although I don't know the background of the calculations, that the p value which used the continuity-correction was maybe done slightly differently than the confidence intervals which maybe used some sort of approximation.

I am not worried about that. I think that the p value is robust and one does see occasionally intervals touching. If they were substantially overlapping I would be more nervous about that.

DR. HUSSAIN: Any questions from any members? Any points to be made? No?

I have another question, and that is to my colleagues who deal with this disease. Coming from a solid tumor background, we generally like to see our responses linked to some other manifestation of benefit. The fact that responders live longer is not necessarily a response-related thing; there could be other things but, clearly, in this setting we had a randomized trial. But a response that does not translate into longer life, longer

time-to-progression, what does that mean in CLL? Dr. Link, do you want to comment perhaps?

DR. LINK: I am a pediatrician. CLL doesn't occur in pediatrics so you are asking the wrong expert.

DR. HUSSAIN: Okay. Dr. Ascensao?

DR. ASCENSAO: Well, I think the question in terms of if patients don't really respond is what is available next. I think that is the big question. I think the point that has been made by a number of people is that for patients who have refractory disease we clearly are in need of some different medications that can address this scenario. Clearly, I think for this particular medication that we are reviewing the statement has been made by both the sponsors and the FDA that we really are not seeing any improved response in that particular patient population. So, I think that is the patient population for which, at this point, we really don't have a number of good options, outside of clinical trials being designed and being implemented around the country.

I think the question comes up in terms of options for patients with relapsed disease. I think there are a number of different options and some of them appear to be effective. I think the issue has been brought up, for example here, that F/C/R may be better than fludarabine and cyclophosphamide but, in all honesty it has not been tested head-to-head and I think we all are aware of caveats.

Those of us who have been around long enough not to think about how long we have been around, remember the CHOP regimen which has good and bad aspects to it, but the fact is that the good aspect is that we were able to prove in a very large, powerful study that CHOP was as good as the supposedly more powerful cousins that were out there. The bad thing about it, of course, is that that brought us back 20 years ago to a regimen with which there seems to be little improvement.

Interestingly, from that aspect, also the addition of a biological response modifier, with which one of the participants here is very

familiar, Rituxan, has clearly shown beneficial effects in the overall population in terms of overall response rate, disease-free and time-to-progression.

So, I think the issue is do we really know what is going to be better for our patients? The thing is that many of these patients, even though CLL certainly occurs across a spectrum of ages, is still a disease of the older individual. And, I think what we have to be very sensitive about is that those individuals have a significant number of co-morbidities and, obviously, choice of treatment outside of a clinical trial where you can define the parameters, needs to take into consideration those issues.

CamPath has been mentioned. CamPath is certainly an alternative that can be used in relapsed disease, F/C/R patients who have not had that particular option, and there are a number of other drugs that are being tested out there. The question, of course, is will they prove to be beneficial and will they improve response rates

over what we have currently available for fludarabine-sensitive disease? For refractory disease I think that is a moot point at this point in time. For fludarabine-sensitive disease I think our question is going to be do we think that this particular agent provides an substantive benefit for these individuals? I think that is the question that we need to discuss amongst us and get some input from different members of the committee.

DR. HUSSAIN: Anybody else with a comment? Doctor, please identify yourself.

DR. RAI: My name is Kanti Rai. I would like to respond to your comment or question about the distinction between your experiences in solid tumors and what is so different about CLL.

I will be very brief. I treat CLL mostly, and there is a distinction. That is, in solid tumors when we are coming to limited options and end of line it becomes quite obvious that it is so and so we deal with the patient honestly and directly to the extent that we can deal and the patient can deal and the family can deal.

In CLL, as you have heard from first-hand testimonies of different presentations, you cannot lump this disease into a single, homogeneous natural history clinical behavior. That is why a response of the type that this particular study aimed for becomes very meaningful and crucial because the numbers, as Susan O'Brien mentioned, and the percentages were relatively low, therefore, they could not impact those CRs and nPRs on the overall universe of CLL patients' behavior.

But if you took individually those patients who had achieved a CR or nPR you have, indeed, those individually so that they have better quality of life, symptom disappearances, and a chance to be able to try something more in case of a relapse, which is not the case with solid tumors.

So, here we have witnessed this morning a clear example that, yes, the benefit is relatively small but for the population that that benefit has accrued it makes a difference of life and death. Thank you.

DR. HUSSAIN: Thank you. Dr. Perry?

DR. PERRY: I would like to ask the FDA if we have an opportunity to modify the statement that we are asked to vote on, or is that fixed in stone?

DR. PAZDUR: Feel free.

DR. PERRY: My problem is that, as I read this, does this single study with a ten percent improvement in CR plus nPR but no demonstrated improvement in overall time-to-progression, survival, or symptomatic benefits between the two study arms demonstrate--my emphasis--substantial evidence of effectiveness of Genasense in the CLL population? Then I am going to have to say no because I don't think it does show a substantial benefit. If I took out "substantial," does it show evidence of effectiveness or benefit, then the answer is going to be yes. Since we are advisory to you, I need your advice on whether you want us to answer the question you like or the one I like.

[Laughter]

DR. JUSTICE: Well, I think the meaning of the word "substantial" is included here in a regulatory sense, that these provide substantial

evidence of efficacy to warrant approval. So, I think it is important to keep the word in the question. In other words, you are basically advising us whether or not the company has provided sufficient evidence to warrant approval of the drug for this indication, and that evidence must come from adequate and well-controlled studies that provide substantial evidence. Is that clear?

DR. HUSSAIN: That is the language, Dr. Perry, in the spirit of the whole regulation.

DR. PERRY: I understand, but I am trying to introduce clarity into the regulations and I am failing.

[Laughter]

DR. PAZDUR: The regulations require substantial evidence of safety and efficacy so that is the way they are written. How you interpret it and how you want to interpret it in this situation, you could give us advice on that in this particular situation.

DR. PERRY: If you wanted to say substantial evidence of efficacy and safety, then

it could have said and safety as well, could it have not?

DR. PAZDUR: Could have.

DR. PERRY: So, it has been modified a little.

DR. DAGHER: I think also the main distinction is that the wording is trying to get at a situation where you are not just talking about evidence of activity but beyond that, as was described. In part the wording is there to make that distinction.

DR. HUSSAIN: Dr. Bukowski?

DR. BUKOWSKI: I am trying to understand why a drug that may have an effect on the entire population of CLL cells, which is what we are told it does, will not have an effect on a subset that has this response called PR but will in a smaller subset that has a complete or nodular response. I don't understand how we can differentiate those. Can anybody shed light on that? Because I think it is crucial for us to understand why we should be selecting out a small subset of patients rather

than that population as a whole because it is critical.

DR. O'BRIEN: I actually find it pretty logical, the way I think about it at least, which is as follows, this is not a new chemotherapeutic agent; this is a chemosensitizer. That is how I see it. So, if I am going to sensitize a patient I am only going to sensitize a patient who has some inherent sensitivity to the chemotherapy to begin with. So, I would hardly have expected that adding this agent to a chemotherapy regimen I would take a complete non-responder and turn that patient into a responder.

Where I think it is logical to expect to see a benefit is that in some patients, not all, the magnitude of the response, because they have to have some ability to respond to begin with, is significantly improved with the addition of the chemosensitizer. That is how I see the data.

DR. BUKOWSKI: So, the partial responders, although they do have an effect of drug, obviously, don't have an effect of Genasense--

DR. O'BRIEN: Correct.

DR. BUKOWSKI: And is there a way to select out the individuals who have the complete responses based on any data? Because clearly what we are being asked to do is to select a small group of patients who potentially benefit from this drug, whereas the vast majority do not.

DR. O'BRIEN: Well, the preliminary data certainly suggested that patients who have more sensitive disease, as fits with this type of hypothesis, are the ones who benefitted the most from the treatment.

DR. ITRI: If I may, it is important to remember that we are seeking accelerated, not full approval. We are committed to conducting a study in the up-front setting where we will more fully explore and confirm the findings in this population.

DR. HUSSAIN: Dr. Itri, I have a question and then Dr. Pazdur has a comment. I was under the impression that this was the definitive trial.

DR. ITRI: No, we are seeking accelerated

approval on the basis of the data here. We have designed a large confirmatory study, in agreement with the FDA, in the up-front population. A confirmatory study is a required element of accelerated approval.

Dr. Hussain: Dr. Pazdur?

DR. PAZDUR: One of the issues that we have with this accelerated approval is the following: The accelerated approval process is usually designed for drugs that we don't have evidence of clinical benefit and we are looking during their development course, either in a single-arm study or an interim analysis of a randomized study, to approve the drug on the surrogate endpoint reasonably likely to predict clinical benefit.

We have seen that in numerous cases. For example, single-arm trials that have small response rates; we don't have evidence of time-to-progression or survival. Okay? And, based on a reasonable probability we go ahead and approve the drug with these confirmatory studies.

The situation that we have here is a bit

different. We have a completed randomized trial here. So, it isn't a single-arm trial; it isn't basically an interim analysis of a randomized study. We have mature data which does not show an impact on time-to-progression. As I stated before in my introductory comments, we would take a look at a statistically significant, clinical meaningful impact on time-to-progression as clinical benefit.

So, what we have here is a dilemma. We have a completed study. There is no impact on time-to-progression. How can we say that the endpoint is reasonably likely to predict clinical benefit?

DR. WARRELL: If I can just make a brief comment to Dr. Pazdur? I am Dr. Ray Warrell, with Genta. When this proposal was originally discussed with FDA there was discussion around endpoints obviously. We felt very strongly, for reasons that I think are now apparent not only from historical experience but also the contemporary experience of this trial, that CR and nPR is generally accepted by leukemia physicians as connoting clinical

benefit. To have to prospectively document that there is relief of symptoms and eradication of disease, for a hematologist, this would seem to be self-evident.

We are proposing this for accelerated approval largely because this is the first randomized trial ever done, not only for submission but ever done, in this target patient population. So, it is very, very different from anything that has been done before by sponsors or reviewed by the agency.

We do not find in our trial, and there is no historical experience to suggest that time-to-progression is a validated endpoint in this particular target patient population. There is no specific link to benefit, and from the data that Dr. Itri has shown you, very clearly absent the link to response even at the PR level, the lack of progression is only maintained coincident with administration of very, very toxic, myelotoxic and immunosuppressive therapies. So, it may be true that TTP is a valid endpoint elsewhere. It has not

been validated here largely because of the dearth of clinical information that is available to clinicians.

DR. HUSSAIN: Dr. Pazdur, do you want to respond to that, please?

DR. PAZDUR: Well, as I stated before, it doesn't have to be a confirmed endpoint; it is reasonably likely to predict clinical benefit. And, what we are looking for in looking at a time-to-progression endpoint is an endpoint that captures the effect on the entire population.

One of the other issues that I think was brought out during our discussion here is that we are looking at a ten percent improvement here. So, what you see is what you get. Ten percent of the people get some benefit from this drug. As you pointed out, nine people are treated so one person has a benefit from this drug. So, one has to take a look at this in the risk/benefit analysis of this drug. When you have an effect on a population, for example a statistically important effect or an improvement in time-to-progression, it describes a

population effect so one could assume that there may be some benefit in more than one sees in that population.

Let me give you an example. For example, if you had a ten percent response rate, that means that basically in a single-arm study ten percent of those patients may get some benefit and we may go ahead an approve that drug. Then subsequent studies demonstrate an improvement in, for example, time-to-progression. That would characterize a population effect. That is kind of the issue that we were after, that there is more than just this ten percent of patients that are achieving some benefit from the drug.

DR. O'BRIEN: Could I make a comment?

DR. HUSSAIN: The rule about raising your hand and being acknowledged applies also to the sponsor and all the members of the sponsor's team. So, please, respect that. Dr. O'Brien, you have the floor.

DR. O'BRIEN: Thank you. I think we are a little bit penalizing the sponsor for the fact that

they did a randomized trial. The reason I say that is because every drug that has been approved in leukemia so far has been approved based on response rate, mostly from single-arm trials. The presumption, as has been shown over and over, is that response in leukemia, whether it be acute leukemia where it is more likely CR, or CML where it is cytogenetic response, or CLL where up until now it has been overall response basically because we didn't have any Crs, it has always been response.

So, this was a single-arm trial that showed a benefit in response compared to historical data. Nobody would be raising this issue of time-to-progression. It is only because it is a randomized trial where we have these two groups that this has even come up, and I think we have reasonably explained why the time-to-progression is not longer. But every other drug that has been approved has been approved on a single-arm study on the basis of response.

DR. HUSSAIN: Dr. O'Brien, if I may play

the devil's advocate here, the reason I brought up the issue of solid tumors is I am trying to figure out here how do you quantify clinical benefit. We throw this word out and it is based on personal experiences, so my patient did well; my patient did not do well. I brought up the solid tumor for a purpose in that in the case of a randomized Phase 3 trial, if you had a clear advantage across the board that this response translated into something, then there is no question that there would be clinical benefit there.

The reality is that you did a Phase 3 trial that gave you slightly better responses that did not translate to anything else that is accepted as a manifestation of clinical benefit. The fact that things were accepted historically is no justification for this committee to say, well, things were based on something, therefore, we agree it ought to be that way forever.

So, help me understand, if a clinical benefit is a response why is it that there are no quality of life tools there? If you are trying to

say that to get a response, no matter how you define it, complete or nodular PR translates into people being able to do better, function better, it seems to me then the primary endpoint ought not be that there be a response but that there be quality of life or disease-related quality of life to show that, yes, you did something good to patients. But it really is very hard to understand how a response translates into a clinical benefit.

DR. O'BRIEN: I thought the data was presented but, I mean, it was very clear that the patients who got a CR or nodular PR had resolution of all of their symptoms.

DR. HUSSAIN: But this is not a formal assessment of quality of life. This was captured information. Correct?

DR. O'BRIEN: Yes.

DR. HUSSAIN: This was not a tool that was utilized.

DR. O'BRIEN: Well, it was prospectively captured but each patient may only have one of five symptoms. So, if you look at each symptom, let's

say weight loss, maybe that is in 15 percent. B-symptoms might be another 15 percent. So, if you are going to look at each one symptom you are not going to see big differences because the numbers are too small. That is why all the symptoms were added together and there, there was very dramatic benefit where you saw that the patients who achieved CR/nPR were symptom-free, for the most part, for almost two years. I think you even heard from some of the patient testimony today that even some kind of a response correlated with symptom benefit.

So, they were prospectively captured. The issue was that they were combined, all of the symptoms were combined for this analysis.

DR. HUSSAIN: I want to just point out one more thing. I would go back and say this was captured not through a formal quality of life assessment tool and that is the point here. So, it is not written by the patient where the patients actually filled in a form. Correct?

DR. O'BRIEN: Right.

DR. HUSSAIN: So, this is really sort of a random other thing, systematic but not really formally done.

DR. O'BRIEN: The symptoms were prospectively--

DR. HUSSAIN: I understand, but not using approved tools. Dr. Rodriguez?

DR. RODRIGUEZ: Actually, I have been meaning to say something to respond to your very first question. You asked of the clinicians who treat patients with lymphomas which are not exactly CLL but use similar drugs. And, I want to make a comment.

It has been mentioned that patients have other alternatives like CamPath. Those chemotherapeutic agents or immunomodulating agents generally have far more toxicity than this compound seems to have. Also, to bring into perspective that this is an illness that is repeatedly treated and, therefore, an important issue is whether the clinician has--the word "armamentarium" has been used--whether the clinician has alternatives that

can either be rotated or that patients can have breaks or lapses in time from very toxic treatments. I think that is an issue to consider in terms of alternatives for the patients.

Yes, there are at least a couple of other drugs that are possibly FDA approved and that could be used as an alternative in fludarabine refractoriness, but the truth is that one clinically needs to appraise each individual. Age has been mentioned. We have seen some unusual patient histories today of persons who were diagnosed relatively early. The truth is most people are old and have limited physiologic resource to accept or live with toxic treatment.

So, I want to bring that perspective, that we are talking about people who have been treated already, have been exposed already to toxicity, whose immunity is compromised by the disease itself and who then are treated with drugs that are in themselves fairly immune toxic. Fludarabine has immune toxicity. Rituximab is immune toxic and the combination of fludarabine and rituximab is very

potently immune toxic, and so is CamPath.

So, this is probably the one drug that we have heard of so far for the past five years or so that is not immune toxic to the patients. I wanted to make that point because you were asking about the clinicians' point of view.

DR. HUSSAIN: Dr. Link?

DR. LINK: I am willing to show my ignorance here of this disease as a pediatrician, but I am certainly not used, as a pediatrician, to seeing a ten percent response rate as being a huge advance.

But I do have a question about the validity of combining PRs with what is called nPRs and CRs as really the same thing. Because in acute leukemia, which is what pediatricians treat a lot of, a PR is like kissing your sister, as Vince Lombardi used to say.

[Laughter]

It is not worth much. But everybody understands that a CR is worth a lot because you can get a patient to an alternative therapy, a

transplant or something like that, and you don't really need a weatherman to know which way the wind blows in terms of a person in CR being asymptomatic, or relatively asymptomatic.

I am just wondering why we are looking at patients who get complete responses or very near complete responses who have reduction in their symptoms. Why would you in looking at time-to-progression include a group of patients who clearly, you know, we know don't benefit very much? That is my first question. My second relates to the rule and I would like to get back to that.

DR. HUSSAIN: Your question is directed to whom?

DR. LINK: I guess to the people who did the FDA analysis. Why would you lump PRs with CRs, if it is analogous to acute leukemia where you wouldn't expect a PR to translate into anything useful?

DR. HUSSAIN: Dr. Kane?

DR. KANE: Well, number one, it is not analogous to acute leukemia. I think that would be

the first point. Number two, I think that the responder categories--we have to recall these are consensus driven and they have a degree of arbitrariness to them. We don't, in fact, know a great deal about what achieving a particular category denotes.

There is a problem also with the statistical issue of performing responder analyses. That is to say, those who exhibit a response always do better than those who do not exhibit a response and we don't always know the causation, that Dr. Harrington was getting to earlier.

I think another way to evaluate this would be to remove the categorization of patients by response; remove the response. Remove the response; do not consider the CR, PR or nPR or not responder and then look at the whole population. In doing that, there is no difference in the quantitative elements of TTP, overall survival, and there is no difference in any of the individual symptomatic, symptom-related endpoints that the sponsor pre-specified in the study. When you do

composites of these symptoms post hoc and you use discontinuous times you can get anything you want to get.

DR. LINK: Can I ask my second question?

DR. HUSSAIN: Yes, but Dr. Harrington was going to respond to your question also.

DR. HARRINGTON: Dr. Link, one important thing, of course, about time-to-progression is that since it is evaluated on the entire population it is something that is available to the clinician prior to starting therapy because prior to starting therapy, in the absence of a good method for predicting in advance who the likely responders are you are exposing people to treatment where you can't differentiate who the responders are or who will clearly benefit from the therapy.

So, to just push on this point a bit to help integrate the two endpoints, one of the things that doesn't correspond to my intuition about the study is that overall there was I think a 17 percent CR plus nPR rate on the Genasense-containing arm. So, that is almost 20

percent of the patients there with a substantial increase in the durability of their response.

I would have expected in those situations that the time-to-progression curves would start to show a trend in favor of the Genasense arm, but not significant because you don't have really the whole population benefitting. You actually have a subset of the population benefitting. But, in fact, what the time-to-progression curves still show is that over the majority of the curve the arm that didn't get the Genasense has a slightly longer time to progression. In the tails where things are very noisy it is very hard to see what is going on.

So, the conundrum for me is that I see not just a little bit of evidence in the entire population of benefit to the population here because of the benefit in that small subset but no evidence in the entire population. So, it doesn't seem to have pushed the progress forward in the population.

So, as a platform for building research on, setting aside the obvious personal benefits

that some people have gotten once they got into CR, I guess I don't share the confidence that there is a platform there for building results because it is not moving the population. It is giving very durable responses to a small subset but it doesn't appear to affect the population statistics at all.

DR. HUSSAIN: Dr. Link?

DR. LINK: My second question has more to do with the word "substantial" because I have the same problem with it. Is there a difference in terms of the accelerated approval because it is all based on one trial? I understand that this is the same, but would three trials with sort of more modest but definitive advantage be equal to one with, like, a p value with six zeroes in?

DR. PAZDUR: The word "substantial" evidence comes from the regs and our guidances regarding approvals in general. As Bob mentioned, there is not a discrepancy between accelerated approval versus full approval or regular approval. There should be substantial evidence of safety and effectiveness here.

The question here that I want to point out is that really accelerated approval is an endpoint issue. Okay? Does that endpoint reasonably likely predict clinical benefit in the patient population that you are giving the drug to? It is difficult, as I said before, for us to see this data with the impact of ten percent on this CR plus nodular PR that does not translate into an improvement in time-to-progression. And, we would accept that, as we said, as a reasonably likely endpoint for clinical benefit, and then say that this is a surrogate that is reasonably likely to predict clinical benefit.

In other words, we have the completed confirmatory trial sitting in front of us here and we are not seeing that impact on clinical benefit defined as TTP, which is the same clinical endpoint that they are using in their clinical benefit study in an earlier stage of the disease here.

So, this is the dilemma that we are facing here. Again, it is a population issue here because we are giving this drug to all patients with CLL

with the given provisions of prior treatment here. This drug obviously, as you were pointing out, Ron, and other speakers, begs for some type of identification of who are these patients that are more likely to respond.

DR. HUSSAIN: Dr. Kane?

DR. KANE: I would like to add two points. The substantial benefit requirement is a federal legal requirement. That is federal law and the statement is "substantial benefit."

The other thing, thinking backwards with regard to your question about the PR patients, in the definition of PR by the CLL working group, it states that patients should have some improvement in blood counts, for example, as a correlate of a clinical effect and that this also should last at least two months. So, there is more than just a shrinkage of a lymph node in that PR category, not a great deal, not what we would like but there is something there.

DR. HUSSAIN: Dr. Ascensao?

DR. ASCENSAO: In this venue of sort of

asking clarification questions, it was mentioned by the sponsor that they are doing, quote, a confirmatory trial. So, my question to the FDA is if the confirmatory trial is really negative, what then does that do to this, quote, accelerated approval should this drug be approved and the confirmatory trial becomes negative? I have a couple of other questions.

DR. HUSSAIN: FDA, do you want to respond?

DR. DAGHER: I want to take one step back before I answer that question. That is, when Dr. Pazdur and Dr. Kane were clarifying a little bit more about what we have seen so far, and to take it one step further and look at that versus the proposed study, clearly, the proposed study is of interest. It is a randomized trial. It is an add-on design. But there are two issues. One is what was mentioned already, which is that it is a slightly different population, that you are treating the up-front population.

The second is that you are dealing with a different baseline regimen. As Dr. O'Brien

mentioned, if we view Genasense, in her words, as a chemosensitizer, and given the other information we know which is that we do have at this point, for whatever reason, a lack of effect on the time-to-event endpoint or other endpoint from the study that was completed, one would have to question then how would information from this proposed study translate into an interpretation of the perceived benefit in the population that was already studied in the completed study.

So, the population is slightly different. You are talking about first-line versus patients who have previously been treated. The second is that you have a different baseline regimen in the proposed studies, fludarabine and rituximab. Based on what was already presented, I don't know what the potential relationship would be between an effect of adding Genasense to fludarabine/rituximab regimen versus what was already studied.

The other is that Dr. O'Brien made the point that it is not surprising that we don't have an effect on, let's say, TTP/PFS endpoint given

that only a certain proportion of patients were influenced if we are looking at an element of response. I guess my question in terms of the overall development, kind of related to your question, is why would be expect an effect on PFS in the proposed study if we didn't see an effect on time-to-event endpoint in the completed study? Is it because there is some belief that the chemosensitization effect of Genasense with the fludarabine/rituximab regimen is somehow going to be different? That would be something that would be of interest I think, if we had some discussion of that. I think that relates to the questions raised already.

DR. HUSSAIN: Due to time, I am going to ask that we take one more comment from Miss Mackinnon. Dr. Ascensao, you have more questions?

DR. ASCENSAO: I have a couple, yes.

DR. HUSSAIN: Brief or not so brief?

DR. ASCENSAO: Brief.

DR. HUSSAIN: They had better be very brief!

DR. ASCENSAO: Another question was basically, just as in issue of clarification like Dr. Perry asked, if you remove the indication for refractory disease, because, you know, it has been shown very clearly that there is no indication or advantage, is that possible? Doable? That is a clarification issue.

DR. HUSSAIN: FDA?

DR. JUSTICE: The committee can certainly make that recommendation but it is a subset analysis that you are looking at.

DR. ASCENSAO: No, I understand that and I am not trying to discuss the issues about subset analysis. Other people in this room are better qualified for that and that is not the issue. But in response to Dr. Rodriguez also, you mentioned fludarabine refractoriness and, obviously, this doesn't really affect that. We are talking about fludarabine sensitive, if at all. And, I would say that there are a number of drugs that work, like pentostatin for example. CamPath, albeit toxic, is a medication that has been tested alone and in

combination in other settings. So, I think there is a dearth of other possibilities.

The question is what should come next and, as some of the patients have pointed out when they have consulted different clinicians they have been offered different alternatives to therapies.

DR. HUSSAIN: Miss Mackinnon?

MS. MCKINNON: I want to actually make the point that as a patient with an nPR, I was really happy to get it. In case some of the people here didn't understand, an nPR is a really good thing and it has been a great thing for me, and it has been every bit as good as for some people I know with CRs.

I want to reinforce what Dr. Rodriguez in her clinical work has, with this disease you can't predict much of anything except in some very bad cases or some very good ones. For the vast majority of the patients that fall in the middle, no one knows how they are going to progress, the speed and what drugs they will respond to well. Nobody knows. Doctors make their very best guess,

like they do all the time. That is their job. And, the more weapons they have in their arsenal, the greater chance of a patient--because patients do have more than one chance to get treated in this disease. It is not like acute diseases and it hopefully will become one more of maintenance and management of a disease. A cure would be great but I don't even worry about that at this point.

I run a support group and I am familiar with at least 50 patients, none of whom have had the same treatments over the life of their disease; none of whom have responded identically. It is just a totally non-homogeneous disease and it does put a heavy burden on the doctor to choose well, very, very heavy burden, and a patient's burden to ask the right questions, of course.

But adding another weapon to the arsenal, and they all do get refined once they get out there for a while and we all have to admit that that is what happens. But I am always hesitant when I do see 20 people versus 8 people getting a good response to cut off that possibility to a group of

patients, in particular given the nature of this crazy disease and the diversity of the patient base that is out there. That is all I have to say.

DR. HUSSAIN: We are going to go to the vote. Can we have the question up? While the question is being put up, I wanted to ask Dr. Itri a quick question. Will this drug be available, irrespective of what the vote is here today, should the FDA decide not to approve it? Will this drug be available for compassionate use?

DR. ITRI: No, it will not.

DR. HUSSAIN: It will not? Thank you.

So, the question before us is does this single study, with a ten percent improvement in CR plus nPR rate but no demonstrated improvement in overall response rate, CR plus nPR plus PR, time-to-progression, survival or symptomatic benefits between the two study arms demonstrate substantial evidence of effectiveness for Genasense in this CLL population?

We are going to ask when you begin voting, and we are going to begin with Dr. Perry, to first

identify yourself. Dr. Rodriguez, you are not a voting member and we are beginning with the voting people.

DR. GRILLO-LOPEZ: I am Dr. Grillo-Lopez--

DR. HUSSAIN: Dr. Grillo-Lopez, I apologize.

DR. GRILLO-LOPEZ: --but as a matter of personal privilege or of order, I would like my opinion to be heard.

DR. HUSSAIN: All right. We have a statement that is to be read.

MS. CLIFFORD: For the record, although CDER greatly values the scientific and technical input of its industry representative, as per the committee charter, the industry reps are not authorized to vote and such a vote will not be counted. Just as an FYI. Thank you.

DR. GRILLO-LOPEZ: Not a vote; it is an opinion. Again, as a matter of personal privilege or an issue of order, I would like my opinion to be heard.

DR. HUSSAIN: Thank you, Dr. Grillo-Lopez.

We are going to begin with Dr. Perry. Each member is to identify themselves; give their vote, a yes or a no on this question. I would like you to give the committee a reason, a one sentence reason why you are voting a yes or a no. I think that would be very helpful to understand where people are coming from in their votes.

DR. GRILLO-LOPEZ: Could you clarify then for me, does that mean that this committee will not listen to my opinion on this matter?

DR. HUSSAIN: Dr. Grillo-Lopez, we will hear your opinion after the vote. The vote is intended for voting members. Your opinion is valued but, unfortunately, it doesn't count towards the vote. Consequently, I will begin with Dr. Perry who is a voting member. Dr. Perry?

DR. PERRY: Perry, and I vote no. I vote no because I don't believe it has demonstrated substantial evidence of effectiveness. If it could be reworded as minimal or moderate demonstration of effectiveness I would feel more comfortable. But by including the word "substantial" in there, I

don't think ten percent means substantial to me.

DR. BUKOWSKI: Ron Bukowski, Cleveland Clinic. I vote no. I don't see the data to support the efficacy of this drug in the randomized setting, namely, the surrogate endpoints of time-to-progression or symptomatic improvement. I think those are critical to see in this kind of a trial. We didn't see it and I just don't understand why they weren't there in that case.

DR. RODRIGUEZ: I vote yes because in the setting of the patient population--

DR. HUSSAIN: Please identify yourself.

DR. RODRIGUEZ: Dr. Rodriguez, and I am medical oncologist. I vote yes because comparative to other drugs that are used for the same application that this drug is being applied for, it has equitable efficacy.

DR. LINK: Michael Link. I vote no because I do not believe that the results show compelling clinical benefit.

DR. HARRINGTON: David Harrington. I vote no because I don't see that the results show any

evidence at all translating into a population benefit, and the lack of ability to predict in advance with some likelihood who the responders will be.

DR. HUSSAIN: Hussain. I vote no for the same reasons that my colleagues listed.

DR. LYMAN: Gary Lyman. I vote no for the reason that the drug has not shown what I would define as a substantial evidence of benefit, and also concern over the doubling of serious adverse events with this agent.

MS. HAYLOCK: Pam Haylock. I am an oncology nurse. I vote yes, primarily because I think within the population there clearly are people who do respond well to this who would not have responded otherwise so well, and I think that the population does include this group who respond well and I think that this should be available to them.

MS. MACKINNON: Diane Mackinnon. I vote yes just because I think that there will be some value added sufficiently to satisfy me and a number

of members who have this disease.

DR. ASCENSAO: Joao Ascensao. I vote no. I don't believe the drug provides substantial improvement as defined. I would like to make a qualifier. I think perhaps in other settings this drug may provide a useful addition to our common use of available options for our patients.

DR. HUSSAIN: So, there were three yes and seven no. Correct? Three voted yes; seven voted no. Dr. Grillo-Lopez, your comments, please?

DR. GRILLO-LOPEZ: I am the industry representative on this committee going on for three years now. I guess because I am the industry representative I am assumed to be biased and, therefore, the FDA does not grant me a vote. But I do have a voice and I would like to be heard, and since this is not possible during the voting itself, and this is new as of today because previously I have been able to express my opinion during the voting, I ask that from now on I be given a turn before the voting begins so that I can express my opinion. After the fact it has less of

an impact.

In addition to being the industry representative, I am also a hematologist/oncologist and I have treated a significant number of CLL patients in my time. I have also had a large number of CLL patients in my clinical research studies so I do think of the patient. I am also a cancer survivor myself, which is another reason why I think of the patient.

In this case I have three issues that, to me, are very important and that I have considered. The first one is that, clearly, CR plus nPR is important and it is better than getting a PR or not responding at all. Genasense more than doubles the CR plus nPR rate compared to F/C. I think that is clear. You can say it is a ten percent increase or you can say it is more than a doubling. And, as a patient I would be interested in something that more than doubles my chance of getting a CR plus nPR.

Secondly, this population, those that do achieve a CR plus nPR, does have a longer duration

compared to the F/C-treated patients. It is a smaller population. It is a subpopulation and may not significantly affect duration in terms of TTP, PFS etc. However, we have to consider that the appropriate endpoint is not the duration for the entire population as a whole since they are not all subject to this improvement, but perhaps that of the patients achieving CR and nPR. If I were a CLL patient and were to achieve a CR or an nPR, I would like to know precisely what has been shown in this study, that I can get a better response with Genasense plus F/C than with F/C alone.

Thirdly, previous approvals, namely fludarabine and CamPath--the results of those studies have been mentioned today and some emphasis has been placed on the duration of response in those studies, but those studies were single-agent studies. Even though in one case there may have been mini-pooling, and in the other case those durations were short, there was no comparative arm. There was no control arm in those studies and, thus, they are meaningless in terms of comparison

and what would have happened if there were a control arm. So, basically, those approvals were based on response rate, just like this one could have been based, or may still, because the FDA has a decision to make, based on CR and nPR. Thank you.

DR. HUSSAIN: Thank you, Dr. Grillo-Lopez. Just to comment on your statement earlier on, you were given the opportunity to give your opinion during the discussion so your opinion was not blocked or excluded, certainly not by myself.

DR. GRILLO-LOPEZ: Yes, but this is the first time in the three years I have been a member of this committee that my opinion has not been heard during the vote, and I did not know that that was going to happen, otherwise I would have expressed it earlier.

DR. HUSSAIN: The vote is a vote; it is not an opinion. Thank you.

Thank you very much for this morning's session. I would like to conclude it and we will assemble here for this afternoon's session at

precisely one o'clock. Thank you.

[Whereupon, at 11:55 a.m., the proceedings were recessed, to resume at 1:00 p.m.]

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