DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

Wednesday, December 1, 2004

8:00 a.m.

Holiday Inn, Silver Spring
8777 Georgia Avenue
Silver Spring, Maryland

PARTICIPANTS

Victor Santana, M.D., Acting Chair (a.m. session)
Silvana Martino, D.O., Acting Chair (p.m. session)
Johanna Clifford, M.S., RN, Executive Secretary

MEMBERS

Otis W. Brawley, M.D.
Ronald M. Bukowski, M.D.
Bruce D. Cheson, M.D.
Stephen L. George, Ph.D.
Pamela J. Haylock, RN
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Maria Rodriguez, M.D.

INDUSTRY REPRESENTATIVE (NON-VOTING)
Samuel Maldonado, M.D.

CONSULTANTS (VOTING)

For clofarabine

Joanne Kurtzberg, M.D.
David Poplack, M.D.
Victor Santana, M.D.
Alan Wayne, M.D.

For Marqibo

Michael Bishop, M.D.
Wyndam Wilson, M.D., Ph.D.

PATIENT REPRESENTATIVES (VOTING)

Ruth Hoffman - for clofarabine
Susan Krivacic - for Marqibo

PARTICIPANTS (Continued)

FDA

Martin Cohen, M.D.
Ramzi Dagher, M.D.
Ann Farrell, M.D.
Maitreyee Hazarika, M.D.
Steven Hershfeld, M.D.
Richard Pazdur, M.D.
Robert Temple, M.D.
Grant Williams, M.D.

C O N T E N T S

C O N T E N T S (Continued)

Afternoon Session

P R O C E E D I N G S

Call to Order

DR. SANTANA: This is a meeting of the Oncology Drugs Advisory Committee for the FDA with additional pediatric oncology representation this morning because we are going to discuss a new drug application for the proposed drug clofarabine.

With that brief introduction, I want to make two comments. First of all, I really want to keep the agenda on schedule. We will allow all the presentations to occur both from the sponsor and from the FDA, and then we will proceed with a period of discussion and comments, have our break, and then come back and deal with questions and the advice to the Agency.

So, I really want to keep on schedule as much as possible, because there is another schedule this afternoon that the Committee has to abide to, and I want to make sure that they get their opportunity this afternoon, too.

Secondly, I want to go ahead and do a very brief introduction of all the members of the

Committee, since we have additional pediatric oncology representation today. So, if we could go around the table starting with Dr. Poplack on the left corner, introduce by name and affiliation.

Introductions

DR. POPLACK: David Poplack from Baylor College of Medicine.

DR. KURTZBERG: Joanne Kurtzberg from Duke University Medical Center.

DR. WAYNE: Alan Wayne from the National Cancer Institute, Pediatric Oncology Branch.

MS. HOFFMAN: Ruth Hoffman, Patient Rep., Candlelighters Childhood Cancer Foundation.

DR. MALDONADO: Samuel Maldonado from Johnson & Johnson, Industry Representative to this Advisory Committee.

DR. GEORGE: Stephen George, Duke University.

MS. HAYLOCK: Pamela Haylock, Oncology Nurse, Consumer Representative.

DR. HUSSAIN: Maha Hussain, University of Michigan.

DR. PERRY: Michael Perry, University of Missouri, Ellis Fischel Cancer Center.

DR. MORTIMER: Joanne Mortimer, University of California, San Diego.

DR. SANTANA: Victor Santana, St. Jude Children's Research Hospital in Memphis.

MS. CLIFFORD: Johanna Clifford, Executive Secretary to the ODAC.

DR. MARTINO: Silvana Martino from the John Wayne Cancer Institute.

DR. BRAWLEY: Otis Brawley from Emory University.

DR. CHESON: Bruce Cheson, Georgetown University, Lombardi Comprehensive Cancer Center.

DR. BUKOWSKI: Ronald Bukowski, Cleveland Clinic Foundation, Cleveland, Ohio.

DR. COHEN: Martin Cohen, FDA.

DR. DAGHER: Ramzi Dagher, Pediatric Oncologist and team leader in the Division of Oncology Drug Products, FDA.

DR. WILLIAMS: Grant Williams, FDA.

DR. PAZDUR: Richard Pazdur, FDA.

DR. SANTANA: With that, I will hand it over to Johanna. She needs to read the Conflict of Interest Statement.

Conflict of Interest Statement

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 the 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 conflict of interest at this meeting with the following exceptions:

Dr. Victor Santana has been granted a waiver under 21 USC 355(n) for owning stock in a competitor. The stock is valued from $5,001 to $25,000. A waiver under 18 USC 208(b)(3) is not required because of the de minimis exception 2640(b)(2) applies.

Dr. Stephen George has been granted a

waiver under 18 USC 208(b)(3) for serving as a consultant to the competitor on an unrelated matter. He receives less than $10,000 per year.

Ms. Ruth Hoffman has been granted a waiver under 18 USC 208(b)(3) because her husband serves as a consultant to two competitors on unrelated matters. He receives less than $10,001 per year.

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to note that Dr. Samuel Maldonado has been invited to participate as the Non-Voting Industry Representative acting on behalf of all regulated industry. Dr. Maldonado is employed by Johnson & Johnson Pharmaceutical Research and Development.

In the event that the discussions involve any other products or firms not already on the agenda for which am 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. SANTANA: Thank you, Johanna. Any other Committee member want to disclose any conflict at this moment?

[No response.]

DR. SANTANA: Thank you. We will go ahead and have Dr. Pazdur give us the introduction from the FDA perspective.

Opening Remarks

DR. PAZDUR: Good morning. The sponsor of the application in this morning's session requests marketing approval of clofarabine for the proposed indication of the treatment of pediatric patients with refractory or relapsed acute leukemia.

The presentations will focus on one single-arm trial conducted in 35 patients with

relapsed, refractory AML and a second single-arm trial in 49 patients with relapsed, refractory ALL. A Phase I study was also conducted in 25 patients with relapsed or refractory acute leukemia.

For the treatment of acute leukemia, the Division has recommended the use of improved survival or a complete response rate of a sufficient magnitude and duration to ensure the demonstration of clinical benefit.

Complete response rates of sufficient duration are considered clinical benefit, because they are usually associated with reductions in infection rates and blood product transfusions, and may be considered established surrogates for survival in this disease.

Response duration is usually measured from the time of initial response until documented tumor progression. One problem encountered in this application is the introduction of bone marrow transplantation in patients who have received clofarabine, but have not had documented disease progression.

The addition of transplantation prior to the documentation of disease progression confounds any interpretation of clofarabine's response duration. No consistent prospective criteria were used to determine patient selection for transplantation. Some patients went to transplantation with only a clofarabine partial response or even without a response in these single-arm trials.

A clofarabine induction response may simply indicate a chemosensitive-leukemia and the patient might do as well with transplantation without clofarabine induction.

In patients who did not go on to transplantation and, hence, response duration, can be measured. These response durations were generally short and many of these responses were of uncertain duration because they were not confirmed by a repeat marrow aspirate.

These results are presented in the preamble to your ODAC questions. In 35 patients with AML, there were no complete responses, only 1

complete response without complete platelet recovery, a so-called CRp, and 8 partial responses.

Of the 9 responding patients, 2 patients did not go on transplantation prior to disease progression. These patients had PR's. Their response duration was short, 12 and 34 days.

Of the 49 patients with ALL, there were 6 CR's, 4 CRp's, and 5 PR's. In this population, response duration was not confounded by transplantation in only 9 patients. The 5 patients with CR's had response durations of 43, 50, 82, 93+, and 160+ days. Only 3 of these 5 CR's had a confirmed response. As in AML, PR's had a very short duration of only 7, 16, and 21 days.

As stated previously, the Agency has recommended a substantial complete response rate and duration at endpoints for regular approval in hematological malignancies denoting clinical benefit.

In 1992, the accelerated approval regulations allowed the use of additional endpoints for the approval of drugs that are intended to

treat serious and life-threatening disease and that either demonstrate improvement over available therapy or provide therapy where none exists.

The FDA may grant accelerated approval based on the effect of a surrogate endpoint that is "reasonably likely" to predict clinical benefit.

A drug is approved under accelerated approval on the condition that the manufacturer conduct studies to verify and describe clinical benefit. The regulations stated an expectation that post-marketing studies would usually be underway prior to accelerated approval, however, this is not a requirement.

At a March 2003 ODAC meeting, the ODAC reinforced the Agency's view that these confirmatory trials should be ongoing at the time of accelerated approval is granted. Approval with subsequent commercial availability of the drug may interfere with subsequent enrollment to the confirmatory trial.

We, the Division, are asking your opinion regarding the accelerated approval of clofarabine

based on the data presented. The ALL indication should be considered separately from the AML indication. There exists uncertainty regarding the response duration because of the lack of subsequent bone marrow biopsies to confirm a response and the introduction of transplantation prior to the documentation of disease progression.

Where durations can be measured, the Division considers, with some exceptions, these response durations to be limited. We have asked the sponsor to present ongoing planned trials in both pediatric and adult leukemia. Presently, we have not identified any study that has been designated as a confirmatory trial for the subsequent demonstration of clofarabine clinical benefit.

For our Division, this is the first time we are considering a pediatric application for accelerated approval. Pediatric drug development in the treatment of pediatric malignancies differs from adult drug development, therefore, we have supplemented this ODAC membership with voting

members from the pediatric oncology community.

Pediatric drug development has been blessed by an exceptionally high rate of patient enrollment compared to enrollment in adult studies. Great strides have been made in curing and prolonging the survival of children in the past decades. Most children, especially with the diseases under consideration this morning, are treated on protocols at referral centers rather than in the community.

Your discussions should consider the ramifications of accelerated approval for the pediatric development of clofarabine. Approval of the drug for a pediatric indication should not be at a lesser standard than that expected for an adult indication.

Approval decisions should be based on a risk-benefit determination. A reasonable question is whether the necessary information regarding this risk-benefit relationship can be derived from a single-arm study where the primary endpoint is confounded by the introduction of a subsequent

therapy, specifically bone marrow transplantation.

Your decision regarding the approval status of this drug should be based on the above scientific decision, not simply a desire to provide drug access to patients. Access to a yet approved drug, especially with a limited patient population encountered in these applications, can be accomplished through additional registration trials and expanded access programs.

We are interested in your discussion on the impact of this drug's accelerated approval at this time, and the timely completion of any confirmatory trials in pediatric oncology. An appropriate question is whether the drug approval at this time, especially since the designated confirmatory trial is not underway, may interfere with the conduct and completion of confirmatory trials.

Discussions may focus on whether approval of this drug, with its response rate and uncertainties regarding response duration, is appropriate, or whether additional data should be

available before a definitive approval decision is made.

Thank you.

DR. SANTANA: Thank you, Dr. Pazdur.

I want to note for the record that Dr. Temple has joined the table. If you would briefly introduce yourself, Dr. Temple.

DR. TEMPLE: Good morning, everyone, sorry I am late. I am Dr. Robert Temple. I am the office director of the office in which oncology lives.

DR. SANTANA: Thanks. We will go ahead with the sponsor presentations, and I would ask the sponsor to go ahead and follow the schedule, and after each speaker, the next speaker can get up and follow with their presentation.

Thank you.

Dr. Weitman.

NDA 21-673, Clolar (clofarabine)

ILEX Products, Inc.

Sponsor Presentation

Introduction

DR. WEITMAN: Good morning. I am Dr. Steve Weitman, Chief Medical Officer for ILEX Oncology. I am also a pediatric oncologist.

I would like to start by thanking the ODAC panel members, as well as the FDA today, for the opportunity to be here today to present the results of our clofarabine studies in pediatric patients with acute leukemia.

[Slide.]

I would also like to start by just recognizing some of the pediatric leukemia experts that are here with us today, as well as the investigators in a number of our trials that are also here, that may help present and also answer any questions that may come up during later parts of this discussion today.

[Slide.]

Following my brief introduction, I am going to introduce Dr. Robert Arceci, who is here today to talk about pediatric leukemia and the need for new treatments. I will then return to the podium and talk about the results from our two

pivotal studies in pediatric patients with acute leukemias.

Then, Dr. Steve Sallan will come up to the podium. Again, he was not an investigator on any of our studies, but will provide his perspective as a pediatric oncologist and caregiver regarding what clofarabine means to him.

Then, I will return, as Dr. Pazdur alluded to, to talk about our plans moving forward with clofarabine both in the pediatric population, as well as in adults with acute leukemias.

With that, let me introduce Dr. Robert Arceci.

Pediatric Leukemia: Need for New Treatment Options

DR. ARCECI: Thank you, Steve, and thank you, Dr. Santana and the Committee for allowing us to present these data. I am a pediatric oncologist and was an investigator on the clofarabine trials.

[Slide.]

What I want to try to do is to give you an overview of the situation that we deal with in pediatric oncology particularly with regard to

pediatric acute leukemias.

Currently, treatments for newly diagnosed patients with acute lymphoblastic and acute myelogenous leukemia all use very aggressive combination chemotherapies, quite intensive and have been become increasingly intensive over the past 10 years.

The overall survival for pediatric patients with ALL and AML has improved significantly, but over the past 5 to 10 years, has started to approach plateaus. This is in spite of a maximum intensification that we are using, so new drugs clearly and new approaches are needed in this group. Despite that intensification, 20 percent of patients with acute lymphoblastic and possibly a little more than 50 percent of patients with myelogenous leukemia will have disease recurrence.

[Slide.]

Those numbers lead to the following conclusion, that that is, relapsed acute leukemia represents the third most common cancer that we deal with in pediatric oncology, so although an

orphan disease, this is a major problem for those of us treating patients in pediatric oncology.

[Slide.]

Now, the challenge to approach that group is immense. We know that at relapse and even at diagnosis, these relapsed leukemias represent a very heterogeneous group of diseases. At the time of relapse, they are usually multi-drug resistant, and that resistance crosses most of our conventional drugs, so it is a major problem and multifactorial.

Dose intensification with combination chemotherapies, as I mentioned to you, for newly diagnosed patients often leads to much more heavily treated patients than we did 10 or 15 or 20 years ago, so this group of patients have highly resistant disease, and they often have co-morbidities in terms of organ toxicities when they relapse.

In many respects, transplantation is not only the best, it is possibly the only curative therapy we have for these children. So, getting

them to transplant in a state of what we would expect to be minimal residual disease is a vital and important component of how pediatric oncologists approach these children.

[Slide.]

This just shows you some data. Although from 1997, the fact of the matter is the data have not changed significantly since these data were published. These are patients and their outcomes who had relapsed and refractory pediatric leukemia treated with chemotherapy only, and this is primarily data from pediatric oncology group studies, Phase II studies. In 2004, these results are really no different.

Transplantation, I should note can improve the outcome of those patients somewhat.

[Slide.]

Now, in spite of what I have told you, few agents have been approved for pediatric leukemia. The most commonly used agents that have been approved, have been approved many years ago, 1950s onward.

The development of new agents that are well tolerated and more effective becomes an increasingly important part of what we are trying to accomplish in our field in pediatric oncology.

[Slide.]

So, to conclude, and I hope this gives you a bit of a feeling for what we are dealing with, is that relapsed leukemia is the third most common cancer we deal with. Successful treatment for relapsed and refractory pediatric leukemias remains an enormous challenge for us.

These are children who often don't have very much time because of the progression and rapid rate of growth of their leukemias. Patients with these multi-drug resistant leukemias also have these co-morbidities because of prior intensification therapies, therefore, we conclude at least that we need well tolerated, new, and effective agents to induce minimal residual disease states, to get responses, so we can then move towards a more curative approach.

Thank you very much.

DR. WEITMAN: Thank you, Dr. Arceci.

What I would like to do now is tell a little bit of a story, really a story of how we got to this podium today to present the results of our pediatric studies in acute leukemia.

I think, as most pharmaceutical companies do, we started our adult Phase I study back in 1999, and that was followed shortly thereafter, approximately 18 months later, by our Pediatric Phase I study.

For those of you who are familiar with pediatric oncology, I think most of us would recognize it is becoming a more and more traditional pathway in which new agents are introduced into the pediatric environment.

The results that we saw of this study, though, were very striking as regards to the Phase I study, and particularly in a very heavily pretreated population of patients and with an acceptable profile.

The results of these studies, though, were

extremely impressive and really propelled the studies and the program in pediatric oncology forward at a much faster rate than otherwise would be expected.

In addition, because of the fact that there was a lack of other opportunities in other protocols for these patients, because many of these patients would not qualify for other studies, we saw an increase in demand for access to this drug by pediatric oncologists.

Because of this, we also opened up an expanded access program that was focused almost exclusively on the pediatric population.

[Slide.]

This next slide shows somewhat of a timeline of our program to date, and if I can just walk you through this. As you can see on the top of the slide, the adult studies are in blue. On the bottom of the timeline, the yellow represents the pediatric studies.

As you can see here, again, the Phase I study in adults was started back in 1999. This was

followed 18 months later by the pediatric Phase I program. Subsequent to this, two adults Phase II programs were started with a predominant focus on patients with AML.

We then started our two pediatric programs, one in AML and one in ALL in 2002. Again, following that was the Phase I/Phase II combination studies with clofarabine and ara-C in adult patients, again predominantly with AML.

You can see, moving forward, our plan is to do a Phase II study with clofarabine and ara-C in patients with AML, but there has also been interest in the same study in patients with ALL through the Children's Oncology Group.

But I think this slide shows you again the stepwise approach that we have taken where the adult studies preceded the pediatric program, but it was really the results of the Phase I study in the highly refractory-resistant population of patients that propelled our program in pediatrics forward at a much faster rate than what otherwise may have happened.

What I would like to do now is to talk a little bit about that Phase I program because again I think it was pivotal in our decision to move forward with this program.

[Slide.]

As you can see here, and as Dr. Pazdur noted, 25 patients were enrolled in this program. Dose levels ranging from 11 to 70 mg/m 2 with MTD or recommended Phase II dose being 52 mg/m 2 for 5 days. The dose-limiting toxicities of this study were increases in bilirubin, as well as skin rash.

Now, most Phase I studies are not designed to really characterize the response rate in this population of patients. However, again, I have conducted a number of studies in both solid tumors and pediatric patients with leukemia, and what really struck us was an over, really impressive response that we are seeing in this patient population. There were 5 CR's noted in this patient population.

I should note that 4 of these CRs lasted more than 50 weeks. One of these CRs was in a

patient with AML that had failed fludarabine and ara-C before coming onto the clofarabine study.

Following this, this patient refused to go on to transplant and stayed on clofarabine for 8 cycles, and then stayed in remission for 43 weeks after clofarabine treatment. Again, that was a patient with AML.

As you can see here, we also had 3 patients who had a PR, and 7 of these 25 patients went on to a bone marrow transplant or stem cell transplant.

[Slide.]

Because of these results, we again moved forward with 2 studies, one in acute myelogenous leukemia, the other one in ALL. The primary endpoint for both of these studies was overall response rate defined as complete remission, as well as complete remission without full platelet recovery.

A Fleming 2 stage design was used in these studies. However, we began to see very early on in this program that patients much more heavily

pretreated than we had ever anticipated began coming on to study. In fact, most of the patients that were being enrolled had undergone a bone marrow transplant, in come cases 2 transplants, before coming on study.

In addition, as you can see here, some of the patients had up to 6 prior regimens before being treated with clofarabine. In addition, one other confounding factor, that has already been alluded to, many of these patients were being taken off study very quickly to move to transplant, and I will talk about that a little bit later on.

Again, a lot of these patients were PR in which they had 0 to 5 percent blasts, but did not have full ANC recovery, so because of that, they were still considered a PR, but were going to transplant.

In addition, a lot of these patients did not go on to second or third cycles of treatment because they had a donor that was identified and wanted to move to transplant.

Following discussion with our external

thought leaders, and well as the FDA, we decided to expand these studies to get a better determination of the response rate in this highly refractory patient population.

What I would like to do now is just walk you through a couple slides that I think again highlight how heavily pretreated this patient population is.

[Slide.]

This slide shows the number of unique agents that these patients were exposed to prior to coming onto the clofarabine study. As you can see here on the left-hand axis, this is the number of unique agents, and across the bottom is the patient number.

This first slide is for patients with ALL. This first patient had 12 unique agents before coming on to clofarabine, and then had also a bone marrow transplant.

[Slide.]

The next patient, patient 7, I just want to highlight had 9 unique agents, a bone marrow

transplant that included total body irradiation. As you can see here, for the rest of the patients, again, this was an extremely heavily pretreated patient population. In most cases, the patients received anywhere from 9 to 12 unique agents.

Some of the patients received up to 16 unique agents before coming on the study. Many of them also had bone marrow transplant and many of them have also had total body irradiation.

[Slide.]

This patient here, that had 16 unique prior agents, also had two prior transplants, as well as total body irradiation as part of the conditioning regimen for the transplant. This patient went on to achieve a CRp after treatment with clofarabine.

[Slide.]

This next slide again is a very similar presentation of the number of unique agents that these patients had been exposed to prior to coming onto the clofarabine study.

As you can see here, again, your first

impression, or at least my first impression, was the fact that these were patients who were less heavily pretreated than those with ALL. In fact, they were probably more heavily pretreated than the patients with ALL.

Both sets of diseases, ALL and AML, the patients had been exposed to a median of 3 prior regimens before coming on study. It appears that there are a fewer number of unique agents that these patients were exposed to, where, in fact, I think that represents two important findings.

Number one, that there are fewer options for patients with AML particularly at the time of relapse. In addition, many of these patients received the same agent over and over and over again during their treatment courses, so again, they appear to be less heavily pretreated, but, in fact, I think again they were just as heavily pretreated and likely just did not have many options as far as new agents to be used.

[Slide.]

What I would like to highlight is one

patient in particular, just because I think this again shows how heavily pretreated this patient population was, and it also points out a number of other key findings.

This is a 4-year-old with AML that was, as you can see here, treated with multiple regimens before coming on to this study. This patient I think was most notably exposed to a number of nucleoside analogues including cytarabine, thioguanine, gemcitabine, fludarabine before being treated with clofarabine.

I think again it is important to note that this patient received cytarabine 4 times in different treatment regimens during the course of his disease. Regimen 3, asparaginase/cytarabine, this patient was refractory to that treatment, and then went on to receive a multi-agent regimen, again was refractory to that treatment. Then, went on to receive cytarabine and idarubicin.

This patient did go into remission in October of 2001, and again as it very commonly seen when there is a donor available, this patient moved

very quickly to transplant. So, in December, approximately two months later, this patient went into transplant, being conditioned with TBI, thiotepa, and fludarabine, and then underwent a stem cell transplant.

This patient stayed in remission until July of 2002, approximately 30 weeks from the very start of cytarabine/idarubicin until relapsing. In July, this patient underwent clofarabine treatment, received 1 cycle, and then went into complete remission.

This patient went on to receive 5 additional cycles of clofarabine before undergoing a bone marrow transplant, and as data cutoff, this patient is alive with no evidence of disease.

The period of remission from the start of clofarabine to the date of cutoff was over 70 weeks, nearly twice as long as the period of remission from the start of the cytarabine regimen until relapse.

I think this slide also shows again the fact that this patient had been exposed to a number

of nucleoside analogues in the past, as well as cytarabine multiple times before coming onto the clofarabine study, also had been proven to be refractory to a number of the best agents that we have available right now in pediatric AML.

[Slide.]

What I would like to do now is focus a little bit on the efficacy results from our two studies.

[Slide.]

Before I talk about the two studies, I do want to highlight the database that was used in our analysis. As was noted earlier by Dr. Pazdur, we did analyze patients with ALL separately from those with AML.

However, for safety analysis, we did combine these two patient populations together, and we also included the patients from the Phase I study. So, that is why there is a little bit difference in the patient numbers for the database size for these two analyses.

[Slide.]

Key endpoints of the study were overall response rate, again CR and CRp. It should be noted that an Independent Review Panel reviewed all patients enrolled in the study, and their determination of response was used in all determinations of efficacy moving forward.

In addition, at the time that they determined that a response occurred, that was then used to determine duration of remission.

We also looked at post-transplants, survival, and obviously, the safety profile.

[Slide.]

Now, with regards to patients with ALL.

[Slide.]

Again, I will focus initially on the efficacy results of this study.

Forty-nine patients were enrolled in this study with a median age in years of 12, ranging from 1 to 20. These patients received a median of 3 prior treatment regimens before coming onto the study with a range of from 2 to 6.

Approximately, two-thirds of the patients

were refractory to their last therapy before coming on study, and most of these last therapies again were multi-agent regimens. Whenever there was an evidence, for the most part, of palliative therapy, such as oral etoposide, we would go back to the previous regimen before that.

As you can see here, approximately a third of the patients had bone marrow transplant with ALL before coming onto this study.

[Slide.]

The Independent Review Panel found that 20 percent of the patients enrolled in the study had either a complete response or complete response without full platelet recovery with confidence intervals ranging from 10 to 34 percent.

Patients with at least a PR had a 31 percent response rate, again with confidence intervals ranging from 18 up to 45 percent.

The patients that were deemed refractory to their most recent prior therapy had a response rate of 17 percent. Again, this was for CR and CRp.

[Slide.]

This next slide shows a duration of remission for patients enrolled in this study. As you can see, for patients with at least a PR, the duration of remission was approximately 10 weeks. For patients with a CR and a CRp, the duration of remission was 20.2 weeks.

[Slide.]

Of these patients, again, one of the critical next steps in a curative approach is to try to take these patients to transplant. As you can see here, 14 percent of these patients went on to transplant, 2 with CR, 2 with CRp, and 1 with PR.

The median time to transplant was 32 days, but as you can see here, again, they moved very quickly to transplant in many cases, where in as little as 16 days, the patient would go to transplant, and this was after following remission induction.

The median number of cycles before transplant was 2, and 5 of 7 patients are alive post-transplant.

[Slide.]

This slide represents the overall survival of patients enrolled in the ALL study. The bottom green line represents overall survival for patients enrolled in the study of 11.7 weeks. If you look at the top line, this is for patients with a CR or a CRp where the overall survival was a little bit over 1 year.

[Slide.]

Now, to move on to our studies in patients with AML.

[Slide.]

Thirty-five patients were included in this study. The median age was 12 with a range of from 2 to 22. Again, as I noted earlier, the number of median regimens was 3 prior to coming onto this study. Sixty-three percent of these patients were refractory to prior therapy, and over half of these patients had some form of bone marrow transplant before coming onto this study.

[Slide.]

The Independent Review Panel found that 1

patient had a CRp and that there were 26 percent of patients who had at least a PR. Again, as has been noted, PR's are not typically viewed in hematologic malignancies as a benefit, however, this PR allowed many of these patients to move on to transplant that may not have otherwise had that opportunity.

Four of the patients that were refractory to prior therapy did have a PR. It should be noted that 3 of these patients went on to transplant and 2 of these 4 patients are still in remission today following clofarabine and transplant. One of these patients had failed cladribine and idarubicin before coming onto the study.

Again, this was a patient with AML, received 1 cycle of clofarabine and went into remission, and that he had zero percent blasts in this bone marrow, his ANC was increasing, however, it did not reach the threshold of 1,000, which was needed for a CR. Before reaching that threshold, the patient went on to transplant, and is now in remission 58 weeks since undergoing clofarabine and bone marrow transplant.

[Slide.]

This slide shows the duration of remission for all patients that had either CR, CRp, or a PR in the AML study. The median duration was 16.2 weeks.

[Slide.]

Again, one of the key endpoints for any patient at this stage is to get to transplant, particularly in patients with AML where a PR may be more meaningful than certainly in patients with ALL.

As you can see here, over a third of the patients went on to transplant, 1 patient with a CRp, 6 patients with a PR. As has been noted in your briefing document and some of the questions that you received, 2 of the patients had treatment failure, still went on to transplant.

I think these 2 patients are worth noting and explaining in a little bit more detail.

The first patient had 98 percent blasts at study entry. After a cycle of clofarabine, this patient dropped down to 2 percent blasts in the

bone marrow. However, when the IRP looked at that patient's report and smear, they noted that there were still some myelomonocytic cells present, so they considered that patient a treatment failure. However, this patient still went on to transplant because the treating investigator felt that the 98 percent blast at entry down to 2 percent was substantial cytoreduction to allow this patient to go on to transplant.

The other treatment failure that is listed on this slide is a patient with monosomy 7. Again, I think most of the pediatric oncologists would recognize that as a fairly resistant to leukemia. This patient came on study with 68 percent blasts at study entry, went down to zero percent blasts after 1 treatment, and was proceeding to transplant when this patient did, in fact, have a relapse. However, because of that substantial cytoreduction that was still present, and the fact that there was a haplo-identical donor available, the treating investigator still wanted to go to transplant, so while both patients were deemed as treatment

failures by the IRP, there were still significant cytoreduction and benefit afforded these patients, so they could move on to transplant.

I do want to mention just a couple others really quick. Again, the median time to transplant for these patients was 38 days, again, as little as 21 days after remission induction, they would go to transplant.

The median number of cycles was 2, but particularly in AML, they were very interested in going to transplant as soon as possible, because this disease is so difficult to treat.

As you can see at the bottom of the slide, 7 of the 12 patients are alive post-transplant, and 4 of these patients are still in remission.

[Slide.]

This slide shows the overall survival curve for patients with AML enrolled in this study. As you can see, the bottom line is for all patients where the median survival was 21 weeks. The top line represents those patients who had at least a PR where the median survival was 39 weeks.

So, at this point, in summary, as far as the efficacy results, again, recurrent pediatric acute leukemia is a substantial unmet medical need especially for patients with AML where new agents are desperately needed.

We saw impressive response rates for clofarabine in pediatric patients with ALL and AML that had become cross-resistant to most standardly available agents. The duration of remission was long enough and sufficient enough to allow these patients the opportunities for those with donors to be able to proceed to transplant. Long-term survival was observed in patients with both ALL and AML who responded to clofarabine.

[Slide.]

Now, I would like to touch on the integrated safety analysis. Just as a reminder, again, this was combined data from both patients with ALL and AML into one database, as well as those patients from the Phase I study.

[Slide.]

This slide shows all Grade 3 and Grade 4

adverse events that occurred in greater than 10 percent of the patient population regardless of causality. As you can see here, the most common Grade 3/Grade 4 adverse event was fever and neutropenia. This was followed by nausea, fever, epistaxis, hypotension, sepsis, and anorexia.

A couple of factors should be noted here. Number one, most of these patients had been in relapse many times, weeks, if not months, before coming onto this study. If you look at the list of concurrent conditions, many of these events were present at the time of study entry.

[Slide.]

This slide shows the drug-related adverse events as determined by the investigators. Again, these are Grade 3 and Grade 4 events only, that occurred in greater than 5 percent of the patient population.

As you can see here again, fever neutropenia was the most common event, nausea, fever, diarrhea, neutropenia, vomiting, and dermatitis. In almost all cases, Grade 3 was much

more common than Grade 4.

[Slide.]

We also looked at the laboratory abnormalities that were observed in this study. Again, this represents Grade 3 and Grade 4 hepatobiliary and renal abnormalities that were observed.

By far the most common were elevations in transaminases, both ALT and AST. In almost all cases, these tended to occur very early, approximately one week after starting drug, and then would resolve over the next week or two back to baseline. We also saw increases in bilirubin, creatinine, and alkaline phosphatase, but again, in almost all cases, Grade 3 was much more common than Grade 4.

[Slide.]

Deaths during study were fairly equally divided between those from disease progression, as well as those from non-drug or drug related AEs. A couple of factors really stand out when you look at these patients.

Number one, they were extremely heavily pretreated patients before coming on study, many with a variety of concomitant conditions and on a variety of different medications before coming on study. Many of them also had persistent disease or progressive disease, as well as bacterial and fungal infections. We also saw a number of cases of capillary leak in this patient population.

[Slide.]

In summary, again, this study was conducted with extremely heavily pretreated patients. Most of the adverse events were consistent with the underlying leukemia, and the events were not unexpected particularly for a cytotoxic agent, and most adverse events were reversible, and not again unexpected.

At this point, I would like to introduce Dr. Steve Sallan. Again, he was not an investigator on these studies, but he is here today to provide his perspective on clofarabine as a pediatric oncologist and caregiver.

Clinician's Perspective

DR. SALLAN: Thank you very much. Good morning.

[Slide.]

My name is Stephen Sallan and I have been a pediatric oncologist for over 30 years, and have been treating this patient population nearly every working day of my life during that time, and have been very blessed, as have been all the other members of the pediatric oncology community, to watch huge success being made in the 20th century and getting to a point where childhood acute lymphoblastic leukemia is really cured in 75 to 80 percent of children using multidrug chemotherapy, multidrug chemotherapy that you have all seen already, all of which was developed before the 1970s.

In AML, the cure rates are in the 40 to 50 percent range, again principally with multidrug chemotherapy and enhanced by bone marrow transplantation. Clearly, for us, the successful treatment of relapsed and refractory pediatric leukemias is our major challenge.

[Slide.]

Shown on these curves is really a picture of the success story that I have alluded to, and mostly from my medical oncology colleagues at the table, I would like to reiterate that while we are justly proud of these accomplishments, if one looks at the curves, these really end in the '90s.

If one looks at what has happened in the last decade, there has been incremental-only increases, and as Dr. Arceci already alluded to, these are approaching plateaus of about 80 percent in ALL and somewhere between 45 to 50 percent in AML.

[Slide.]

Now, there is no child on those curves who has been cured who probably has not received 6 MP and methotrexate if they had ALL, or cytarabine if they had AML. Interestingly, when we look at these data today, the question is what is the expectation of a single active antileukemic agent, in this case, against de novo ALL, so for this, we really have to look at historic data, and I have adapted

this table from a textbook from 1974.

What you can see is that the workhorses in these diseases, when they are tested against de novo ALL as single agents, gave complete remissions in this 20 to 25 to 30 percent range. I might also say that the stringency of that definition of complete remission, as you look at the old literature, is highly variable.

So, when one sees a population of today's relapsed, refractory patients, it is very difficult to have any comparative population, and, in addition, what impressed me when looking at the clofarabine data, was that we saw a CR and CRp rate that was really in the similar ballpark as effective drugs are against de novo disease.

I think, although I am showing this for ALL, you saw similar results with clofarabine generating principally a CRp and PR's in that population.

[Slide.]

What impressed me about the availability of a new drug again as you have heard, in part, is

that 1 in 5 children with multiple drug resistant ALL achieved a clinical response--sorry for the CR--principally, the majority of those who went to transplant had CR's or CRp's, and as you saw, some PR's, as well, and similarly, for this relapsed, refractory AML population, 1 in 3 children with again multiple drug resistant disease was able to come to transplant.

We strongly believe, as a community, that transplantation is the curative therapeutic option in the early 21st century for children with drug-resistant childhood AML.

[Slide.]

So, in closing, what really impresses me, as a clinician, is that we have a drug, clofarabine, which is well tolerated, very importantly, the absence of overlapping toxicities, so that we can treat these children without additive cardiac, renal, or other organ toxicities permitting them to be good candidates when they get into the transplant setting; that the drug provides a clinical benefit, as shown in our responses, in a

very heterogeneous population, which right now, in 2004, is critically important.

I mean we are all focused in part on targeted therapies, very few, none of which have really come to this population, so the fact that we have a drug that gives a clinical benefit in a very heterogeneous population is extremely helpful, and most importantly, for these children, there are no meaningful alternatives.

I would say it is the last point that really causes me to feel very positive and enthusiastic and really desire to have something that is well tolerated, that is beneficial, and is available now, and that is why this data is important to me.

Thank you very much.

Clofarabine Development Plan

DR. WEITMAN: Thank you, Dr. Sallan. We feel that in some ways, we have embarked on really a historical approach, an approach that is different than what has been in the past when it comes to pediatric oncology patients.

[Slide.]

The approach that we have taken potentially is a new paradigm for getting access to pediatric new agents into the pediatric community.

The sponsor, moving forward, commits to several factors including the further development of this agent in the pediatric oncology population.

Number 1. To continue to follow these patients that are enrolled in these two studies for long-term follow-up data. We also have a commitment to move to less heavily pretreated patients, both patients with ALL and AML, and to ultimately, at some point, proceed to a randomized study with clofarabine in newly diagnosed patients.

This commitment includes a very close working relationship particularly with the Children's Oncology Group, but also through CTEP.

[Slide.]

Just to highlight the program through the Children's Oncology Group, we have two studies moving forward there. One is in AML, and again this is a combination study with ara-C and

clofarabine. This is actually a Phase II study in patients with first relapsed AML.

The study chairs for this are Dr. Razzouk from St. Jude, as well as Dr. Cooper from the University of Alabama.

Again, in ALL, the parallel companion study is a combination of cytoxan with clofarabine, but there has also been interest from the Children's Oncology Group to look at clofarabine in combination, not only with etoposide, but also with ara-C.

Again, this is a different population of patients that we have studied in this submission. In these follow-up studies, we are looking at less heavily pretreated patients, in this case, second relapsed patients.

Again, many of the patients enrolled in our study would not have been eligible, and certainly would not have been eligible for these follow-up studies.

[Slide.]

To bring it full circle, our program in

the adult community is also moving forward, although it has a little bit different focus. The focus in the adult oncology community is particularly focused on AML, because that is where most of the activity has been seen.

Combination studies, particularly with ara-C are moving forward, and there has been an interest in the elderly population of patients again because of some of the early pilot studies in adults that have shown considerable activity in this group of patients.

One study that I would like to highlight is a CLO-141 study. Again, this was the combination study of clofarabine with ara-C. This study has met full accrual, but is still open.

Interim results of this study were just recently published in Blood where the overall response rate was 40 percent, again in a refractory population of patients with leukemia, and the overall response rate was defined as complete remission and complete remission without full platelet recovery.

Because of these results, our plans are to move forward, and we have already discussed this in brief with the FDA, as far as two potential randomized studies, one with clofarabine and ara-C in elderly patients newly diagnosed, as well as clofarabine with ara-C in recurrent or refractory adult patients with AML.

[Slide.]

At this point, I just want to return again to the fact that we are here today presenting the results of our pediatric studies in acute leukemia. We found that clofarabine had an acceptable profile particularly in this extremely heavily pretreated population of patients, that impressive benefits were observed including meaningful clinical responses, such as CR, CRp, and even PR's and again in this highly refractory patient population, that allowed many of these patients to move on to transplant.

As you can see here, 23 percent of the patients were able to proceed to transplant, 14 percent of the patients with ALL, 34 percent of the

patients with AML. At data cutoff, 22 percent of the patients with ALL, and 26 with AML are alive.

So, in conclusion, we believe that clofarabine does meet an urgent unmet medical need in a population of patients that frequently has not been included in many other current protocol opportunities, and the fact that activity has been seen in a very highly resistant and refractory group of patients.

[Slide.]

Again, I would like to thank the ODAC panel members, as well as the FDA, today for the opportunity to present the results of our pediatric studies with clofarabine in patients with acute leukemias.

Thank you.

DR. SANTANA: Thanks also to Drs. Weitman, Sallan, and Arceci.

I want to recognize for the Committee, and ask the individual to introduce himself by name and affiliation, Dr. Hershfeld has joined the meeting.

DR. HERSHFELD: Steven Hershfeld, Food and

Drug Administration.

DR. SANTANA: Thank you.

With that, we will proceed with the FDA presentation. Dr. Cohen, please.

FDA Presentation

DR. COHEN: Good morning. My name is Martin Cohen, and the NDA being presented today is No. 21-673. The study drug is clofarabine, which structurally is chloro-fluoro-Ara-A. The sponsor is ILEX Products, Incorporated.

Clofarabine is a second-generation purine nucleoside analogue. It is a prodrug that must be metabolized to its triphosphate conjugate by deoxycytidine kinase within tumor cells. Clofarabine has a greater affinity for this enzyme than does other purine nucleoside analogues.

[Slide.]

The proposed indication for this NDA is that clofarabine is indicated for the treatment of pediatric patients 1 to 21 years old with refractory or relapsed adult leukemias including both pediatric acute myelogenous leukemia and acute

lymphoblastic leukemia.

[Slide.]

Regarding clofarabine dose and schedule, a Phase I study in pediatric acute leukemia patients indicated that when a daily times 5 schedule was used, the selected dose was 52 mg/m

2. Clofarabine treatment cycles are repeated every 2 to 6 weeks following recovery to acceptable organ function.

[Slide.]

The pertinent clinical trials in this NDA submission are summarized on this slide. There were two, Phase II trials conducted by the sponsor, one in pediatric AML, the other in pediatric ALL. In addition, there was a pediatric Phase I study conducted at M.D. Anderson Hospital.

[Slide.]

For both of the Phase II studies, the primary efficacy objective was to determine the complete response rate and the complete response rate in the absence of platelet recovery, that is, the CRp rate.

Secondary objectives were to document the

partial remission rate and also to document time to event parameters including remission duration and overall survival.

[Slide.]

Study inclusion criteria for both the AML and ALL studies included an age less than or equal to 21 and the presence of greater than or equal to 25 percent bone marrow blasts.

Eligible AML patients were in their first or subsequent relapse and/or they were refractory, having failed to achieve remission following one or more different regimens.

Eligible ALL patients were in their second or subsequent relapse and/or they were refractory, having failed to achieve a remission following two or more different regimens.

Patients had an ambulatory performance status and had adequate bone marrow, liver, and renal function.

[Slide.]

Response definitions are listed on this slide. A complete response, or CR, required no

circulating blasts, no extramedullary disease, and an M1 bone marrow defined as having less than 5 percent myeloblasts or lymphoblasts.

There also had to be recovery of peripheral blood cell counts to a level of greater than or equal to 100,000 platelets/microliter, and an absolute neutrophil count greater than or equal to 1,000/microliter.

A complete response in the absence of platelet recovery meets all the criteria of a CR except that the peripheral blood platelet count has not recovered to 100,000/microliter.

A partial response is defined as no circulating blasts along with an M2 bone marrow defined as having 5 percent to 25 percent blasts accompanied by the presence of normal progenitor cells.

In addition, an M1 marrow without peripheral blood count recovery would be classified as a PR.

[Slide.]

A total of 18 Unites States sites

participated in the two, Phase II pediatric acute leukemia studies. Thirteen of these sites enrolled patients in the acute myelogenous leukemia study or CLO-222, and 14 sites enrolled patients in the acute lymphoblastic leukemia study, CLO-212. As mentioned previously, an independent response review panel was established to confirm response to therapy for each patient. Independent pathology review was also available.

[Slide.]

Demographics and Karnofsky Performance Status of patients participating in the acute myelogenous leukemia study are shown on this slide. A total of 35 patients were enrolled and treated. As indicated, the median age was 12, and ranged between 1 and 22.

Approximately, one-third of patients were female, and two-thirds were male. The majority of patients were Caucasian. Despite the fact that patients had relapsed and/or were refractory to one or more prior regimens, performance status was good with 89 percent of patients having a Karnofsky

Performance Status of 80 or better.

[Slide.]

Therapy is administered prior to entry into the clofarabine AML study are listed on this slide. The median number of prior induction regimens was 3 with a range of 1 to 5. Five patients received one prior regimens, 12 patients received two, and the remaining 18 received three or more prior regimens.

A total of 18 of the 35 patients, or 51 percent, received at least one transplant before study entry, 13 of 35, or 37 percent, having received one prior transplant and 5 of the 35, or 14 percent, having received two prior transplants.

[Slide.]

As previously indicated, the rate of complete response and complete response without platelet recovery were the primary efficacy endpoints. Responses were determined by an independent response review panel and confirmed by FDA.

There were no complete responders and only

1 CRp. There were 8, or 23 percent, partial responses. Seven of the 35 study patients were not evaluable for reasons listed on the slide.

[Slide.]

This slide shows pediatric AML patients who received a transplant after initial clofarabine treatment. Because stem cell or marrow transplant in pediatric AML may be associated with durable remissions, there is pressure to proceed with a transplant if a suitable donor is available.

In the clofarabine AML study, 12 of the 35 study patients underwent transplant including the 1 CRp patient, 6 of the PR patients, 2 of the 7 non-evaluable patients, and 2 of the 19 treatment failures.

Transplants were performed after patients had received 1 to 5 cycles of clofarabine treatment. Because of the transplants, it was not possible to determine duration of remission after clofarabine treatments alone.

[Slide.]

This slide indicates some of the

difficulties encountered when evaluating this application. As listed and as mentioned by Dr. Pazdur earlier today, the traditional endpoints for evaluating acute leukemia studies include the confirmed complete response rate, complete response duration, and overall survival.

Confounding factors in evaluating this NDA submission were that some patients were transplanted early, either before clofarabine response could be confirmed or response duration determined.

Further, some study patients received 1 or more transplants prior to entering the clofarabine study, and some did not. Whether these groups can be compared must be considered today by the ODAC Committee.

Because of the above difficulties, I chose to evaluate an exploratory endpoint, namely, longer time to progression with clofarabine treatment with or without transplant, then, with the therapy immediately preceding clofarabine, whether or not it also included the transplant.

[Slide.]

This slide summarizes 4 pediatric AML patients with a longer time to progression with clofarabine plus transplant, then, with the therapy that immediately preceded clofarabine.

One of these patients also had a longer response duration to clofarabine plus transplant than he had with his prior transplant.

Reviewing each of these patients individually, Patient 14-03 had a time to progression of 270 days for the treatment regimen preceding clofarabine study entry. He had received a prior transplant with a time to progression of 150 days. He received 5 cycles of clofarabine and was a CRp. His clofarabine plus transplant time to progression was 519+ days.

Patient 15-17 had a time to progression of 60 days for the treatment regimen preceding clofarabine study entry. He had not received a prior transplant. He received 1 cycle of clofarabine and was a partial response. His clofarabine plus transplant time to progression was

465+ days.

Patient 06-36 had a time to progression of 30 days each for the 2 treatment regimens preceding clofarabine study entry. He had earlier received 2 prior transplants with response durations of 365 and 485 days, respectively. He received 5 courses of clofarabine and was a partial response. His clofarabine plus transplant time to progression was 130+ days.

Patient 14-31 had a time to progression of 30 days each for the 2 treatment regimens preceding clofarabine study entry. She had not received a prior transplant. She received 2 cycles of clofarabine and was a partial response. Her clofarabine plus transplant time to progression was 93+ days.

[Slide.]

Turning now to Study CLO-212, the acute lymphoblastic leukemia study, this slide summarizes the demographics and Karnofsky Performance Status of participating patients.

A total of 49 patients were enrolled and

treated. As indicated, the median age was 12 and ranged between 1 and 20. Approximately 40 percent of patients were female and 60 percent male. Hispanic and Caucasian patients comprised the bulk of the study population.

Despite the fact that patients had relapsed and all were refractory to 2 or more prior regimens, performance status was good with 31 percent of patients having a Karnofsky Performance Status of 100, and 39 percent a Karnofsky Performance Status of 90-80.

[Slide.]

Therapies administered prior to entry into the clofarabine ALL study are listed on this slide. The median number of prior induction regimens was 3, with a range of 2 to 6. A total of 15 of 49 patients, or 31 percent, had received at least 1 transplant prior to study entry, 13 of the 49, or 27 percent, having received 1 prior transplant and 2 of 49, or 4 percent, having received 2 prior transplants.

[Slide.]

Best response to therapy as judged by the independent response review panel and confirmed by the FDA for the pediatric ALL study is shown on this slide. There were 6 complete responders and 4 complete responders in the absence of platelet recovery. There were 5 partial responses and 8 of the 49 study patients were not evaluable for response.

[Slide.]

This slide shows pediatric ALL patients who received a transplant after initial clofarabine treatment. As previously noted in the AML study, marrow transplant in pediatric ALL may be associated with durable remissions, thus, marrow transplant is often recommended if a suitable donor is available.

In the clofarabine ALL study, 7 of the 49, or 14 percent, of study patients underwent transplant including 1 of the 6 CR's, 3 of the 4 CRp's, 2 of the 5 PR patients, and 1 patient who was non-evaluable because of a poor quality bone marrow.

Transplants were performed after 2 cycles of clofarabine treatment in 5 patients and after 3 cycles of clofarabine treatment in 2 patients.

[Slide.]

In the pediatric ALL study, it was possible to evaluate complete response duration in patients who did not receive a transplant. As previously indicated, 6 patients achieved a complete response and 5 did not have a transplant. The 2 CR's listed on this slide had a longer time to progression with clofarabine treatment than was achieved with their immediate prior therapies.

Another 2 of the 5 non-transplanted complete responders remained in remission, but follow-up is brief. As seen on this slide, Patient 07-18 had a time to progression of 60 and 30 days for the 2 treatment regimens preceding clofarabine study entry. She had not received a prior transplant. She received 3 cycles of clofarabine and was a complete response. Her clofarabine time to progression was 143 days.

Patient 6-47 had a time to progression of

30 days each from the 2 treatment regimens preceding clofarabine study entry. He had not received a prior transplant. He received 2 cycles of clofarabine and was a complete response. His clofarabine time to progression was 76 days.

[Slide.]

As shown in this slide, 3 of the 4 CRp patients, 2 with a transplant, 1 without, had a longer time to progression with clofarabine with or without transplant than with immediate prior therapy.

Reviewing each patient individually, Patient 09-24 had a time to progression of 120 days for the treatment regimens preceding clofarabine study entry. He had received a prior transplant with a time to progression of 60 days. He received 3 cycles of clofarabine and was a CRp. His clofarabine plus transplant time to progression was 259 days.

Patient 12-14 had a time to progression of 30 days for the treatment regimen preceding clofarabine study entry. He had not received a

prior transplant. He received 2 cycles of clofarabine, was a CRp. His clofarabine plus transplant time to progression was 168+ days.

Patient 14-40 had time to progression of 30 days for the treatment regimen preceding clofarabine study entry. He had not received a prior transplant, nor did he receive a transplant after clofarabine. He received 2 courses of clofarabine, was a CRp. His clofarabine time to progression was 64 days.

[Slide.]

Turning now to the supporting trial in this application, the CLO Phase I study performed at M.D. Anderson Cancer Center is summarized on this slide.

In this study, patients 21 years or younger with refractory leukemia or lymphoma, who had a Zubrod Performance Status no greater than 2, and who had adequate organ function were eligible for enrollment.

There were 25 acute leukemia patients entered, 17 with ALL, 8 with AML. Using M.D.

Anderson response criteria, complete response were noted in 5 of the 25 patients 4 with ALL and 1 with AML. In addition, there were 3 PR's.

ILEX convened an independent response review panel to review the 5 M.D. Anderson complete responses using the same modified COG review criteria that were used in the sponsor's Phase II studies. The independent response review panel reclassified the 5 CR's to 2 CR's, both in ALL patients, 1 CRp in the AML patient, and 2 PR's.

[Slide.]

Turning now to safety, this slide summarizes clofarabine exposure by cycle. The database includes 113 patients derived from the sponsor's Phase II studies, the M.D. Anderson study, and from adult trials that included pediatric patients.

As indicated, all 113 patients received at least 1 cycle of clofarabine, 68 received 2 cycles, and 24 received at least 3 cycles. Dose reductions were necessary as is expected for heavily pretreated patient population.

[Slide.]

Some of the clinically more important baseline conditions present in the 113 clofarabine-treated patients are listed on this slide. Despite ambulatory performance status, the patients appeared to be relatively fragile with CTC Grade 3 to 4 baseline toxicities including tachycardia, pyrexia, nausea, and anorexia.

[Slide.]

An overview of adverse event occurrence is shown on this slide. Ninety-nine percent of patients had 1 or more adverse events, and 83 percent had 1 or more serious adverse events. Four percent of patients discontinued therapy because of an AE. Fifty-three percent of patients had at least a Grade 3 AE, 23 percent a Grade 4 AE, and 20 percent a Grade 5 AE.

[Slide.]

Frequent adverse events are summarized on this slide. Gastrointestinal toxicity in the form of vomiting, nausea, and diarrhea occurred commonly. Grade 3-4 vomiting occurred in 10

percent, Grade 3-4 nausea in 16 percent, and Grade 3-4 diarrhea in 10 percent of patients. Grade 3-4 febrile neutropenia occurred in 58 percent.

Constitutional symptoms, such as headache, pyrexia, rigors, fatigue, and anorexia were also common and occurred in 30 percent to 48 percent of patients.

[Slide.]

Other adverse events noted during treatment are listed on this slide. Infections were an important adverse event because of prolonged immunosuppression and myelosuppression from both current and prior therapies. SIRS, or systemic inflammatory response syndrome, capillary leak syndrome manifested by the rapid onset of respiratory distress, hypotension, and multi-organ failure occurred in 10 patients. It most often occurred in conjunction with rapid tumor lysis.

Renal insufficiency was multifactorial in etiology included nephrotoxic antibiotics, hyperuricemia from tumor lysis, and hypovolemia and hypotension. Hypotension was a component of SIRS,

but was also associated with sepsis and dehydration.

Hepatobiliary toxicities were frequently observed as the liver is a known target organ of clofarabine toxicity. Approximately one-third to one-half of study patients had Grade 3 elevations of transaminases during study.

Left ventricular systolic dysfunction was noted in 15 study patients. This might have been a direct cardiotoxic effect of clofarabine as clofarabine cardiac toxicity has been seen in preclinical rat studies.

Numerous contributing factors were present, however, including sepsis, prior anthracyclines, and prior whole body radiation therapy. Hand-foot syndrome was noted in 12 percent of treated patients.

[Slide.]

To summarize standard efficacy results for the study population of relapsed, refractory pediatric acute myelogenous leukemia patients, there was 1 CRp, or 3 percent, and 8 PR's, or 23

percent, among the 35 treated patients.

Remission duration could not be determined because 12 patients went on to transplant.

[Slide.]

To summarize exploratory efficacy results for the study population of relapsed, refractory acute myelogenous leukemia patients, 4 clofarabine plus transplant AML pediatric patients had a longer time to progression of clofarabine plus transplant to time to progression of immediate prior therapy with or without transplant.

One of 2 patients with a prior transplant also had a longer time to progression with clofarabine plus transplant than with his preceding transplant. The other is too early to evaluate.

[Slide.]

To summarize the standard efficacy results for the study population of relapsed, refractory pediatric acute lymphoblastic leukemia patients, there were 6 CR's, 4 CRp's, and 5 PR's among 49 treated patients.

Two CR's who did not have a transplant had

a longer time to progression than was achieved with their immediate prior therapies. Another 2 of the 5 non-transplanted CR's remain in remission, but follow-up is brief.

One CRp who did not have a transplant also had a longer time to progression than was achieved with his immediate prior therapy.

[Slide.]

To summarize exploratory efficacy results of the study population of relapsed, refractory pediatric acute lymphoblastic leukemia patients, 2 CRp patients had a longer time to progression with clofarabine plus transplant than with the treatment immediately preceding clofarabine.

One of the 2 above patients had a pre-clofarabine transplant. This patient also had a longer time to progression with clofarabine plus transplant than with his previous transplant regimen.

[Slide.]

As to safety conclusions, toxicity was as expected for a heavily pretreated relapsed,

refractory acute leukemia population. Principal toxicities were gastrointestinal including nausea, vomiting, and diarrhea. As expected, there was significant hematologic toxicity, fever and febrile neutropenia, hepatobiliary toxicity, infections, and renal toxicity.

SIRS, tumor lysis syndrome, multi-organ failure, hypotension, renal insufficiency, and left ventricular systolic dysfunction also occurred. With attentive patient care, however, the drug appeared to be tolerable.

[Slide.]

To conclude, I would like to come back to a slide that I showed earlier. This slide indicates some of the difficulties encountered when evaluating this application.

As listed, the traditional endpoints for evaluating acute leukemia studies include confirmed complete response rate, complete response duration, and overall survival.

Confounding factors in evaluating this NDA submission were that some patients were

transplanted early either before clofarabine response could be confirmed or response duration determined.

Further, some study patients received one or more transplants prior to entering the clofarabine study, and some did not. Whether these groups can be compared must be considered by ODAC.

Because of the above difficulties, I chose to evaluate an exploratory endpoint, namely, longer time to progression with clofarabine treatment with or without transplant, then, with the therapy immediately preceding clofarabine, whether or not it also included the transplant. Whether this appropriate must also be considered by ODAC.

Thank you for your attention.

DR. SANTANA: Thank you, Dr. Cohen, if you would remain on the podium, there may be some issues of clarification or questions for you.

I want to go ahead and open up the session for questions, and I want to reiterate to the Committee, it is primarily to ask clarifications or questions related to the presentations, comments

that have been made, or anything that is in your briefing document. I really don't want to get into the issues or the questions for discussion later in the morning.

Questions from the Committee

DR. SANTANA: I will go ahead and get started with one question. I want to focus a little bit on the issue of toxicity as it may help me define clinical benefit for these patients.

When you looked at toxicity across the board, then specifically at those patients that did not go to transplant, but had either a CR or a PR, did you notice any difference in toxicity rates, particularly serious infections, hospitalizations, that nature, that would help me assess whether those patients that did not have transplant really benefited?

DR. COHEN: Well, I think all of the toxicity data was gathered before patients went to transplant. It represented the effects of clofarabine treatment--

DR. SANTANA: Could you point to patients

that were not transplanted? I believe there were 9 ALL patients and a few AML patients.

DR. COHEN: I did not break it down that way, I did not look specifically.

DR. SANTANA: Maybe the sponsor can comment on that later, if they have looked at the data that way.

Kind of a follow up to that toxicity issue, this theme of hepatobiliary toxicity and its resolution, were you able to assess whether that required dose modifications in subsequent courses or even extending it a little bit, did it impact those patients that went on to transplant?

DR. COHEN: Well, the protocol, depending on the level of hepatobiliary toxicity, the protocol called for dose modifications, and those modifications were followed.

DR. SANTANA: Yes.

DR. MARTINO: A question to the sponsors. Within the protocol, can I assume that there were some guidelines as to when a patient might be taken to transplant? How was that decision made, by whom

was it made, did the protocol restrict or simply allow judgment truly to the individual clinician?

DR. WEITMAN: The protocol did allow patients to go to transplant, and again, as in many of these studies, if they had available donor, that was pretty much the primary requirement. There wasn't a requirement for number of cycles or anything else before going to transplant.

DR. SANTANA: Dr. Cheson, did you have a question?

DR. CHESON: Yes, actually, I have three questions for the sponsor.

Number one, if you could please flash Slide 26 of your slide kit, and while you are doing that, let me ask my other one while he is taking time to do this.

You included the Phase I patients in your toxicity analysis and give a percent of toxicities. Were those all the patients in the Phase I, including those who had rather low therapeutic doses or only those closer to the MTD or DLT?

DR. WEITMAN: It included all patients

including those at the lower dose.

DR. CHESON: So, is that really fair to include the patients at the really low doses?

DR. WEITMAN: We thought it was. Well, first of all, we also included patients at a higher dose, as well. When you look at the numbers of patients, 13 patients out of the 25 were at the MTD, at the 52, so the majority, if not more, 51 percent were at that dose, plus there is additional patients treated above that.

DR. PERRY: What proportion of responses were seen in that group of people who got 52 milligrams or more?

DR. WEITMAN: The responses were spread throughout from 30 to 40 to 52 mg/m 2. So, it was spread I will say fairly equally, but certainly at the 52 mg dose, that is where the majority of the patients were treated at.

DR. CHESON: The second point. Looking at these curves, you said the CR and CRp, which is the upper curve, has a median of 20.2 weeks. The 50 percent dotted line seems to hit smack right around

12 weeks. Am I missing something here? Take that 50 percent line, you draw it across, it hits there.

DR. WEITMAN: Which curve are you looking at?

DR. CHESON: The upper curve.

DR. WEITMAN: The yellow?

DR. CHESON: The yellow curve. The 50 percent seems to hit at about 12, and not 20.2.

DR. WEITMAN: If I can, I will ask Brett Wacker to comment on this.

DR. WACKER: The way that the median is calculated when it goes all the way across, it takes the average from the first point where it hits the 50 to the end of it, so that is why the 20.2 is in the middle of that interval.

DR. CHESON: So, we would need longer follow-up to see what really happens to that. Okay.

The third, this CRp thing that you have got there, there have been several published, at least in adult response criteria in AML, one in 1990 and the other about a decade or so later, in

neither of those was CRp included as a response criterion, and, in fact, it was discouraged in the most recent International Working Group as being included because it really hadn't been validated as being different from CR. In other words, there was some evidence that CRp's, in fact, don't do as well as CR's, and the recommendation of that International Group was that CRp's not be included with CR's.

Are there data from the pediatric studies to suggest, to validate CRp as an endpoint? It snuck in here with the gemtuzimab study, the pivotal trial there, and it has kind of hung on ever since, but the most recent response criteria have clearly suggested that it not be used.

DR. WEITMAN: I think you will see that in some of the pediatric leukemia studies going forward, that CRp is becoming more of an endpoint that they are looking at.

What we felt, at least looking at the study, number one, was that patients with CRp, most of these patients, realize came into the study

following bone marrow transplant and rarely had any platelet recovery even coming into the study. So, it was somewhat hard to know whether lack of platelet recovery after clofarabine really was any sign of lack of activity.

When we looked at the patients with overall survival, there were small differences, but again small numbers comparing CR with CRp. But I think it is a valid point that just needs to be continued to be followed particularly in the pediatric population.

If I can--

DR. SANTANA: Sorry, go ahead.

DR. WEITMAN: I just wanted to get back to your question earlier, Victor, about toxicities. Clearly, those patients that received multiple cycles, the toxicity that really was dose-limiting at least as far as giving the subsequent cycles was bone marrow suppression, and that particularly of patients that have received 8, 10, 11 cycles of treatment, that was predominantly what was requiring a delay in treatment or dose reduction

was myelosuppression.

I don't know if that gets to your question.

DR. SANTANA: Sort of. What I am trying to assess is those patients that did not get transplant, that remained on study drug because they had either a CR or PR. That was particularly the ALL population, so I believe you had 9 patients, and there were a few patients there that were in the 100+ day kind of remission status, which indicates to me that they must have received a few cycles of therapy.

DR. WEITMAN: Correct.

DR. SANTANA: I was trying to get a sense of what impact the therapy had on their infection, hospitalization, liver toxicity, to get at this issue whether they were truly benefiting or whether the drug was giving them toxicity that they otherwise considered difficult to manage.

DR. WEITMAN: Right. I think I will ask, if I can, Dr. Steinherz, Peter Steinherz, to comment on that, because he had probably the most

experience with these patients that went on multiple cycles.

DR. STEINHERZ: Patients who received multiple cycles of clofarabine had a near normal quality of life. They did fairly frequently after a cycle of chemotherapy, have a brief fever and neutropenia admission, but the cycles were done every 28 days, and other than the two, three day hospitalizations, the rest of that time was at home with full quality of life.

DR. SANTANA: Did any of the serious infections that were reported in the briefing document occur in those patients?

DR. STEINHERZ: Not once they achieved remission. The infections that were serious were really during remission induction.

DR. SANTANA: Dr. Hussain.

DR. HUSSAIN: I have a couple of questions, please. I don't think I heard in any of the slides, other than a description of statistics being traditional, what were the actual efficacy assumptions that would have been desirable that you

put in prospectively in the trial?

The second question is in comparable settings, I assume transplant and the description from the experts were that there are multiple drugs available in the last 10 years, so I assume there may have been other agents that might have been tested in previously pretreated or heavily pretreated patients, that made it to approval.

What were the efficacy or the characteristics of those agents that led them to be approved in terms of whatever criteria they were looking at?

DR. COHEN: In terms of criteria for approval, in those days, in the 1960s, 1970s, I don't know for sure, but I would expect it would be response rate.

DR. HUSSAIN: In the past five years, have there been no drugs approved in this setting?

DR. COHEN: In pediatric acute leukemia, I don't think so.

DR. HUSSAIN: Or 10 years?

DR. SANTANA: I don't think there has been

any pediatric leukemia drugs approved in more than a decade.

DR. HUSSAIN: I am sorry, the second question was dealing with the efficacy endpoint that were prospectively put in the Phase II trials.

DR. WEITMAN: I will ask Dr. Tannen to come up and comment on that, please.

DR. TANNEN: Can I have Slide 101, please. This trial was designed based on using Fleming 2-stage design, and at that time, we have the data available on the Phase I trial based on 25 patients, and the response rate at that time, they were observing is 30 percent response rate. The 40 percent response rate was hypothesized for the clofarabine treatment groups with the control group of the 20 percent, a 2-fold increase with the clofarabine.

So, Fleming design basically says that you look at the data with the 20 patients and observe the response rate. At that time, the response rate was observed with ALL, about 20 percent, and the activity was seen, and the criteria to move to

second stage was not met at this time, but based on the advice from the investigators, as well as the FDA, it was decided to move to the Stage 2.

Activity was seen at the first stage, and you have to see what is the clinical significance of 20 percent response, which was observed in this trial, and as mentioned by Dr. Weitman, the number of patients, about 34 percent in AML patients, went to transplant.

So, the response rate is what we saw here, the 20 percent, which we believe is clinically very meaningful, and has to do with the patient population that is very heavily treated. In the AML patients, it has to do with the patient management that is the key issue.

DR. WEITMAN: If I can, I would like to ask Peter Adamson to step up, as well, and make a comment about this.

DR. ADAMSON: So, without a reasonable comparative database to look at, to say, well, where should the bar be in ALL or AML, I personally think the assumption of 40-20 was an incorrect

assumption, and it missed the mark by a large measure.

As Steve Sallan had pointed out decades ago, single-agent activity in newly diagnosed patients are in the 20 to 40 percent range, and I think you can count on two fingers the single-agent activity in ALL above that.

So, setting the bar in this population at 40 percent, my personal view was way off the mark. Where should it be? I think it is a more difficult question, but maybe I can share with you very briefly the Children's Oncology Group challenges in the same population, so with a concurrent population, the challenges that we are facing.

We have three, Phase I studies in ALL and AML going on. For Phase I, as you know, a criteria for evaluability, they have to make it through a cycle of therapy, which is 28 days.

We are nearing the point where we are going to have to abandon that design, because we have about a 70 to 80 percent inevaluability rate in Phase I. These patients are so heavily

pretreated and are so rapidly progressive, we can't get Phase I data anymore in leukemia, because we can't get them through four weeks of therapy.

So, that will set the stage saying the mere fact that they got through a Phase I, to me, was an indicator that there is something going on, because we can't get through Phase I's right now.

Now, in Phase II, where are we putting the bar? That is a moving target, and maybe I can take this brief opportunity to come back to Dr. Pazdur's initial introduction where CR, duration of response and overall survival are the three criteria.

I certainly agree with those, but it is a shifting paradigm, because I no longer think we are going to be able to get duration of response data in this population, and there are two reasons for that.

In AML, it is very clear that the current standard of care is that we whisk these patients to transplant as soon as feasible, as soon as you have had cytoreduction, they go to transplant.

So, as much as scientifically, we would

all like to see a duration of response that is not confounded, we are not going to. We are not going to do it in our trials, and I don't think industry is going to do it, because the standard of care won't allow it.

Now, in ALL, duration of response becomes somewhat of a different challenge. Yes, they are going to transplant, but I think Dr. Pazdur correctly pointed out that a reasonably high fraction of responders didn't have a repeat marrow assessment.

This is where our scientific desires run head to head with some ethical concerns, as well as current standards.

As everyone or many of you know, in pediatrics, there are additional safeguards afforded, FDA, DHHS regulations, and for studies that offer no potential for direct benefit, we can't mandate those studies in children.

So, as much as we would like to see repeat marrows done, the reality is once a child is in CR, it is hard to describe what the benefit to the

child is to repeating a marrow later on.

The reality in ALL, for those of us who take care of it, is it is no secret when a child recurs. We don't need to look in their marrow. We look in their marrow to confirm it, but it is not a secret.

So, it becomes difficult once you have documented a CR, to go ahead and confirm it later. We absolutely would like to do that. The reality on the front lines is that it becomes exceedingly difficult to.

So, the criteria we have put forward as far as CR's, duration of response and overall survival, the CR's, we need to document. AML gets confounded, ALL, less so, but duration of response is going to be a pretty difficult standard right now.

I know I have gone off on a tangent a bit, but the design as far as 40-20, I think was misplaced, and I would right now say for ALL, we are tending to set designs in our studies at 25, so the Fleming 2 stage at 25 with a 20 percent

response rate of interest.

DR. SANTANA: Dr. George, you had a question and since this is kind of in this area of discussion. Go ahead.

DR. GEORGE: Well, it is related. I have a question for the sponsor. In the duration of response, and, for that matter, the overall survival curves, it appears that the transplant issue was handled by simply ignoring it. I mean the analysis would have been exactly the same if no one had gotten a transplant, is that correct? This is the clarification question.

DR. WEITMAN: Well, again, we looked at those patients that went on to transplant, correct, and we included that in our duration of remission and overall survival as part of that.

DR. GEORGE: Well, just to be clear, that means that if someone did get a transplant, and then later relapsed, I mean that time to relapse was taken, whatever it is, just as is.

DR. WEITMAN: Correct.

DR. GEORGE: Another issue that just came

up, that I hadn't thought of before, was this issue of confirming the relapse. I assume all those were done with some marrow samples, so they were confirmed.

DR. SANTANA: Let me go back to that issue, because I got confused, too, reading the documents. Are we talking about not confirming the response with follow-up marrow, or not confirming the relapse with a follow-up marrow?

Can the sponsor clarify that for me? Did all patients have a confirmatory response for the tagging of response, and it was that when they recurred or progressed, a marrow was not repeated to document that?

DR. WEITMAN: It depends, Victor. Most of the cases did have repeat marrows done, but clearly, if there were patients who had no evidence of relapse, and all of a sudden developed, 20, 30, 40 percent blasts in their peripheral blood, then, again, a lot of those patients did not have confirmatory marrows done at that time, but at that point, that was considered disease progression

without necessarily requiring a confirmed repeat marrow.

DR. SANTANA: So, this issue of not doing bone marrows was at the time of progression, is that correct?

DR. WEITMAN: Correct.

DR. BRAWLEY: I didn't understand it that way either. Can we clarify that?

DR. COHEN: The issue in terms of confirmed marrows was not confirming the response, that is, a second marrow was not done within a month of the first marrow. It had nothing to do with progression.

DR. BRAWLEY: This is very important. Can you just slow down just a little bit. You did not do a marrow to confirm complete response. You sort of looked at the blood and accepted complete response on some sort of religious basis, is that right?

DR. WEITMAN: Otis, no, not exactly.

DR. BRAWLEY: Okay.

DR. WEITMAN: Confirmatory marrows were

done in most of these patients. Now, clearly, at the time that that first marrow that was done that showed remission, if that patient was in remission and had a donor, they would go right to transplant.

Many of those patients would still get a repeat marrow the day or so before transplant, but again, most of those patients had, first of all, had a marrow done to confirm response or to show that they were in remission, and then they would go either to transplant or would continue on the study, and those patients that continued on study without a transplant would get marrows as dictated by the protocol.

DR. HUSSAIN: Is it possible to put a slide about that, because I think right now I am totally confused about what was confirmed, what was not confirmed.

DR. SANTANA: Do you have a summary of that?

DR. WEITMAN: Again, what I can just highlight again is that for patients, I think there is one slide that has the confirmatory marrows. It

should be in the briefing document, as well, that I believe the FDA has supplied to you, as well.

DR. PAZDUR: If you take a look at the questions for the Committee, it does go through on Table 2 and Table 4, the differences, and these are in patients that did not have transplants, because we look at transplants as really confounding this whole issue of what a response is.

You could see the data and a single asterisk means the responses were not confirmed, double asterisks, responses were confirmed. What we are talking about here is a discrepancy of whether these had a confirmatory bone marrow biopsy.

I guess as the sponsor said, and perhaps he could give this information because I don't have it off the top of my head, if you take a look at all of the patients, how many had a confirmatory, a bone marrow at, for example, 4 weeks, because that is what you are after, the CR's.

DR. WEITMAN: Again, just to reconfirm that all patients had a marrow to document

remission. Now, as far as confirming remission, the majority of those patients, and I don't have the exact numbers, but the majority of those patients--

DR. PAZDUR: That is the question. What is the majority?

DR. WEITMAN: Let me get it.

DR. SANTANA: Ruth Hoffman had a comment or a question?

MS. HOFFMAN: This is for the sponsor, as well. The overall survival for ALL median was 11.7 weeks at the close of study, and for AML, it was 21 weeks. Because the study for a lot of these patients was January or February of this year, this is now 10, 11 months later, do you have the status of the survivors, how many are still alive?

DR. WEITMAN: If I can show the follow-up on some of the additional patients.

DR. SANTANA: Go ahead.

DR. WEITMAN: I will ask for the slide that looks at follow-up patients and survival.

I would like to, if I can, show the

response follow-up first.

DR. SANTANA: Since you have the survival, why don't you just do that first.

DR. WEITMAN: Okay. We will start here. This is just a follow-up for the patients that were on the study. Again, what was submitted in the NDA, and again I will comment that the updated data has not been reviewed by the FDA, and they have not seen this follow-up data.

Essentially, all it shows is that the response rates were similar with the additional follow-up data or additional patients that have been treated with clofarabine for both ALL and AML.

If I can show the survival slide. In follow-up, this shows 22 percent of patients alive with median follow-up of 28 weeks, and I believe this is as of November, actually, this was the beginning of November, September 30th of this year with 18 percent patients alive with median follow-up of 47 weeks.

DR. SANTANA: Thank you.

Dr. Maldonado, you had a question or a

comment?

DR. MALDONADO: Just a couple of questions. This is just for my own clarity on the biological plausibility of the results we are seeing here. I hate to take you out of the clinical, but I want to go back to the basics seeing that the sponsor had been surprised by the higher unexpected results.

What is known about the mechanism of action of clofarabine, and why do you think this is a different nucleoside analogue?

Pardon my ignorance, but it appears that that is basically what has been the surprise for the sponsor, and is that because the cells that have more permutations to elicit the resistance? I still don't understand much about the biology and molecular biology of the drug here.

DR. WEITMAN: I will make two comments. I will first start by asking Dr. Gandhi to come up and talk about the preclinical mechanism of action.

DR. GANDHI: Clofarabine is very similar to other nucleoside analogues with regard to its

metabolic aspect, that it does require deoxycytidine kinase to get phosphorylated.

It resembles to some extent to cladribine and to some extent to fludarabine. With cladribine, it resembles regarding metabolic aspect, that is, it is a favored substrate for phosphorylation.

With regard to clofarabine, it resembles that once it gets incorporated into DNA, it results in chain termination, whereas, with cladribine, there is no chain termination.

Does that answer your question regarding the comparison with other nucleoside analogues?

DR. MALDONADO: So, you think that the activity or the efficacy we are seeing in clinic is because this is a chain terminator versus the other comparisons?

DR. GANDHI: There are several other factors. One, especially, in the clinical pharmacology, which goes a little bit away from the mechanism of action. When you look at the clofarabine triphosphate in the leukemia cells

during therapy, it is very different from cladribine triphosphate and fludarabine triphosphate.

All these three nucleoside analogue triphosphate, they live for a long time in the indolent leukemia setting in the leukemic lymphoblasts, but when you compare it for the acute leukemia setting, fludarabine triphosphate half life is 7 hours, cladribine triphosphate half life, which hasn't been tested very well, in fact, we have the guru right here for all the cladribine studies, but it was about 7 hours half life, and for clofarabine triphosphate, the half life is more than 24 hours.

So, we think there is a benefit with clofarabine because it remains for a long time in the acute leukemia blasts.

DR. SANTANA: Dr. Pazdur, you had a comment?

DR. PAZDUR: I wanted to follow up on Maha's question about response rate and what is the appropriate response rate here.

I want to stress that remember this study was done as a Phase II trial, and one of the concepts of a Phase II trial obviously is an exploratory trial where you would get data and a response rate which would indicate whether the drug should be carried on further in drug development. That was the original intent of when we talk about what a Phase I study, Phase II, Phase III paradigm is.

What we are talking about here, though, is drug approval, and I want to stress that simply a mere screening for drug activity does not necessarily constitute the requisite information that one should have for approval of a drug.

Remember, when we are talking about approval of a drug under accelerated approval, you have to be reasonably likely that this response rate can predict clinical benefit.

Now, you know, we have in the past with other diseases in adults, for example, lung cancer, colon cancer, taken a look at single-arm trials in very refractory diseases, in some of the

hematological malignancies where we were able to take a look at duration.

If we can't take a look at duration, maybe this paradigm of taking a look at very, very refractory disease patients and trying to approve a drug on that basis, is not the appropriate paradigm to have in all clinical scenarios here, and I think that is an important point.

Somebody could actually do one day a randomized study for drug approval and surprise the FDA.

DR. SANTANA: I will not comment on that. Dr. Martino?

DR. MARTINO: Actually, I want to ask this question of Dr. Arceci. It is a clinical understanding that I need.

In these children, when you achieve a partial remission with this agent or any agent, what does that mean to you clinically? Is that meaningful, to what degree is it meaningful, and what does it mean in terms of their survival?

DR. ARCECI: In terms of the practical

side of what a partial remission means is that it usually buys time, and usually, it improves quality of life during that period of time. It also means a chance to proceed to a more definitive therapy.

If a patient does not have at least a good partial remission, it essentially buys that extra time to finish marrow typing, finish insurance approval for transplant, then, we don't get to transplant.

So, a PR has enormous utility in our business although it, of course, is not going to result in a cure. Those patients with PR's are going to relapse clearly and progress, but it gives us a chance that if we can move that process forward, we can often cure it, or at least in a percentage of those patients can cure them.

Is that answering your question?

DR. MARTINO: You gave me a sense of what I needed to hear. Thank you.

DR. SANTANA: Dr. Poplack.

DR. POPLACK: I just want to go back to the point that Dr. Pazdur made two comments ago,

and that related to the ALL patients who were judged to have responses.

In the data that we received, it is not possible to determine which patients did or did not have that confirmatory second marrow, and I think it is critically important for us to get that information. So, that is the first point.

The second one is--and that is on Table 2 of the questions that were given to us--the second question I have for Dr. Weitman is, what would be the plans--and I assume this is a fair question, and it seemed like what you stated was a little vague to me--for a confirmatory study were this, for example, to be approved?

DR. WEITMAN: With regards to your first question, my helpful colleagues here pointed out that 9 of the 15 patients with ALL had a confirmatory marrow, again a second marrow after the initial marrow was done, so there was 9 of 15 for ALL.

Two of 9 for AML had a confirmatory marrow. The remaining patients went on to

transplant or probably had either progressive disease at the point, so again, 9 of 15 for ALL, and 2 of 9 for AML.

DR. POPLACK: I think the information I would like to get is which of those responses, if we look at the patients who responded, which ones did have or didn't have a subsequent marrow.

DR. WEITMAN: If I can then also touch base on your second question, and that is, again, our plans are to work with the Children's Oncology Group towards a randomized study.

As you know, I think doing a randomized study in this patient population is very difficult, if not heroic, efforts to undertake, but our plans would be to move forward with the cooperative groups and at some point go into a randomized study where clofarabine is added on to the backbone therapy of either patients in first relapse or newly diagnosed patients at the appropriate time, where this drug was added onto the backbone, looking for changes in survival or duration of remission.

DR. SANTANA: I don't think I heard the answer to the first question yet, and I think we need to get an answer because it has come back now three or four times in the last 10 minutes.

So, of the patients in ALL and AML, who actually were coded as having a response, how many of those had a subsequent marrow that confirmed that response? Can somebody give us that information?

DR. COHEN: If you look at the FDA review, Table 11 on page 25 is the AML, and Table 23 on page 33 is the ALL, and the seventh column down is patients who had confirmatory marrows.

DR. SANTANA: Can you summarize it publicly because I think some people don't have the documents in front of them? I hate to put you in a position, but--

DR. WAYNE: And also remind us of the page and the table number, please.

DR. COHEN: This is Table 11, page 25, FDA briefing document. It lists 9 responding AML patients and 2 of the 9 had confirmatory marrows,

and the other 7 did not, of the responders, this is just responders.

DR. SANTANA: So, 2 of the 9 AML patients that were coded as having an initial response, had a confirmatory marrow, is that correct?

DR. COHEN: That is correct.

DR. KURTZBERG: I still don't understand if that means they had the first marrow that confirmed their response, and then they did have a second.

DR. COHEN: This is the second. The confirmatory marrow is the second one.

DR. SANTANA: It's the follow-up bone marrow.

DR. COHEN: And for ALL--

DR. PERRY: Excuse me. Just for clarity, they had a bone marrow that met response criteria, but only 2 of the 9 had a second bone marrow at least a month later establishing the came criteria.

DR. SANTANA: That is my interpretation.

DR. COHEN: That is mine, too.

For ALL--

DR. SANTANA: That is Table 23 on page 33.

DR. COHEN: Right. There are 15 patients, confirmatory marrows were 9, 9 of the 15 had confirmatory marrows.

DR. SANTANA: Thank you.

DR. WEITMAN: Can I ask Dr. Arceci to comment about Dr. Poplack's question regarding the COG and plans moving forward?

DR. SANTANA: Yes, I think that is an important point to clarify.

DR. PAZDUR: While he is coming up to the table, I would also like to emphasize for Dr. Poplack that the confirmatory study can be done in an earlier stage of the disease. We have repeatedly done this in adult disease where somebody might get an approval in a very refractive population of colon cancer patients and then the confirmatory study is done in the same disease in an earlier stage.

We have interpreted that as a way of moving forward drugs and trying to escalate the speed of drug development basically.

DR. ARCECI: I would just comment briefly on David's point, and that is, a randomized study of this drug in newly diagnosed patients, or even in the relapse setting, is very unlikely to happen, but the cooperative groups right now are, in fact, moving towards combination trials, and both in AML and ALL, those studies are moving very rapidly through the cooperative group mechanism.

We have plans to then try to randomize those combinations in the setting of newly diagnosed patients. We are doing that now in upfront studies with new agents and combining them to see if we can offer an advantage over standard therapy.

So, what will probably happen I suspect with the combinations is that because of the somewhat noncross-resistant toxicity profile of clofarabine, in pediatrics, for instance, anthracyclines are tremendously concerning agent, and we would eventually love to be able to introduce combinations that, in fact, don't have those anthracyclines in cardiac exposures.

So, that is the plan right now, at least in the leukemia trials. I think I will stop there.

DR. MARTINO: Can I ask a question. I appreciate the word randomization, and we all get excited over it, but I have yet to hear what exactly you are thinking to randomize, to what?

DR. ARCECI: Amen. In the Phase III trial. So, depending upon the results of those combination studies, what we would very likely do, for instance, in AML, is to introduce a combination clofarabine/ara-C, if that combination looks as promising as we hope.

We would then try to randomize that against a standard course of intensification or induction therapy or consolidation therapy, so we would try to have one arm, for instance. What we are using now, for instance, is MRC-based therapy with the modification now--

DR. SANTANA: The adult oncologists maybe don't recognize the acronym.

DR. ARCECI: I am sorry, the Medical Research Council. So, we are basing 5 courses of

intensive therapy in AML based upon the Medical Research Council out of Britain. In the U.S., we are randomizing the addition of gemtuzimab ozogamicin to that upfront trial.

One group will get several courses of combination and the other one will get the standard therapy. In the setting of a combination with clofarabine and ara-C, it would be particularly advantageous to try to have a group that would get that standard therapy versus an introduction or replacement of an anthracycline, for instance, containing regimen or another regimen that would be potentially more toxic, and see if we could get the same or better outcome. That is the type of randomization we are currently pondering.

DR. PAZDUR: Could I comment? We are very concerned about this aspect, and that is why I spent some time in my introductory comments on the need for confirmatory studies. I would like to remind the ODAC Committee that in March of 2003, we spent an entire I think day and a half or two days on this issue.

Basically, the regulations, although it is not a requirement, stipulates that there is an expectation that these trials should be ongoing. We have not met with the sponsor regarding this issue. There may be differences on what cooperative groups need to do versus what our appropriate studies that would meet a requirement for a regulatory purpose, i.e., isolating the effectiveness of the proposed drug.

Here again, we would have to discuss this in detail with the sponsor. It is quite bothersome that we are at this point of talking about approval of the drug, and not having met with the sponsor.

This is something that you will have to take into consideration regarding this drug. Other points that I would like to bring up for further discussion perhaps at the next hour is whether this confirmatory study needs exclusively to be done in pediatrics or could be looked at in an adult indication. Here again, that is something for the pediatricians to discuss.

I am very concerned about this. The

Division is very concerned about the lack of ongoing studies at this time. Remember, these studies are to be done with due diligence. One has to question, if they haven't been done to date or even initiated to date at due diligence, has the sponsor demonstrated due diligence if they haven't been even initiated at this point.

That is a consideration that I think you need to bring into consideration, whether children are best served with the approval of this drug at this time or whether further study needs to be done.

DR. SANTANA: As a follow-up to that, because I think you leave us with a sense that we need to discuss this, but it is, from my own view, is it a procedural issue that hasn't occurred, you know, give us some of the reasons why it hasn't occurred.

DR. PAZDUR: Usually, the sponsor would come in and discuss these trials with us throughout the course, and the drug has been in development for a lengthy period of time here. It is not that

this drug was developed just within the past year.

One of the things that we stressed at the previous meeting in March is that there should be a comprehensive development program for drugs, and this would include perhaps an exploratory study, however, we encourage early initiations of randomized studies, not late, not, well, let's get the drug approved and then let's talk about randomized studies.

I would like to emphasize that a lot of sponsors have been very responsible with this after our meeting of bringing forth a single-arm study and discussing a single-arm study, but also making a commitment and having ongoing accrual to a randomized Phase III study.

An example of this, for example, is Velcade, where we approved the drug on a single-arm study, however, 40 or 50 percent of the patients were already randomized to a study. This is the type of drug development program that we are looking at, a real commitment to drug program.

DR. SANTANA: Yes, go ahead.

DR. PERRY: I understand exactly I think what you said except for me there is a difference between adult and pediatric oncology. In the adult world, we have lots of patients who aren't going on cooperative group trials. In the pediatric community, 90 percent of patients are on cooperative group trials.

So, it seems to me the sponsor can almost only work with the cooperative groups, and work at their pace. They can't very well dictate to the COG and say do my study and do it now, and do it in this direction, because I need further approval from the FDA.

In the adult world, it is an entirely different playground.

DR. PAZDUR: And specifically, I think this is why we wanted to discuss this issue here.

DR. SANTANA: I think that is a very important point. I think there are limitations in terms of patient resources that pediatric oncology has, and when we get into Phase II trials that require a larger number of patients or we get into

Phase III trials, you know, we have to work with the existing structure of the cooperative group to get those studies done.

So, I think your point is very well taken and the Committee needs to recognize that. I am not here to defend either side, I am trying to be impartial, but I think it's a reality of how the process occurs in pediatric oncology.

DR. PAZDUR: And here again, Victor, this is why we wanted a public discussion of this.

DR. TEMPLE: I think the crucial point is that accelerated approval was thought of originally as something that happens if you get surprised, that is, you are doing ordinary development, whatever that requires, but the results are so impressive in the early studies that you reach the reasoned judgment that it is better to make it available before you have the final data and get those data later.

For obvious reasons, this isn't really to blame anybody, it has also become, to some degree, an alternative path to approval where the only

thing that people think about at least sometimes is accelerated approval, and they don't really spend a lot of time thinking about what the whole program is going to look like.

We recognize the realities of availability and things like that. Sometimes people go to other countries to do the trials where there might be possibilities that aren't available here.

But I think the main point that Rick wants to make, and I do, is that it should be playing a part of a coherent plan, and we would be happy to talk with them, we would be happy to talk with the pediatric oncology groups, but it ought to be part of the thinking process, and we are concerned that sometimes it doesn't seem to be.

DR. SANTANA: Joanne.

DR. KURTZBERG: I have a question for the sponsor along these same lines, if accelerated approval is granted, and if trials were planned as part of the arrangement, would the sponsor's support both drug and data collections costs for those trials even after drug approval?

DR. WEITMAN: I would just like to make a couple comments also. Again, that is, at least historically, if you look at what the sponsor has done with Campath in the past, is that we have met I guess requirement for that drug as far as doing a post-commitment study. That study is fully accrued and is completed, and we are in the last phases of really data collection follow-up on that, so we do have a track record of meeting that requirement.

As far as going forward, we are fully willing to support these studies going forward, certainly with drug, but also financially as needed to make these studies come to completion.

I think, Joanne, you and I have both been in the position where drug all of a sudden disappeared as we have been trying to do these studies in the pediatric oncology community, and I think as a sponsor, we fully accept that responsibility to provide drug, as well as financial support going further for these studies.

Now, when you go through the cooperative groups--and I think the point that was made was

very appropriate--doing these studies outside the cooperative group, I think is extremely difficult.

In fact, at this stage, one of the reasons why it was done early, because a lot of these patients just weren't eligible for any studies that were in the cooperative groups going forward. A lot of these patients now would be, particularly as we move into less heavily pretreated patient populations.

So, I think going into that population now is really where we need to be with this drug. The support for this agent going forward clearly depends on I will say a little bit on the Children's Oncology Group. When I have met with them and talked to them about just that point, how to support these studies going forward, there was a couple of options.

One, they actually asked if we would provided some support for particularly outside studies, correlative science studies, and so forth, but a lot of that support would come through the CTEP mechanism, and they actually preferred that

versus sponsor support, but we are willing to support it either way depending on what works best for the cooperative group, as well as to get this agent moving forward.

DR. SANTANA: Dr. Wayne.

DR. WAYNE: So, though, we are asked to consider the data presented in the application on the pediatric trials in regard to the accelerated approval, it might help to have additional adult data that might be extrapolated. I was somewhat pleased and surprised to see on page 112 of your briefing document, in Table 46, 60 percent, 63 percent CR with cycle 1 in adults on a Phase II trial with single agent.

Are there data that can be shared further in that regard? It is the IST study, and no further mention, or I didn't find any further mention of that in the briefing document.

DR. WEITMAN: We have had obvious a continued program, but mostly with the focus on adult AML. There has been a few ALL patients treated, but most of it is in the adult population

with AML.

The responses again, as I mentioned, in the combination study, were about 40 percent. Again, this was pretty much echoed in the single-agent study, as well, in adult patients with AML with a fairly high response rate. In fact, some of the patients, the elderly patients have had response rates in the 60 percent range with adult AML previously untreated patients.

That is why the program in adults is really moving in that direction more than in ALL, because of the activity we have seen in that disease subtype.

DR. WAYNE: Do you have more formal data in regards to that AML trial? Clearly, the very limited data you have shown us in regard to AML in pediatrics, and that single-agent agent might be helpful in regards to extrapolation in AML.

DR. WEITMAN: Well, I don't have a slide with me today on that, but clearly, again, that has shown activity. The response rate in the combination was 40 percent CR and CRp. The adult

elderly patients was over 60 percent response rate with AML. Against, that was in an IST STUDY, that wasn't a pilot study.

I think across the board, that is where we have seen the response essentially confirmed right between 40 and 60 percent with AML.

DR. SANTANA: Dr. Brawley.

DR. BRAWLEY: Steve, I have two questions really, if you could respond. One of the things that some of us are concerned about, those of us who are a little bit more orthodox in our design of clinical trials, like to set the endpoint and then not move the endpoint during the trial. Sometimes we can be accused of tailoring the endpoint to fit our data.

Can you just respond and assure us that that hasn't happened here?

DR. WEITMAN: No, absolutely not, Otis, that hasn't happened here.

DR. BRAWLEY: The next thing, and I don't want to make any allegations or implications against anyone, but out of a sense of fairness, can

your academic advisors disclose for us their financial relationships with the company, who own stock, who has taken honoraria, and that sort of thing?

DR. SANTANA: Johanna, where is the Executive Secretary? Can you help us with that? Do we have--before anybody gets to the podium--do we have any information from the consultants for the company in terms of their conflict of interest?

DR. BRAWLEY: Also, is it even appropriate to ask that question?

DR. SANTANA: It is appropriate publicly to ask that question, because the consultants should have cleared that.

There is a question on the table whether the consultants for the sponsor have cleared issues of conflict of interest. What is the process?

MS. CLIFFORD: We don't do that.

DR. SANTANA: We don't do that, okay.

DR. PAZDUR: They don't do that. Obviously, it is up to the individual people that have presented here if they would like to avail

that information.

DR. SANTANA: I personally have no issue with that. If other members of the Committee feel differently, this is the time to raise your concern. I have no issue with the sponsors and their consultants.

DR. TEMPLE: Just to be clear, I mean our presumption is that the people who are advocates for the company have an interest. So, you have listened to them, and you listen to what they say, but they are not neutral parties like the advisors here.

DR. SANTANA: Dr. Mortimer.

DR. MORTIMER: I am just curious. The cytogenetics, I know you had cytogenetics on one patient, but what was the impact of cytogenetics pre- and post?

A second question is after completion of therapy, did patients receive additional treatment afterwards, or all these patients stopped with the study drug?

DR. WEITMAN: Your first question about

cytogenetics, I was very interested in that myself and tried to take a look at it. As you can imagine, in these patients that have gone through five, six prior regimens including transplant and total body irradiation, their cytogenetics ended up running onto several lines, and trying to really tease out anything in particular was very difficult to do.

Certainly, a number of these patients did have 922, monosomy 7, and some of those patients, I think there is one of each did respond. But again, looking at them, trying to make any correlation between cytogenetics proved extremely difficult in these multiply relapsed patients.

Your second question?

DR. MORTIMER: Treatment after completion.

DR. WEITMAN: The only patients that received essentially treatment after study were those that relapsed and went on to something else, and that was the same before going to transplant, as well. The only treatment they received before transplant was a conditioning regimen before

transplant.

If I can, I would like to just comment on Dr. Wayne's question about other results in the adult population. The Phase II study results, again, there was 31 patients with AML in that patient population. Thirteen of those 31 had a CR and 4 had a CRp, for a total of 55 percent response rate in that patient population.

There were patients with ALL. That was 12 patients with ALL. Again, these are recurrent disease patients. Twelve patients had ALL with 1 CR and 1 CRp. Again, because of that difference with the propensity towards AML's, is where we are moving with the program in adults.

DR. SANTANA: Dr. Hershfeld, I will give you the last comment.

DR. HERSHFELD: Well, I will briefly just comment on the data that Dr. Weitman just stated, and if I may, I would like to ask a question too.

The Pediatric Subcommittee of this Committee has been a big proponent of extrapolation and has previously had discussions about data

between adult and pediatric leukemia, and had some recommendations in that regard, but I should note that the data that were just cited were not submitted to the FDA, nor reviewed by the FDA, therefore, that should be taken into account.

I wanted to ask briefly, if I could, a risk-benefit question. That is, in risk-benefit, the risk and the benefit are more or less separated and then one integrates the two.

I wanted to ask Dr. Weitman if there was a gain or change in either the risk or the benefit that was gained with experience with the drug, that is, patients that sought early on maybe had a different risk or a different benefit than later on.

Somewhat related to that, and this relates to Dr. Brawley's question about the endpoint that wasn't in the protocol, the transplant goal, the CR/CRp sum in the ALL patients was 20 percent, and yet half of those went on to transplant. The CR/CRp in the AML was 3 percent, and yet 34 percent of the patients went on to transplant.

Why the differences or what was the criteria?

DR. WEITMAN: With regards to your first question about sort of gaining experience with the drug, clearly, at least my impression of seeing the patients going on study, when the study first opened, we were seeing very heavily pretreated patients going on study.

As you alluded to, with more experience with the drug, as people began to see this drug's activity, they began to put better patients on study. But we also began to I think get a better idea of how to manage some of the problems.

Quite frankly, we weren't anticipating the extent of tumor lysis that we were seeing. These patients would many times come on with white counts of 100,000, and within a few days drop their white count to 0.1, 0.2.

So, again, having considerable tumor lysis that probably wasn't recognized was going to be a problem early on, was managed much better as the study went further, with extra fluids and just

realizing that this drug has potent activity in some of these patients.

I believe one of the patients of Dr. Arceci, that he treated, actually had a uric acid that went up to like 17 or 18. In my pediatric experience, I have not seen many patients with a uric acid of 17 or 18. Again, I think that just reflects the activity of this drug.

But as time went on, and we began to realize that, I think we were able to improve that risk-benefit ratio by again extra fluids, monitoring, and so forth, just as we learned as we went forward.

With regards to your other question about AML and why there was a higher number of those patients going to transplant, it is a good question. I am not sure I honestly have an answer for it. It is what we did see.

Clearly, I think a lot of patients with AML from the very early point, tried to identify a donor whenever possible, probably much earlier than patients with ALL, but again, there was more

interest in particularly patients with AML going to transplant.

There is also more willingness in that group to take patients in partial remission, where their ANC may not have fully recovered, to go to transplant, and that is probably not the same situation with patients with ALL, where they want to see a complete remission, solid remission more likely than not than in patients with AML.

So, I think the threshold particularly for patients with AML, because those patients do do reasonably well even if they PR going to transplant as opposed to patients with ALL.

If I can ask Dr. Arceci and Dr. Sallan maybe to step up for a second.

DR. SALLAN: I just wanted to step up to address Dr. Brawley's question. I have no interest in the company whatsoever other than getting paid for my time to review the data and to be here.

DR. ARCECI: I, too, think it is an important question to clarify. My involvement has been to participate in the study and my interest in

drug development, and they paid for my transportation from Baltimore to Silver Spring.

[Laughter.]

DR. SANTANA: We won't ask how you got here.

I think we will conclude this part of the session. We are going to reconvene exactly at 10:45, because we do have a couple of individuals that have signed up for public hearing.

Thank you.

[Break.]

Open Public Hearing

DR. SANTANA: I have a public paragraph that I need to read for the record, so let me go ahead and do that.

Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of this Advisory Committee meeting, the FDA believes that it is important to understand the context of an

individual's presentation.

For this reason, the 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, with its product, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, your lodging, or other expenses in connection with your attendance at this meeting.

Likewise, the FDA encourages you at the beginning of your statement to advise this 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.

So, I think we have a number of public speakers. You have a list? Go ahead.

MS. CLIFFORD: We will start with Hal Wilson.

DR. WILSON: My name is Dr. Hal Wilson. The only relationship I have with ILEX is they flew me here and allowed me to stay in a hotel, which is nice, because it's a long walk from Phoenix, Arizona.

The reason why I am here, first, I have a little background about me. I am a board-certified family practice physician and I run and own a practice in Phoenix called Maxel [ph] Medical Group. I also do a lot of emergency room work with a group called Emergency Physicians Professional Association.

I had the opportunity to have dinner last night with a number of parents of children who suffered from the diseases that have been discussed today. I am not such a parent. The reason why I am here is because I am an uncle, and, Dr. Weitman, when you had your slides up with the description of the patient population, I felt like you had a little picture of my niece on every one of them as far as being in multiple drugs and failed bone marrow transplantation, and the whole thing, ended

up in M.D. Anderson, and went on clofarabine.

So, that is why I am here. As I was thinking about what to say today, I thought it might be a good idea to approach this situation with a sense of appreciation. I am not here to crunch numbers or toxicities, risks and benefits.

I just want to say thank you to ILEX and Dr. Weitman for bringing this drug as far as it has come along so far. In this particular instance, I realize it's a case of one that had some benefit. Dr. Weitman and staff, I appreciate the commitment you have made to pediatric oncology.

A couple of things that came up in the discussion today, which I thought was really interesting, which was fascinating to me, was the idea that not very many new pediatric drugs have come down the pipeline for a number of years.

I also heard it said that relapsed leukemic patients and pediatric oncology patients, regarding those patients, one of the major challenges for a pediatric oncologist is the relapsed patient, and I really appreciate what you

do as far as dealing with those situations, because, as everybody knows, by the time the patient makes it to you, they don't have a lot of options left.

So, basically, in conclusion, I would just like to say I remember at the beginning of the presentation, there was a discussion about approving a drug based on scientific data versus providing drug access to patients. In this particular patient population, I think it is important to remember that really, they don't have any other options left.

Thank you.

DR. SANTANA: Thank you for your comments.

MS. CLIFFORD: Colleen McCarthy.

MS. McCARTHY: First, I would like to disclose that my travel arrangements and my air fare were paid for by ILEX Oncology.

My name is Colleen McCarthy and I am a clinical research nurse at Children's Hospital in Los Angeles, and I work with the Leukemia and Lymphoma Program.

For the past 12 years, I have been a pediatric oncology nurse working In a variety of settings, inpatient, outpatient, bone marrow transplant, nurse education, and now clinical research, but always my focus has been pediatric oncology.

I want to tell you a story about one of our patients that we took care of. In August of 2002, we enrolled our first patient onto the clofarabine trial. In total, we treated 8 children on this study. One little boy, I would like to tell you a quick story about.

We enrolled a 3 1/2-year-old, ALL relapsed patient, who was diagnosed when he was 1 1/2 years old. He had had 4 prior regimens before coming onto this treatment. He had had a bone marrow transplant included in that.

When he first started his therapy with clofarabine, he was very irritable, very clingy on mom. Mom would try and put him down, he wouldn't walk. Mom was very, very upset that he wouldn't act normal.

We gave him his clofarabine and lo and behold, a week later, walking, feeling great, eating, interacting with his siblings, feeling great. Mom was very, very excited, and most importantly, he was able to be discharged from the hospital.

Now, he had been in the hospital for two months prior to clofarabine, dealing with fevers, et cetera, from toxicities from prior therapies. The fact that mom got to go home was so wonderful for she and her family.

This young child ended up getting 3 more cycles of therapy, 2 of which were outpatient, so he was home for about 3 months before he came in for his last cycle, had a fever, and stayed in for a few weeks before going home.

The reason I want to bring up this little boy is because the mom shared with me, when we started this drug, that she really wanted this drug to work for as long as it could because she wanted time with her young son.

The father was not in the house at the

time. He is returning to the house about a month after the child had relapsed. She wanted to make sure that there would be enough time for this young boy to be able to be with his dad prior to him passing away.

He did get 2 months with his father, and the last thing the mom told me right after the child did pass away, was the fact that after getting the clofarabine, after cycle 3, the family went to Disneyland together, mom, dad, little 1 1/2-year-old sibling, older cousin, and grandma, and they had a normal day.

For that family to have that one normal day, she was so thankful. After the fact, when the child did pass away, she called me and said thank you for letting my child be part of that study. So, that is my little story about our 3 1/2-year-old.

As a nurse taking care of patients with leukemia, when you first meet a family when they are newly diagnosed, they will ask you what is next, what should we expect, what treatment, and

all these wonderful questions, and those questions, as a nurse, you are able to answer when the child is newly diagnosed.

When that same family comes back to you a few years later with relapsed or refractory and asks you those same questions, it is very difficult to answer those questions, because you are not sure what is next, or what to look forward to, or what they can expect.

So, I just wanted to point out those quick little things. Thank you.

DR. SANTANA: We appreciate your comments. Thank you.

MS. CLIFFORD: The next speakers are Tasha and Steven Virostek.

MS. VIROSTEK: I am Tasha Virostek and I do not have a financial relationship with ILEX. They did, however, pay for dinner last night.

My son Jeffrey lost his battle on September 25th, 2003, to acute myelogenous leukemia. I am not here as a scientist, I am not here as a doctor, but I am here as a mother who has

been deeply affected by this terrible disease.

Jeffrey was diagnosed with AML at the age of 2 1/2. At the time, we knew we were dealing with a terminal illness, but we had hope that with the best doctors, the best medicines that were available, and the best facilities for him, we would conquer this disease.

Jeffrey received his induction of chemotherapy beginning in November of 2001. When he did not receive a remission, a protocol was abandoned, and a new regimen was sought. What I found out today is that many of these drugs are 30, 40 years old.

Christmas of 2001, he spent in the hospital fighting infections, affected by rigors from medicines given to wipe out fungal infections, bacterial infections, and viral infections. His body was too weak to fight infections and also too weak to combat the side effects of the drugs. It was depressing and frightening.

Miraculously, he did pull through and he came home to celebrate his third birthday. His

next round of chemotherapy also left him weak and susceptible to infection.

In March of 2002, we began treatment which led us to our first bone marrow transplant. This was our only option, and luckily, we did have a donor, his sister who was 5 at the time. She was a perfect match.

This was an extremely difficult process on Jeffrey because he received even more toxic chemotherapies which compromised his immune system and again left him vulnerable to infection. The chemo made his appetite diminish, prompting the need for fluids and nutrition via his double lumen port. Mucositis became prevalent. The intense pain that accompanied this was unbearable at times and had to be managed by morphine, which, in turn, caused him to be lethargic.

This treatment kept Jeffrey from doing what a 3-year-old should be doing, playing, learning, laughing, enjoying being a child. As a parent, it was agonizing to watch your child struggle with the vary basic functions of life. No

one should have to endure so much.

This process also brought many anxieties. We worried about the short- and long-term effects of the chemotherapies on his body, liver damage, damage of the heart and the lungs. We worried about his future physical and psychological development, and we worried about the effect on his spirit. We worried about graft versus host disease.

Jeffrey's diagnosis with cancer and his treatments had other consequences on our family. Being his full-time caregiver, I had to rely on my extended family to take care of my daughters that were at home. They were too young to understand and my absence caused resentment and anxiety amongst our young children.

Jeffrey's diagnosis brought a lot to our family, but luckily, when he came home we were able to have 9 months of remission. During that time, our lives began to resemble, quote, unquote, a "normal" life, and in October of 2002, Jeffrey experienced a Make a Wish trip to Sea World to meet

Shamu.

But around his 4th birthday, he relapsed. We returned to Children's Hospital where we faced limited choices. We could redo the bone marrow transplant or we could do nothing. We decided to fight the cancer. Once again, we spent weeks upon weeks in the hospital, confined to our small room. Visits from family and friends were prohibited.

The second bone marrow transplant was especially difficult on my daughter Megan. With much trepidation, she received daily shots to increase the number of stem cells in her peripheral blood. Placing the catheter in her artery was a painful experience that she still remembers today. She then endured a long and difficult extraction process.

Despite using the best doctors and treatments available, Jeffrey's cancer returned just a few weeks after his treatment. Our options were limited. We had exhausted all known treatments and he was not eligible for any drug trials at this time. So, our last-ditch effort was

to give Jeffrey additional stem cells combined with interleukin-2 in the hopes that the good cells would outnumber the cancer cells.

At this time, our main goal was to maintain Jeffrey's quality of life. We wanted him to remain with us at home, so that he could play with his sisters, he could be a little boy and play with his friends and visit public places. We wanted to enjoy each day that we were together and we were frustrated by the lack of treatment options.

Jeffrey did experience some pleasures like a trip to the beach before the cancer took over. His last weeks with us, however, were filled with intense pain and suffering. The cancer took his life.

We know that Jeffrey's story is not an isolated case. Since the time of his death, our family has personally known more than half a dozen individuals who have relapsed and many have since died.

The professionals in this room have the

knowledge, the resources, and the influence to make a difference in the lives of children with cancer. I encourage you to conduct your work with the utmost diligence and expedience to bring new treatments which will combat leukemia more effectively, with fewer side effects, that allows a higher quality of life. So many lives are depending on you.

DR. SANTANA: Thank you so much for your comments. I know it is difficult for you to talk today, but I think it is a very honorable way to remember your son to share your story with us. Thank you.

MS. CLIFFORD: The next speaker is Ms. Nadia Hendry.

MS. MAROUN-HENDRY: Good morning. Thank you for this opportunity to share my experience with you.

As I was listening earlier, I want to clarify that Dr. Steinherz can confirm we have had many bone marrow follow-ups, and thank you to the doctors who quickly do that for us parents who are

waiting anxiously and chase them down the hall to get those good and not so good results.

I consider it an honor, not only to speak on behalf of my son, but hopefully, my remarks will represent countless children and their families whose lives, hopes, and future have been derailed by the horrors of childhood cancer.

Throughout my son Matthew's 4-year ordeal, struggling with the ravages of leukemia, I came to see myself as something of an expert on the topic, but please, make no mistake, I am here only as a mother, more specifically, I am here as a heartbroken mother, having lost our beloved son on March 25th, 2003.

When Matthew was only 3 years old, filled with wonder and the joy of life, we were informed that he had cancer, telling you on that day, September 9th, 1999, our world stopped and lost its sunlight does not begin to express how profound our grief was from that day on.

But as so many other parents have known before me, we had to take our grief and turn it

into hope and action. We had to become educated. Despite having been plummeted into a world of protocols, side effects, frequent hospitalizations of over 500 days in the hospital, new relationships, financial and family turmoil, somehow with the grace of God, supportive family and friends, excellent medical care, and faith in the promise of medical research, we managed never to lose hope until Matthew drew his last breath.

During his illness, Matthew rose to the challenge and rigors of numerous protocols and treatment, including a bone marrow transplant and subsequent boost. Each course of treatment renewed our hope that this would be the last.

From the point of diagnosing to his passing 3 1/2 years later, he only was free of any drugs or treatment for two months of his life. Matthew relapsed two months after his first bone marrow transplant. Prior to his relapsing, he was diagnosed with Epstein Barr Virus, a possible side effect that we were aware of to transplant.

After 9 months of treatment at Memorial

Sloan-Kettering, preceded by 2 years at Albany Medical Center, we were devastated with the lack of options. There was nothing, it was dismal.

Matthew's doctor, Dr. Peter Steinherz, offered to include him in a clinical trial using clofarabine. We were given all the necessary information and eagerly grasped at this one last opportunity to save Matthew's life.

Remission followed shortly thereafter the clofarabine was starting, allowing us to go ahead with the second transplant. This was our last chance. He stayed in remission and was 100 percent donor cells, but oddly, we couldn't figure out what was going on. He was having seizures and numerous lesions to the brain.

As the seizures became more numerous and more severe, a decision to treat for a possible fungal infection was made. After weeks of treatment with no improvement, it became obvious that this was not a fungal infection.

By this time, Matthew's speech was impaired, his thought processes sluggish, he was

unable to walk. The severity of his weakened condition was cause for several hospitalizations and increased medication.

Matthew's little body was broken and weary, but never did he lose his spirit. He had a strong sense of self. Our darling little boy, this dear old soul told me it was time to face my fears, and he asked me that I promise there would be no more hospital.

After years of hope, we had to now turn our love towards acceptance and making his last months comfortable and peaceful. We were faced with what no parent should ever have to deal with, arranging for the end of our son's life.

It was through his strength of spirit that we requested an autopsy to determine the cause of death since he had been on the clinical trial. A month after Matthew's passing, we learned that he was clear of leukemia upon time of death, and it was the Epstein Barr virus that caused his death. Therefore, we knew the clofarabine has worked.

We had to know, we had to know for

ourselves, and we had to know for the other Matthews that this treatment had been effective. We were happy to know that the clofarabine had been effective and could only wonder, with very heavy hearts, what if he had gotten this sooner.

Matthew only had 6 years on this earth. I will have the rest of my life to wonder what if.

I failed to mention my trip was paid by ILEX and dinner and my room, and I thank them for giving us the opportunity to have an extra 8 months with my beautiful son. Without that, we would not have had that time. We were living in New York City for over 9 months. Silly me, I thought the chance that we would be home in 2 months and everything would fine, and 9 months later, all Matthew wanted to do was go home and be with his dog and his brother and the rest of his family, and he was able to do that because he took part in this. It gave us time, and I don't think time can be measured, and it is priceless.

Thank you.

DR. SANTANA: Thank you for sharing your

story with us.

MS. CLIFFORD: The next speaker is Jan Manlapaz.

MR. MANLAPAZ: Good morning, ladies and gentlemen. I am Jan Manlapaz. I come here as a parent. We originally came from the Philippines. I have a son, who is right now on my left side, who is an AML patient.

He got multiple relapses, 5 relapses, 1 bone marrow transplant relapse, and I am speaking on a good tune because this is our bible right now, got multiple relapse and one bone marrow transplant, and on July of 2002, the doctors advised us that he going to live only for around three months, and with the decision and advice of Dr. Steinherz, they introduced clofarabine, and they use it for him. He is now in 22 months in remission, and we would like to thank you, thank ILEX for this medicine, and thank all the people who are in this research.

I want to give the microphone to my son just for a simple note to say thank you.

Thank you for all the doctors for making me well and thank you, Dr. Steinherz, for giving me some medicine. Good morning.

[Applause.]

MR. MANLAPAZ: Thank you very much.

DR. SANTANA: I don't think anybody can beat that comment. So, next.

MS. CLIFFORD: Mr. Dahlman.

MR. DAHLMAN: Thank you. George Dahlman.

I have no interest in ILEX. I didn't go to dinner last night, and I live in the Washington area.

My name is George Dahlman. I am the Vice President of Public Policy for the Leukemia and Lymphoma Society of the nation's second largest voluntary cancer organization and the world's largest dedicated to blood cancers, but probably more importantly, I am the father of a childhood cancer survivor, or now, more accurately, an obnoxious teenager.

In the first capacity, I represent a lot of patients and family members, and we lobby for

government funding, we fund our own research. We run patient services programs, and we lobby for better care.

Now, we all know that the leukemia survival rate has improved dramatically over the last 30 years. It has gone completely upside-down. It used to be that survival rates were more like 20 percent, and now they have flipped around, they are more like 80 percent.

Most of the credit for that dramatic change is really with the physicians, many of you pediatric oncologists who have tweaked and changed the protocols and had the vision and creativity to really make those differences.

Now, even with that progress, though, there are no real cures yet as long as there are kids that still have to go through this, and that is the cold fact that parents have to face and many parents have to tragically experience like those here today.

There is still too many kids who don't make it, and as a parent who had to look at that

prospect, I can tell you there is nothing more frightening than the thought of losing your own child. I have known a lot of people like this that have gone through that.

I would like to say in the memory of those children and for their parents, and all those patients yet to come, we still have to keep tweaking the protocols. That is why I think this hearing and this drug is such an important milestone.

That is what clofarabine offers. As we all know, this is the first one initially labelled for pediatric leukemia in over a decade, and that is really a tragedy. It is a deficiency that should not be allowed to continue.

I am proud to say that my organization and others that we work with are very actively involved with trying to develop incentives, public policy incentives and corporate incentives that will address that issue.

But now, as we all know, the progress in this is incremental, and one in which the FDA has

traditionally accommodated with even the most modest improvements in outcome, and professionals, like yourself, need every weapon in your arsenal to make those incremental improvements, and clofarabine offers that kind of incremental improvement.

Thanks for your attention.

DR. SANTANA: Thank you.

Committee Discussion

We will go ahead and start our questions and further discussions, but before we do that, as I heard the previous discussion, I think there were two central themes that I think would be important to try to reach some resolution or at least some further discussion before we go into the questions, because I think they will be pertinent for answering those questions in the best way that we can.

One has to do with this issue of bone marrow transplantation and how does that impact both of these studies and the indication that the sponsor is requesting.

To me, what I would like some discussion, and I am going to ask Joanne Kurtzberg, who is a bone marrow transplant specialist, to help us with this issue, is to give us a sense of what is the practice of bone marrow transplantations with the pediatric patients that have refractory or recurrent leukemias, in what settings are transplants clearly indicated, and what additional value does treatment prior to transplantation offer to these patient populations.

I think that will be very pertinent as we go to trying to establish this issue of clinical benefit for this drug.

Joanne, can you tackle that one for me?

DR. KURTZBERG: Yes, sir. Well, first of all, we have to separate the discussion into a discussion about ALL and AML, because the answer is really not the same.

In children with ALL, transplant is really not effective unless they are in remission at the time of transplant, not partial remission, not remission with low platelet, real remission, and in

all the diseases that we transplant, the success rates for curative therapy are still the lowest in children with ALL, because the disease appears to be more resistant and maybe there is less of a graft versus leukemia effect.

So, this drug would be helpful or any drug would be helpful if it could take a child with resistant disease and put them into a true remission, but the idea of putting them into a partial remission, I don't think is operative here, because results in children in partial remission, 95+ percent of children relapse, if not all.

One thing that was said earlier that I need to take issue with is that you can certainly have a child with ALL walk in the door, have normal to near normal blood count, and be in relapse, and you cannot tell from the peripheral blood count necessarily that that child is in remission or relapse.

As a transplanter, we get many children referred to us who relapse between the time they left home and the time they arrive at the

transplant center, and when you do that marrow, they have got 20, 25, 30 percent blasts, and you don't know that from their peripheral counts or their physical exam or any clinical parameter.

As much as you want to cure every child that walks in your door, if you take that child to transplant, you are not going to cure that child. So, I think rigor in that setting is really important, and a drug would be valuable in that setting if it produces a true, durable remission.

In AML, the story is different. Children with AML, transplanted in relapse, still have anywhere between a 25 and 40 percent cure rate depending on the nature of their disease, the nature of the transplant, the type of donor, and the type of prep regimen.

So, you could argue in AML that it is not essential at all to get a child in remission. Having a drug that cytoreduces may be valuable to prevent some toxicity, but I am not sure it really contributes in a heavily pretreated, multiply relapsed patient to overall outcome.

I think it would be an interesting question to study, but I don't see anything in this data that helps us know if it really provided an increased cure post-transplant compared to a child that was transplanted in frank relapse.

DR. SANTANA: Just to summarize very straightforward like I like to be, in the setting of relapsed, refractory ALL, there may be some added value of getting those patients into remission prior to transplantation, because those are the patients that ultimately we think do well with bone marrow transplant, but in the setting of a lot of disease in the ALL setting, further transplantation doesn't really add anything.

Am I correct in that simplistic view?

DR. KURTZBERG: I think so. Patients with ALL benefit from transplant if they are in a true remission at the time of transplant.

DR. SANTANA: And then for the AML patients, it is debatable whether cytoreduction really improves their ultimate outcome with subsequent therapy as aggressive as

transplantation, is that correct?

DR. KURTZBERG: Yes.

DR. SANTANA: Comment about that? Dr. Hussain.

DR. HUSSAIN: Just to ask the doctor again, because I think I heard a little bit different, and that is, it is a complete remission that is what is important, not any remission, and the second question is, is that a confirmation of that remission is crucial because you could be in a complete remission today and walk out of the door, and that remission is not maintained, which I think is central to what we are talking about here.

DR. KURTZBERG: In ALL, yes--

DR. HUSSAIN: That is my question.

DR. KURTZBERG: --remission is important, and a child who is transplanted not in remission has an overwhelming probability of relapse, and generally does not benefit from the transplant, and, yes, confirmation is important.

DR. HUSSAIN: I am sorry, but we are talking about a complete remission or any

remission?

DR. KURTZBERG: Complete remission.

DR. HUSSAIN: Complete remission.

DR. KURTZBERG: As defined in 1970.

DR. HUSSAIN: So, complete remission and a confirmed complete remission is crucial.

DR. KURTZBERG: Yes.

DR. RODRIGUEZ: In AML, do I understand you to say that cytoreduction isn't of any value in terms of preparing the child for transplant?

DR. KURTZBERG: It can be of value particularly if the child has a very high tumor burden, because it can minimize toxicity, but to be completely honest, there are many ways that you can do that without achieving a remission. You can use hydroxyurea and BP-16. You can use ara-C, which may not put the child in remission, but will have some lytic effect on the blasts.

So, you know, I don't think this would be the only option in that setting.

DR. SANTANA: Any other questions on that point?

DR. MARTINO: So, it occurs to me that perhaps there are two patient populations. There are patients for whom a transplant is a possibility in the sense that there is someone who can donate the marrow, and then there are patients for whom that appears to be not such a possibility, and the goals that are striking as being somewhat different if I had to design a trial, and one of the problems that I keep struggling with in the data that has been presented to us is were the studies designed in a manner that allowed me to answer the questions that they are suggesting I am able to answer.

I am really struggling with the fact that to me, there really are two populations, there are two endpoint potentials here. One is judging is this good therapy prior to, or concurrent with, or somehow related to who gets to go to transplant, and for whom is that a valuable thing to do.

Then, I have patients who really aren't people going to transplant where I might want to ask a somewhat different question. Yes, ma'am.

DR. KURTZBERG: I agree with you, but I

think the strategy for any new drug for ALL shouldn't really have transplant as an endpoint.

I mean I think transplant came as an endpoint because you are dealing with desperate situations where that is the only possible cure, and that is kind of what everybody looks to when they are in that situation, but I think you are absolutely right, the drug ought to be tested in first relapse or second relapse patients, and there are many of those unfortunately, with an endpoint of response, and it is an additional facet, with additional therapy planned after that based on the standard of care. It might be transplant, it might be more aggressive chemotherapy depending on duration of first remission and many other things.

But the transplant endpoint really confuses the whole situation, and I think it just came to play because of the clinical situation people are in when their child relapses multiple times, not because that would be an appropriate endpoint for proving a drug is good for leukemia.

DR. MARTINO: But what I feel I need to

judge here is whether the data, as presented, allows me to answer the question that the study states it was designed to answer, and I still remain confused because of this transplant issue, realizing its clinical value and applicability, but it doesn't quite allow me to judge what I view as the question posed in the study.

DR. SANTANA: Dr. Temple.

DR. TEMPLE: If I understood you, you are saying that at least in ALL, the question is complete response rate properly documented, and some people get transplanted, some won't, but you are saying that is not the most important thing, it is the complete response rate, which here is in the neighborhood of 12 percent or something like that, subject to subsequent debate.

But in AML, that is not as clear from the sound of what you said. That is not as clear because getting the count down, which you guys say could be done in a lot of ways may be of benefit, so what is the right test there?

DR. KURTZBERG: I think honestly, if I

were doing this, transplant wouldn't be in the discussion, and I would do a standard Phase II trial where the endpoint was response. I think that the drug probably does have activity, I am not questioning that, but I think testing it in first relapses in upfront window, looking at response at a month, you know, and squaring that, clearly is a good thing to do.

DR. TEMPLE: So, in those cases, people might be willing to wait before they--I mean in the AML cases here, they were already transplanted before you got a chance to look at how long the response lasted, so you never could find out. Do you think in earlier disease, that sense of urgency would be less, and you could actually get that data?

DR. KURTZBERG: Yes, I do, and I also think you could get better data because the patients are generally less resistant at that point.

DR. TEMPLE: Okay.

DR. KURTZBERG: I think the response

post-transplant is not interpretable. There are so many kinds of transplants, kinds of prep regimens, kinds of donors, and covariants that are confounding, that you can't make a--

DR. TEMPLE: So, specifically, for these, there are at least a reasonable number of people with ALL whose response was tracked without a transplant intervening, so you got some idea of how long it lasted.

In AML, there were very few who managed to do that, because the all got transplanted pretty early if they looked even reasonably good, so you don't really have duration data, is that correct?

DR. KURTZBERG: Yes, and part of that is the hidden message that most people don't transplant children with ALL if they are not in remission, and these patients weren't in remission, so not so many of them were transplanted.

DR. TEMPLE: Right. They behave just like you say they would.

DR. KURTZBERG: But in AML, people do transplant in relapse.

DR. TEMPLE: So, just to be sure I understand it-- and I am sorry to struggle, I don't do this for a living--in ALL, in these relatively advanced and refractory patients, in ALL, you do get a chance to see, in a small population, what the complete response rate is, and it is not confounded by early transplant that messes up finding out how long it lasts. In AML, it is more of a problem here because you don't.

Would that be true, is that what you are saying?

DR. KURTZBERG: The way the data was presented--

DR. TEMPLE: I am asking you what you are saying.

DR. KURTZBERG: I think you could, but I am not sure it happened in this case.

DR. TEMPLE: No, I mean as conducted here.

DR. KURTZBERG: Yes.

DR. SANTANA: Dr. Bukowski, do you have a question or a comment?

DR. BUKOWSKI: Just a clarification and

maybe you can comment on this. Essentially, what you are saying then is the population in second relapse and beyond in both diseases is not an appropriate one to evaluate a new drug in when using the endpoint of complete response, because of the confounder of transplant, is that correct?

DR. KURTZBERG: No. I think because in many situations, you will take a patient in first relapse to transplant. So, it is not the transplant--I think transplant is confusing the whole story. I think that drugs will have a better chance of being fairly tested in patients in first relapse because they are less resistant and less heavily pretreated, and you are more likely to see activity.

But it could be tested in second, third relapse, but the endpoint should be response, not whether they go to transplant and how they survive after transplant.

DR. BUKOWSKI: So, is it possible, in the pediatric group, to hold the transplant, to look for the complete response? I mean it sounds like

this wasn't--at least it wasn't possible in this particular setting.

DR. KURTZBERG: No, I mean complete response after a first course or maybe two courses at the most, and, yes, that is possible. First of all, you wouldn't take the patient with ALL to transplant without a complete response, and the AML patient, it is a clinical judgment, but if they to on a trial like this, they have a month or two to be assessed.

DR. SANTANA: Dr. Maldonado, did you have a comment?

DR. MALDONADO: It is not related to transplant, it is actually a question that I have been struggling with.

DR. SANTANA: Could you hold onto it then, because I want to finish this discussion as one of the points that I wanted to get clarity on.

DR. MALDONADO: Okay.

DR. SANTANA: Did you have a comment on it, Dr. Poplack, on this issue we are discussing right now, before we go to the next one?

DR. POPLACK: Yes, it's a question. I think, obviously, one of the scenarios that is being put forth here is that the value of this agent is that it can get patients to transplant by putting them into remission.

So, I would like to ask Joanne perhaps to educate the group in terms of from her experience, what percentage of patients who come to transplant don't get into remission and don't get to transplant, and what does she see as a potential for this type of agent in that circumstance.

DR. KURTZBERG: That is a complicated question because it really varies based on the practice of the treating oncologist and their bias for or against transplant and when they refer.

I am a transplanter, so my bias is that any child who relapses should be referred for transplant when they achieve their second remission, but many oncologists don't practice that way, and they believe a child should go through multiple relapses before they prove they need to take the risk that is associated with transplant.

So, that confounds the answer to your question.

I think, you know, a child with ALL on standard therapy who relapses has about a 70 percent chance of achieving a second remission with standard therapy, and if that child didn't achieve a remission with standard therapy, and took a new drug and had a 30 percent chance of achieving a CR, that would be, to me, a valuable activity in that drug.

If you take a child who has had 5 relapses and expose them to any new drug, the chances they are going to achieve a remission, no matter how active the drug is, is much, much less. I don't know how to put a number on it, but that is a clinical practice issue, not whether the drug is active issue.

For AML, the chances of achieving a second remission after relapse, they are about 50, 60 percent with standard therapy, but again it depends on therapy relapse, off therapy relapse, how close to recent therapy, so there are a lot of confounding variables.

My point is that I think this has been too ambitious in taking down the transplant road is just too complicated, and what you really want to know, in childhood leukemia, is do you get a durable response, not that lasts, to me, it doesn't matter as a transplanter, if it would last two months, six months, 12 months. It matters to me the child is really in remission and that you have the time to get them to transplant, which requires another two to four weeks.

DR. SANTANA: So, you would define the clinical benefit for the ALL population as reaching that goal?

DR. KURTZBERG: Right.

DR. SANTANA: Of getting a remission of some reasonable duration to allow you then to get something more definitive.

DR. KURTZBERG: Right.

DR. SANTANA: You would define that as a clinical benefit.

DR. KURTZBERG: Right.

DR. SANTANA: Ms. Hoffman, and then Dr.

Perry.

MS. HOFFMAN: Can you clarify, for the AML population, I guess the benefit of allo- versus auto-transplant, and if there is clinical benefit to taking these AML patients using an auto-transplant?

DR. KURTZBERG: This is my opinion, but there is very little benefit to auto-transplant at all, and if you have a multiply relapsed patient, there is even less benefit. Not only do you have a higher risk of relapse, which is 80, 90 percent, but you also have a much higher risk of secondary malignancies. Long term, the results in those patients using auto cells are terrible.

So, I think allo-transplant is where you need to go in all of these leukemias.

DR. SANTANA: Dr. Perry.

DR. PERRY: I think we have heard from the patients' description and the parents' descriptions that these are desperate people, and when any drug, whether it is this drug or another, produces some benefit, they see the transplant as the next

opportunity for a cure. They are not so naive as to think that this drug is the miracle drug that is going to get them disease-free forever.

So, when they see the opportunity for a transplant, whether the odds are great or small, they are going to leap upon that, and present company excluded, most transplanters basically are hammers, and they see the world as a nail, and if there is a patient, there is a indication.

DR. KURTZBERG: That is a new one for me.

DR. PERRY: I don't think we can fault the company for the actions of the patients and the treating physicians who see a response and then say, great, now is our chance to leap onto a transplant, which might be curative. I don't think the company, in this circumstance, can control that.

So, I don't think the company designed the trial to say this drug is a bridge to transplant. They designed the trial to see does this drug work and to what degree, and I think to some degree it works. The question is does it work enough.

DR. SANTANA: Dr. Maldonado.

DR. MALDONADO: Now, it is about transplant. The question is, I mean transplant was not an endpoint for these trials, and by hearing the experts, I believe that there may be different standards for transplant. It doesn't appear to be a single standard. This is a multiple center trial, so there may have been a standards that occurred in the trial.

It is just like hospitalization. I mean hospitalization is another endpoint that should not be used as endpoint unless there is criteria for that, and I haven't seen that criteria outline in this trial of when a transplant occurs.

More than a transplant, it should be a set of criteria that the patient meets, and in that case, it will be complete response. But was that transplant an endpoint or not?

DR. SANTANA: No, no, that is the confounding issue, that transplant was never part of these trials, but what happened in real practice is, like you have heard comments around the table

and from different experts, is that this drug in a way was used as a bridge for those patients that, at least in the ALL population that were having a response and made it onto transplant, and for the AMLs, everybody decided which patients got transplant, which ones didn't.

So, it was not a study endpoint and we should not fault the sponsor for that, because they didn't have any control over that. That was just the practice of patients and physicians who participated in the trial.

DR. MALDONADO: But at the same time, if that is the reality, why the studies were not designed with that in mind and set up that as an endpoint, so measure it in some way?

DR. SANTANA: I can't answer that obviously, that is a historical issue of why the studies were not designed that day, but the data we have is the data that we have.

I want to put this discussion to an end because we have got to move. I just raised the issue because to me, if this agent gets approved

under the accelerated approval, we have to discuss the issue of the complete responses and the durability of those, and then the additional clinical benefit that those responses provide.

So, I wanted to have the discussion, so that at least we get some sense from the ALL population and from the AML population, the differences in those depending how the discussion of the questions goes on further.

I am going to stop the discussion here for that. One more point that I want to discuss before going to the questions, which is very relevant, and I am going to ask Dr. Poplack and Dr. Hirschfeld to comment on, and it is an issue that was raised earlier by Dr. Pazdur in terms of pediatric drug development and the timing of studies and how what we are discussing with this agent today is relevant to that bigger picture, because I think we are going to have to address that in the context of any new drug that is developed for kids that comes to this Committee.

So, David, can you give me some insight

into that issue, and then I will ask Steve to comment, too?

DR. POPLACK: I think it is pretty obvious to all that this is the worst situation, the worst scenario in which to try and do a study of any new agent. I think that Joanne put it quite well that one would much prefer to do a study on a new agent like this at an earlier stage in the clinical courses of the patients.

That being said, it is not so easy. The whole concept of therapeutic windows is a whole theme unto itself in terms of the pros and cons of that, are the patients really available given the practice, et cetera.

It is a real conundrum and it requires superb cooperation frankly, between the group, the Children's Oncology Group, the sponsors, the FDA, to make these types of things happen. I think this isn't the best situation, there is no question about it.

DR. SANTANA: Steve, would you follow up on that, please.

DR. HERSHFELD: Yes. I will, as I have for most of my life, agreed with Dr. Poplack in that it is a multi-dimensional issue and that it requires coordination and integration of all the involved parties due to the relative rarity of the diseases and the lack of resources.

I would just note that when these two, single-arm studies were developed and they were designed with response rate as the endpoints, much as Dr. Kurtzberg had recommended, it was during the time of transmission of when the Pediatric Oncology Group and the Children's Cancer Group were merging into the Children's Oncology Group, and there was issues of the availability of protocols and logistical issues about setting up collaborations, so the sponsor, in essence, wanting to develop a drug in that time frame, during that historical period, had relatively few options in terms of what would be feasible.

DR. SANTANA: Dr. Temple.

DR. TEMPLE: I want to beg the Chair's indulgence because I thought I understood what Dr.

Kurtzberg was saying, but the questions that come up make me uncertain whether I did. Just one more time.

My understanding was that you think a complete response, let's ignore whether these all were, and whether the rate was high enough for the moment, is meaningful actually whether or not people decide to do a transplant--this is in ALL--whether or not people decide to do a transplant, so that the transplant situation in some sense here is not relevant if you once documented a complete response however you have to do that, for ALL.

That makes ALL sound simpler to me in this case, and the only issues would be whether a 10 percent or 12 percent response rate is good enough and whether the responses were adequately documented. Those are the usual kinds of questions we face.

So, is that correct? So, it doesn't really matter that they didn't specific transplant or they were confounded by the community behavior

or anything in ALL. Is that true?

DR. KURTZBERG: Yes, it's true, and I would say the same thing for AML, and what I am saying is that I don't think this duration of response question for pediatric cancer is important in this kind of population.

DR. TEMPLE: The AML, I guess I thought many of the documentation of the response was truncated by the transplant, so that is perhaps a separate problem in AML.

DR. KURTZBERG: But there still was an initial response.

DR. TEMPLE: All right. Fine. Thank you.

Let's go ahead and deal with the questions.

I am just going to make an introductory reading of the first paragraphs and then I think we have the summary page at the end.

DR. MALDONADO: Dr. Santana, I just have a question for clarity, not related to the questions.

DR. SANTANA: Go ahead.

DR. MALDONADO: I have been hearing how

difficult these studies are to define or to be done. However, when I saw the presentation, I believe Dr. Arceci or somebody on behalf of the sponsor.

We are talking about the third most common cancer in patients and looking at the numbers, the numbers are not small, so where is the difficulty other than the COG might not be acting fast enough. I am just not understanding what the difficulty of the feasibility of these studies may be. I am talking about the confirmatory studies.

DR. SANTANA: Part of it is study availability of when the Phase I or Phase II studies are really available. I mean you heard an example earlier today of a comment from COG how they only have three, Phase I studies open right now, and that studies close and open constantly, you know, depending on the number of patients that are available, so there is a lot more patients out there than there are studies.

Now, the issue of the studies and how well designed the studies are and which centers they

occur, that is a whole separate discussion. I can tell you that I think the COG and CTEP and other major institutions have been advocates to getting studies open, so that these patients can participate in, so independent of the law we had during the cooperative group merger, I think that is an impetus from the Pediatric Oncology Committee to do studies and to get these patients on studies.

Ultimately, the decision is made about the parents, whether they participate or not, so you may always have 500 patients, but parents make the final decision whether they want to participate or not.

DR. MALDONADO: The reason I ask that is because if the drug becomes available, then, it will be even more difficult, because then the sponsor will need to compete with its own drug being available, so patients will tend not to enroll in trials, because it is more difficult for them to comply with the trials than to just get the drug that is available.

DR. SANTANA: I think a general comment to

that, and certainly Dr. Poplack and Dr. Kurtzberg, as pediatric oncologists can add to that, that has never been an issue in pediatric oncology. Most people, even though the drugs are commercial, will try to design new studies to continue to study drugs, and patients participate in them.

So, I think the approval of a drug and making it commercially available in pediatric oncology has not had the difference in practice that it may have in adult oncology, because we still stride to get patients on studies and design new studies to continue to ask the questions that are still unresolved.

So, I don't think that ultimately impacts whether patients participate or not.

So, let's go ahead and get started. So, this is for NDA 21-673, clofarabine from ILEX Products, Inc., for the proposed indication of treatment of pediatric patients 1 to 21 years old with refractory or relapsed acute leukemia.

The was one, Phase II study conducted in 35 patients with relapsed or refractory AML, at

least one relapse or primary refractory. There was an additional Phase II study conducted in 49 patients with relapsed or refractory ALL, defined as a combination of at least two relapses or refractory induction attempts.

Then, in addition, there was a Phase I study conducted in 25 patients with relapsed/refractory acute leukemias, a mixture of ALL's and AML's. Response assessments are presented in Tables 1, 2, 3, 4, and 5. In both of these studies, the primary endpoints as defined by the protocols or the studies, and the ones relevant to possible approval of the drug, are response rate and response duration.

In the absence of a reasonable rate of durable complete responses, which has been considered clinical benefit in some previous applications and which did not occur in these studies, clofarabine can be considered only for accelerated approval under Subpart H. This would be based on the conclusion that the responses seen are reasonably likely to predict a clinical

benefit.

Table 1 summarizes the best responses for ALL, 6 complete responses, 12.2 percent response rate, and then 4 additional patients with CRp, complete response without platelet recovery, an additional 8.2 percent of the patients in that category.

Table No. 2 briefly summarizes the response duration for ALL patients that did not go on to transplant. My interpretation of these columns is that there were a number of patients who had the response confirmed with a confirmatory marrow 3 or 4 weeks later, and those are the ones in the third column, the 43 and 50 for the CR, and then there were 3 additional patients who did have their response subsequently confirmed, and that response duration was 82, 93+, and 160+ days.

Similar data is presented in Table 3 for the AML best response in which there were zero complete responses, for a percentage of zero, and then there was 1 complete response without total platelet recovery of 2.9 percent.

Similar data in terms of response duration for AML patients that did not go on to transplant, which were very few, zero for the CR, zero for the CRp's, and only 2 PR's that were not transplanted, had response confirmed by a subsequent marrow.

Table 5 briefly summarizes the response rates that were seen in the Phase 1 study in which there was documentation of 2 CR's in ALL out of 17 potential subjects and 1 CRp in the AML subgroup out of 8 potential subjects.

So, let's go on to the question. I think you have the introductory paragraph there, so I won't read it again since it is projected in the video, and you have it in front of you. I will give you a minute to read it, and then we will get started with the questions.

I just want to mention to the Committee that Dr. Maldonado, as the industry representative, is a nonvoting member, but everybody else on the table is voting, and we do appreciate your vote.

The first question is although the protocol required responses to be confirmed at

least three weeks later, this was often not done. Do you consider an unconfirmed response useful for considering drug effect?

We will start with you, Dr. Poplack.

DR. POPLACK: It's not confirmed.

DR. SANTANA: Is that a yes or a no?

DR. POPLACK: That's a no.

DR. SANTANA: Anything else you want to add?

DR. POPLACK: No.

DR. SANTANA: Dr. Kurtzberg.

DR. KURTZBERG: No.

DR. SANTANA: Dr. Wayne.

DR. WAYNE: The people that know me know there is no such thing as a one-word answer, so I just have to say I think the data presented, the testimonials we see today suggest to us that there is activity, and the question do you consider an unconfirmed response useful for considering drug effect, I think the responses we have heard about and have seen are drug effect.

But it throws a bomb into the china shop

of drug approval, but I have to vote yes, I think that what we have seen or heard suggests drug effect.

It doesn't meet the standard that has been set for drug approval in my reading of the literature, but the question is, as I read it, unconfirmed response useful for considering drug effect, I think yes. It doesn't necessarily meet the bar that we are asked to prove or disprove in that regard.

DR. SANTANA: Let me clarify that, and maybe the FDA can help me with that. I interpreted that as an extension that it is not drug effect, but drug effect documented as a response.

DR. PAZDUR: As I stated before, we are not looking at the approval process as a screening process, so this has to be a meaningful effect reasonably likely to predict clinical benefit.

DR. SANTANA: Like the response.

DR. TEMPLE: Although that would have to do with the number of the responses, too, but in this case, we are just asking about the nature of

the response.

DR. PAZDUR: It isn't just the screening process.

DR. WAYNE: So, if you have a truly refractory patient population, a response rate, in my view, in fact, supports likely benefit.

DR. KURTZBERG: But that is a question that is confirmed.

DR. TEMPLE: You are saying even in your view, even an unconfirmed response, going with the numbers that are up here, does that for you.

DR. WAYNE: So, this is where we talk science and data, and split hairs. When I have distinguished colleagues who are pediatric oncologists, and loving parents who say that their children had responses and we see data that they were responses, that drug is active in a refractory patient population.

So, that doesn't equate to the sorts of endpoints you are asking to be met, but I believe, in a refractory patient population, that those responses reflect activity of that drug in that

disease, and therefore, is likely in a more systematic study to, in fact, translate to clinical benefit, but I can't prove that.

DR. TEMPLE: Right. I have no brief for what the answer is, but Dr. Kurtzberg at various points said there were certain kinds of activity that really don't tell you anything good is going to happen, and there are other kinds that do.

DR. WAYNE: But I would just argue that if you have a drug that kills leukemia cells, that that is activity. How you apply that activity in a systematic way to be clinical benefit is a separate question, but I am just responding literally to this question. I do believe that unconfirmed response in shades of gray could, in fact, be considered drug effect.

DR. TEMPLE: In the end, though, we are going to be asking whether you think the evidence of activity that is seen is such that there is likely to be a clinical benefit. So, in the end, you have to get to that question.

DR. SANTANA: We will get to that, but we

have to wrestle with the question at hand, and I think you already voted, so we will move forward.

Dr. Rodriguez.

DR. RODRIGUEZ: Yes.

DR. SANTANA: Ms. Hoffman.

MS. HOFFMAN: Yes.

DR. SANTANA: Dr. George.

DR. GEORGE: I have a question before I can answer this. I am assuming this unconfirmed response means there was an initial marrow that was clear, that was a complete response, say, but it just wasn't confirmed later.

DR. SANTANA: Subsequently. That is the discussion we had earlier this morning.

DR. POPLACK: The question is quite ambiguous obviously, and you are talking about--and I didn't do too well on multiple choice tests, which is obvious--but there are many ways to look at this, and I think the real issue is whether one considers an unconfirmed response useful.

You are talking about an unconfirmed complete response? What are you really talking

about?

DR. KURTZBERG: Do you mean the first marrow showed remission, and you didn't have a second one three weeks later? I didn't answer it that way.

DR. SANTANA: I think what they are trying to ask us is, for all those patients who did have a bone marrow that assessed a response, but subsequently, those patients did not have another marrow, how do you interpret that information with the lack of an additional subsequent follow-up marrow? Does that unconfirmed response still tell you that there was drug effect? That is what they are asking.

DR. TEMPLE: That is because the protocol said you were going to confirm them, but we heard why that was in many cases difficult.

DR. POPLACK: Obviously, if the first marrow confirms a response, then, that is evidence of drug activity.

DR. TEMPLE: Confirm here means another marrow.

DR. SANTANA: Confirm means here that they did that third bone marrow, if you want to put it that way. They did the diagnostic relapse marrow, they did a marrow after they gave drug to assess a response, and then my understanding is the protocol required that there should be another follow-up marrow. That is the sequence of events, and obviously, as we heard earlier, there were a number of patients who had a response with the second marrow, who did not get that third marrow.

DR. PAZDUR: Here again, by drug effect, we mean reasonably likely to predict clinical benefit.

DR. KURTZBERG: Then, I change my vote to yes.

DR. SANTANA: So, let us start off with that clarification because I want to make sure people know what they are voting on.

Let's start with Dr. Poplack.

DR. POPLACK: So, it's a yes given that change.

DR. SANTANA: Dr. Kurtzberg.

DR. KURTZBERG: Yes.

DR. SANTANA: Dr. Wayne.

DR. WAYNE: Yes, I didn't change my answer.

DR. SANTANA: We are starting all over. We erased everything.

Dr. Rodriguez.

DR. RODRIGUEZ: Same answer as previously, yes.

DR. SANTANA: Ms. Hoffman.

MS. HOFFMAN: Yes.

DR. SANTANA: Dr. George.

DR. GEORGE: I am glad I brought that up. Yes, I would say.

DR. SANTANA: MS. Haylock.

MS. HAYLOCK: Yes.

DR. SANTANA: Dr. Hussain.

DR. HUSSAIN: Yes.

DR. SANTANA: Dr. Perry.

DR. PERRY: Yes.

DR. SANTANA: Dr. Mortimer.

DR. MORTIMER: Yes.

DR. SANTANA: Dr. Santana. Yes.

Dr. Martino.

DR. MARTINO: No.

DR. SANTANA: Dr. Brawley.

DR. BRAWLEY: No.

DR. SANTANA: Dr. Cheson.

DR. CHESON: I would have to say yes, there is evidence of drug effect.

DR. SANTANA: Dr. Bukowski.

DR. BUKOWSKI: No.

DR. SANTANA: Can you tally the votes for me? Twelve Yes and 3 No.

Question No. 2. Transplantation, especially in AML patients, was common in the data that was presented. Although it is possible that response to clofarabine encouraged physicians to consider transplant when they otherwise would not have, there is no way to know this and there were no criteria for transplantation in the protocols. Some patients went to transplantation without a clofarabine response.

Do the transplantation data contribute to

the assessment of the effectiveness of clofarabine? We need to discuss each of the two diseases separately. So, let's vote on ALL first.

Dr. Poplack.

DR. POPLACK: For the reasons that Dr. Kurtzberg stated, I would say no.

DR. SANTANA: Dr. Kurtzberg.

DR. KURTZBERG: No.

DR. SANTANA: Dr. Wayne.

DR. WAYNE: No.

DR. SANTANA: Dr. Rodriguez.

DR. RODRIGUEZ: No.

DR. SANTANA: Ms. Hoffman.

MS. HOFFMAN: No.

DR. SANTANA: Dr. George.

DR. GEORGE: No.

DR. SANTANA: Ms. Haylock.

MS. HAYLOCK: No.

DR. SANTANA: Dr. Hussain.

DR. HUSSAIN: Yes.

DR. SANTANA: Dr. Perry.

DR. PERRY: Yes.

DR. SANTANA: Dr. Mortimer.

DR. MORTIMER: Yes.

DR. SANTANA: Dr. Santana. Yes.

Dr. Martino.

DR. MARTINO: No.

DR. SANTANA: Dr. Brawley.

DR. BRAWLEY: Yes.

DR. SANTANA: Dr. Cheson.

DR. CHESON: No.

DR. SANTANA: Dr. Bukowski.

DR. BUKOWSKI: No.

DR. SANTANA: Can I get a tally of votes for ALL.

Ten No, 5 Yes.

So, the same question. Do the transplantation data contribute to the assessment of the effectiveness of clofarabine in AML?

Dr. Poplack.

DR. POPLACK: No.

DR. SANTANA: Dr. Kurtzberg.

DR. KURTZBERG: No.

DR. SANTANA: Dr. Wayne.

DR. WAYNE: No.

DR. SANTANA: Dr. Rodriguez.

DR. RODRIGUEZ: No.

DR. SANTANA: Ms. Hoffman.

MS. HOFFMAN: No.

DR. SANTANA: Dr. George.

DR. GEORGE: No.

DR. SANTANA: Ms. Haylock.

MS. HAYLOCK: No.

DR. SANTANA: Dr. Hussain.

DR. HUSSAIN: Yes.

DR. SANTANA: Dr. Perry.

DR. PERRY: Yes.

DR. SANTANA: Dr. Mortimer.

DR. MORTIMER: No.

DR. SANTANA: Dr. Santana. No.

DR. MARTINO: No.

DR. BRAWLEY: No.

DR. CHESON: No.

DR. BUKOWSKI: No.

DR. SANTANA: Can I get a tally of the votes for AML. Thirteen No, 2 Yes.

As noted, in the refractory acute leukemias, the FDA has considered a good complete response with complete responses of good duration to represent clinical benefit.

There was clearly no substantial CR rate in AML, and in ALL, only 2 non-transplanted patients had a response duration of at least 3 months. The partial response duration in AML is not assessable in many responders because they had early transplantation. There is somewhat more information in ALL, and that refers back to Table No. 2, if I remember correctly.

So, the third question is does the ODAC believe that the clofarabine complete response rate with available response duration data is reasonably likely to predict a clinical benefit in ALL?

Dr. Poplack.

DR. POPLACK: I guess I would ask, at the same level? Isn't that the key? At the same level that was indicated in this trial, is that what you are getting at?

DR. PAZDUR: This is the drug approval

question, reasonably likely to predict a clinical benefit, what would be used for accelerated approval.

DR. SANTANA: So, the question is, for accelerated approval in ALL, this question addresses the issue that the available response duration is reasonably likely, the CR rate and the duration of response in those patients is likely to provide some assessment or some idea of clinical benefit.

DR. TEMPLE: The question, of course, highlights the lack of knowledge about duration in a number of cases, but, of course, that is because they got transplanted, and maybe that is not a problem. So, that is the question.

DR. POPLACK: The issue of duration of response, I think is actually quite important here, or lack of follow up, because there are 3 patients who had very short responses, who relapsed during that time period, who didn't have follow up, so you don't know the length of that duration. Those are the ones of 43, 50, and 82 in 82 days, if I am

correct. We didn't have any follow up on those.

DR. SANTANA: No, no, the 82-day did have a follow up, am I correct, if I interpret the columns? Yes, they had a confirmed marrow.

So, referring to Table 2, Dr. Poplack, the last column, as I interpret it, is the 3 patients with ALL that are CR, who did have a confirmed marrow, so obviously, one patient had a confirmed marrow that lasted 82 days, and the other patients had a confirmed marrow at 93, and that patient we think is still in remission, and patient 160 had a confirmed marrow at 160 and is still in remission.

That is how I interpret that table.

DR. POPLACK: So, 43 and 50 that we have no information on.

DR. SANTANA: Forty-three and 50 were the short remissions that were not confirmed with a subsequent marrow.

DR. MARTINO: I need clarification.

DR. SANTANA: Yes.

DR. MARTINO: I need clarification on this issue. Dr. Pazdur, do I understand that the point

to this question is whether the data, as presented, is sufficient, not that it shows a whiff of activity, but is sufficient activity to merit accelerated approval, is that the question you want answered?

DR. PAZDUR: Yes, it is. That is why I said this is the approval question. We are asking, with the data that you have seen in ALL, is the drug approvable, should the drug be approved under accelerated approval conditions.

DR. WAYNE: Can we have more discussion at this juncture about implications of one way or the other, or do you want us just to vote based on this question and call it a day?

DR. PAZDUR: What would be your discussion? We have been discussing this, and, you know, there is ambiguities in this application obviously.

DR. WAYNE: So, I think between the acknowledgment that there is activity, and there is acknowledgment that more systematic studies are required, is a big chasm, and the question is, is

accelerated approval the best mechanism to, in fact, prove (a) activity, in (b) systematic studies, or will accelerated approval complicate that.

Most importantly, are we, as a committee, do we have enough knowledge about that key question, is what next.

DR. TEMPLE: In some ways, that isn't really the primary question. We do worry about whether the confirmatory data will get done, but the point of accelerated approval is that for diseases with no current treatment, we are prepared to accept a different kind of evidence of effectiveness, that is, you don't have survival data, you don't have mature any kind of data, but you may have evidence of an activity that convinces you that there really will be a benefit when you do the rest of the studies.

That is a very complicated judgment. The answer is usually not obvious. It has something to do with how high the rate is. I mean if you only saw one response, you probably wouldn't find that

convincing.

If you found 40 percent, you probably would, and somewhere in between, we line out, but it isn't really about whether the best way to get the data--I mean the best way to get the data is to plan it all out, have properly done studies, and look at them early and say, oh, well, fine, I am ready to approve it now, and then I have got the data in hand.

Well, we try to get people to do that, and as Rick says, more and more people are, that is not our problem here. We don't have that.

DR. PAZDUR: With the available data that you have here, is what you are seeing here reasonably likely to predict clinical benefit for these patients.

DR. TEMPLE: For a group of patients who don't have any other choice. That is what the point of it all was.

DR. SANTANA: Yes, Dr. Martino.

DR. MARTINO: I would like to just restate your words. The way I understand the charge of

this committee is that if we vote yes, then, that basically means that this drug, as of today, tomorrow, or whenever, becomes available to any physician who has such a patient. It is common use in this setting at least, and then beyond this setting, that we are actually approving.

It isn't that, in fact, perhaps someone will then show us more data in the future.

DR. PAZDUR: Correct. You have to go on what is presented here today and make the scientific decision, a clinical decision on a risk-benefit situation on the data that you have at hand on the basis of this single-arm trial.

DR. TEMPLE: And assume that we will, in one way or another, along with the company, actually get the rest of the data.

DR. SANTANA: Yes, I was going to add that.

DR. TEMPLE: We all know that has been a problem, we are being forceful in insisting on seeing the protocols prior to approval. We have, in some cases, urged that there be enrollment in

some of the other studies.

We are worried about that, and we didn't put that question to you. Feel free to comment, but you should be assuming that we will get the ultimate data.

DR. SANTANA: I was going to say an accelerated approval, my understanding, and the Agency can correct me, is that there is a firm commitment that the Agency has regulatory oversight if it doesn't happen that those additional studies be done and be presented.

DR. PAZDUR: Correct.

DR. TEMPLE: And usually, pretty well honored, but there have been troubles, I mean I don't want to hide that from anybody.

DR. SANTANA: Dr. Poplack.

DR. POPLACK: No, you clarified it for me.

DR. SANTANA: So, are we ready to go back to this question? So, for ALL--I won't repeat the question--Dr. Poplack, for ALL?

DR. POPLACK: Yes.

DR. KURTZBERG: Yes.

DR. WAYNE: Yes.

DR. RODRIGUEZ: Yes.

MS. HOFFMAN: Yes.

DR. GEORGE: No.

MS. HAYLOCK: Yes.

DR. HUSSAIN: No.

DR. PERRY: Yes.

DR. MORTIMER: Yes.

DR. SANTANA: Yes.

DR. MARTINO: No.

DR. BRAWLEY: No.

DR. CHESON: No.

DR. BUKOWSKI: No.

DR. SANTANA: Can I get a tally?

Nine Yes, 6 No.

DR. SANTANA: Question No. 4 is the same crux of the matter, now with the AML population. Does the ODAC believe that the 2 clofarabine complete responses p's, (1 in Phase I and 1 in Phase II) are reasonably likely to predict a clinical benefit in AML?

DR. CHESON: Point of clarification.

There was not a CR, it was a CRp.

DR. SANTANA: Can you clarify the acronym that you have put on this question?

DR. PAZDUR: It is CRp, I believe.

DR. CHESON: CRp, it is not a true CR.

DR. PAZDUR: Correct.

DR. SANTANA: Thank you for the clarification.

Dr. Poplack.

DR. POPLACK: Just again to clarify. Does this mean that we think that it has activity or that it doesn't have activity?

DR. PAZDUR: It is not activity. It is a clinical decision that you have to make based on available data, that it is reasonably likely that activity in these patients would represent clinical benefit in the future.

DR. POPLACK: Clinical benefit meaning they are going to live longer--

DR. PAZDUR: The survival, the patient getting some benefit from it.

DR. SANTANA: I think there is two

questions. I think since we have a little bit of time, I will go ahead and let Dr. Wayne, if you have a clarification, not a long discussion.

DR. WAYNE: So, again, I just want to point out that this question literally asks about only the data presented in the pediatric trial.

DR. SANTANA: Correct. We have not seen any adult data presented systematically by the sponsor or the FDA, period.

Ms. Hoffman.

MS. HOFFMAN: And this impacts on labeling in terms of prescribed use for ALL and AML.

DR. PAZDUR: Correct. If the drug is approved only in ALL, the indication will only be in ALL.

DR. SANTANA: Okay. Dr. Poplack.

Can you please identify yourself before you vote, so I don't have to repeat the names. Thanks, Dr. Poplack.

DR. POPLACK: No.

DR. KURTZBERG: No.

DR. WAYNE: No.

DR. RODRIGUEZ: No.

MS. HOFFMAN: Yes.

DR. GEORGE: No.

MS. HAYLOCK: No.

DR. HUSSAIN: No.

DR. PERRY: No.

DR. MORTIMER: No.

DR. SANTANA: No.

DR. MARTINO: No.

DR. BRAWLEY: No.

DR. CHESON: No.

DR. BUKOWSKI: No.

DR. SANTANA: So, there should have been 14 No and 1 Yes.

Does the Agency wish to discuss any additional information to help you, or give you further advice?

DR. PAZDUR: Not that I can think of at this time.

Could we just make an announcement, because we have to be here, back sharp, at what time?

DR. SANTANA: 12:45.

DR. PAZDUR: 12:45, we will start right at 12:45 whether you are here or not, because many people have planes.

DR. SANTANA: Thanks, everybody, for your participation.

[Whereupon, at 12:07 p.m., the proceedings were recessed, to be resumed at 12:45 p.m.]

A F T E R N O O N P R O C E E D I N G S

[12:50 p.m.]

Call to Order

DR. MARTINO: If everyone would take their seats within the next minute or two, I would like to get started.

I have a plane to catch at 4:30, I need to leave here at 4:30, and I mean to do that, so I remind all of you that have something to say, to please be clear and succinct. I can be fairly forceful if need be.

Introductions

MS. CLIFFORD: We are going to start with Dr. Wilson, if you would like to go ahead and introduce yourself and your affiliation, please.

DR. WILSON: My name is Wyndam Wilson. I am in the Experimental Transplantation and Immunology Branch at the National Cancer Institute.

DR. BISHOP: Michael Bishop, Experimental Transplantation Branch, National Cancer Institute.

MS. KRIVACIC: Susan Krivacic, Austin, Texas, Patient Rep, non-Hodgkin's lymphoma

survivor.

DR. MALDONADO: Samuel Maldonado from Johnson & Johnson. I am here as the Industry Representative to this advisory Committee.

DR. GEORGE: Stephen George, Duke University.

MS. HAYLOCK: Pamela Haylock, Oncology Nurse, Consumer Representative.

DR. HUSSAIN: Maha Hussain, Medical Oncology, University of Michigan.

DR. PERRY: Michael Perry, Medical Oncology, University of Missouri, Ellis Fischel Cancer Center.

DR. MORTIMER: Joanne Mortimer, Moores UCSD Cancer Center.

DR. MARTINO: Silvana Martino, Medical Oncology, from the John Wayne Cancer Institute.

MS. CLIFFORD: Johanna Clifford, Executive Secretary to the ODAC.

DR. REAMAN: Gregory Reaman, Pediatric Oncology, Children's Oncology Group, George Washington University.

DR. BRAWLEY: Otis Brawley, Medical Oncology/Hematology from Emory University.

DR. CHESON: Bruce Cheson, Head of Hematology, Georgetown University, Lombardi Comprehensive Cancer Center.

DR. BUKOWSKI: Ron Bukowski, Cleveland Clinic, Medical Oncology.

DR. HAZARIKA: Maitreyee Hazarika, Medical Officer, FDA.

DR. FARRELL: Ann Farrell, Clinical Team Leader, FDA.

DR. PAZDUR: Richard Pazdur, FDA.

DR. WILLIAMS: Grant Williams, FDA.

DR. MARTINO: Thank you. Ms. Clifford will now read the Conflict of Interest Statement for this group.

Conflict of Interest Statement

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 conflict of interest at this meeting with the following exceptions:

Dr. Stephen George has been granted a waiver under 18 USC 208(b)(3) for serving as a consultant to a competitor on an unrelated matter. He receives less than $10,000 per year.

Dr. Michael Perry [technical interruption] for owning stock in a competitor valued between $5,001 to $25,000. A waiver under 18 USC 208(b)(3) is not required because the de minimis exception 2640.202(b)(2) applies.

Dr. Ronald Bukowski has been granted a waiver under 18 USC 208(b)(3) for lecturing for a competitor on an unrelated matter. He receives between $5,001 to $10,000.

Dr. Otis Brawley has been granted a waiver under 18 USC 208(b)(3) for consulting with a competitor on an unrelated matter. He receives

less than $10,001 a year.

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to disclose that Dr. Samuel Maldonado has been invited to participate as the Non-Voting Industry Representative acting on behalf of all regulated industry. Dr. Maldonado is employed by Johnson & Johnson Pharmaceutical Research and Development.

In the event that the discussions involve any other products or firms not already on the agenda for which am 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. MARTINO: Is there anyone on the Committee that needs to make a statement in terms of conflict?

[No response.]

DR. MARTINO: Thank you.

Dr. Pazdur will now make some introductory comments.

Opening Remarks

DR. PAZDUR: Thank you, Dr. Martino.

This afternoon's session focuses on the marketing application of vincristine sulfate liposome for the treatment of patients with aggressive relapsed non-Hodgkin's lymphoma treated with at least two combination chemotherapy regimens. The sponsor is seeking accelerated approval for this agent.

Since there are members of the Committee who did not attend this morning's session, I would like to reiterate several comments made earlier regarding accelerated approval and then comment on issues specific to this application.

The demonstration of clinical benefit is required to achieve full approval. In oncology, the demonstration of clinical benefit has usually been an improvement in overall survival or the amelioration of disease-related symptoms.

In 1992, the accelerated approval regulations allowed the use of additional endpoints for the approval of drugs that are intended to treat serious and life-threatening diseases. These drugs may either demonstrate an advantage over available therapy or provide therapy where none exists.

The FDA may grant accelerated approval based on the effect of a surrogate endpoint that is "reasonably likely" to predict clinical benefit.

A drug is approved under the accelerated approval rule on the condition that the manufacturer conduct studies to verify and describe the clinical benefit. The regulations stated an expectation that post-marketing studies would usually be underway prior to accelerated approval, but this is not a requirement.

At a March 2003 ODAC meeting, the ODAC reinforced the Agency's view that these confirmatory trials should be ongoing at the time accelerated approval is granted. Approval with subsequent commercial availability of the drug may interfere with the enrollment of a confirmatory study.

Accelerated approval had been based on objective response rates with adequate duration in single-arm trials in patients with refractory disease. Since an agent must demonstrate an advantage over available therapy or provide therapy where none exists, we are asking you to consider if available therapy exists for the indication under consideration.

If available therapy exists, a randomized trial comparing the investigational drug to an available therapy arm would generally be needed to demonstrate superiority. Available therapy usually consists of drugs that are indicated in drug labeling for the treatment of a specific disease, however, in oncology, where drugs are frequently

used in non-approved indications as single agents or in combinations, available therapy may constitute therapy substantiated by "compelling" literature evidence of efficacy.

There is no regulatory definition of the word "compelling," hence, we are asking your opinion regarding this word.

We are not asking you to reach a consensus on a specific therapy. Available therapy may be a single drug or it may be a combination regimen. Available therapy may be several regimens or drugs. Where there may be a lack of consensus regarding a single specific treatment, the Agency has even recommended using several regimens or drugs as a treatment arm with the stipulation that superiority is demonstrated by the investigational drug.

The primary endpoint of this single-arm trial is response rate. The interpretation of response rate is complex. We have emphasized that the persuasiveness of the results of a single-arm trial to support accelerated approval hinges on the magnitude and the duration of responses observed in

trials.

In aggressive lymphomas, we have emphasized to sponsors the importance of complete responses with adequate and well-defined durations as an endpoint for drug approval. In selected hematological malignancies where partial responses are observed, we, at the FDA, have been impressed with substantial response durations, and these have led to approval.

For example, the recently approved Velcade for the treatment of refractory multiple myeloma had a median response duration in excess of one year. Similarly, the median duration of disease control for fludarabine in CLL was in excess of one year.

Since the vast majority of responses noted in this application are partial responses with uncertain durations, 13 out of 30 responders did not even have a single repeat scan or progress before a repeat scan could be performed, we are asking your opinion regarding this endpoint. Remember, this endpoint in this study must be

reasonably likely to predict clinical benefit.

In the morning session, we highlighted the need for confirmatory trials to be ongoing at the time of drug approval. This is again not a requirement, however, the ODAC has supported our viewpoint that accelerated approval trials be part of a comprehensive drug development plan with early initiation of confirmatory trials prior to drug approval.

To date, a confirmatory trial for VSLI has neither been started, nor agreed upon with the FDA. In your deliberations, discussion must focus on this aspect and the impact that any approval would have on the conduct and the completion of any confirmatory trial.

I would like to emphasize that accelerated approval is not simply a screening process for drug activity. Mere demonstration of a nominal activity is insufficient for accelerated approval. Response rate and duration must provide convincing evidence that the magnitude and duration of responses are "reasonably likely to predict clinical benefit."

This response rate and duration may vary from disease to disease. The accepted response rate in refractory metastatic colon cancer may have little bearing on the response rate accepted for refractory aggressive lymphomas, hence, we are asking your clinical judgment in this disease setting.

There must be confidence in any recommendation that a drug approved under accelerated approval represent a benefit over available therapy or provide therapy where none exists.

In making a regulatory decision, you must be able to accurately assess a risk-benefit relationship. You must be able to have confidence in the benefit of the drug in relationship to its toxicity.

As stated in the morning session, your decision regarding the approval status of a drug should be based on a clinical risk-benefit decision, not simply a desire to provide drug access to patients.

Access to a yet to be approved drug can be accomplished through registration trials or expanded access programs.

Seeking drug approval exclusively with a single-arm trial is an inherently risky venture, hence, we have strongly urged sponsors to consider the single-arm trials part of a comprehensive drug development plan that incorporates the early initiation of randomized trials to define clinical benefit.

Although single-arm trials are less expensive, less complex to conduct, involve fewer patients, and are performed more rapidly than randomized trials, they frequently do not provide the information required by physicians and patients to make rational therapeutic decisions.

If results are robust in a single-arm trial, then, everyone wins. Most importantly, patients receive needed therapies earlier. If results are nominal, resulting in ambiguity, regarding a risk-benefit decision, randomized trials will be needed to accurately assess the

drug. Unfortunately, this may delay drug approval.

In comparison to single-arm trials, randomized trials provide the opportunity to examine additional endpoints, such as survival, time to progression, and even symptom benefits, and also provide us an opportunity to more accurately characterize adverse events.

I hope these opening comments will focus your deliberations. Thank you.

DR. MARTINO: Thank you, Dr. Pazdur.

At this point, I would like to invite Inex Pharmaceuticals to introduce themselves and present their data to the Committee, please.

NDA 21-000, Marqibo (vincristine sulfate liposomes injection)

Inex Pharmaceuticals Corp.

Sponsor Presentation

Introduction

MS. MANCINI: Good afternoon, Madam Chairman, members of the Advisory Committee, and the FDA. My name is Alexandra Mancini, and I am the Senior Vice President of Clinical and

Regulatory Affairs at Inex Pharmaceuticals.

[Slide.

On behalf of Inex and our co-development partner, Enzon Pharmaceuticals, I would like to thank you for this opportunity to discuss our NDA for Marqibo, which is vincristine sulfate liposomes injection, or what I will call VSLI for short.

The indication we are seeking is for the treatment of patients with aggressive non-Hodgkin's lymphoma previously treated with at least two combination chemotherapy regimens.

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We have several consultants with us this afternoon, two lymphoma experts, a Dr. Fernando Cabanillas from M.D. Anderson, and Dr. Jane Winter from Northwestern University.

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As well as experts in lymphoma pathology, Dr. Randy Gascoyne; Radiology, Dr. Scott Gazelle and Dr. Sandra Chica.

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Neurotoxicity, Dr. Shayne Gad;

Pharmacokinetics, Dr. Jean-Marie Houle; and Statistics, Mr. Louis Gura.

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We are very pleased to have Dr. Fernando Cabanillas with us today. Dr. Cabanillas is a Clinical Professor of Medicine at the M.D. Anderson Cancer Center, as well as the Medical Director of Auxilio Mutuo Cancer Center in Puerto Rico.

He was the Chairman of the Lymphoma Myeloma Department at M.D. Anderson for approximately 20 years, where he led the development of many of the most commonly used chemotherapy regimens for patients with relapsed lymphoma including MIME, DHAP, and ESHAP. He has contributed to over 300 original publications in lymphoma and over 50 book chapters, and he was a member of the International Workshop that developed response criteria for lymphoma.

Dr. Cabanillas will now provide a disease overview aggressive NHL and the unmet medical need.

Overview

DR. CABANILLAS: Thank you, Ms. Mancini.

Good afternoon. I would like to give you a brief overview of non-Hodgkin's lymphoma over the next few minutes. These lymphomas are broadly classified into either aggressive or indolent histologies.

The most common category is the aggressive, which constitutes approximately 35 to 40 percent of all lymphomas. This group is relatively homogeneous since it is made up of essentially diffuse large cell lymphoma and peripheral T-cell lymphomas.

DLCL, however, can frequently present with divergent histologies, which means that there are other areas which contain an indolent cell type. The treatment, however, is driven by the most aggressive histology, and the response is measured in the same way.

At relapse, most patients with aggressive histologies usually die within a few months.

In contrast, the indolent lymphomas, when they release, can survive for years.

Finally, the response rate and duration of

response of aggressive lymphomas are lower than for the indolent cell types. Thus, it should not be surprising that it has been easier to demonstrate efficacy in indolent lymphomas and consequently, four agents have recently been approved in the U.S.A., whereas, there have not been any new agents approved for aggressive lymphomas in the last 17 years.

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First-line treatment of aggressive lymphoma consists of rituximab plus CHOP. This combination will cure approximately 50 percent of patients. Management for patients younger than 65 consists of a standard dose regimen followed by high-dose chemotherapy and autologous stem cell transplant if they relapse.

However, only those patients who respond to standard dose salvage therapy go on to receive transplant. Patients older than 65 usually are not considered candidates for transplant. In addition, there are other reasons for which transplant is not feasible. Less than 10 percent of such cases can

be cured, and their median survival is only six months.

Finally, with each relapse, the response rate, as well as the duration, drop considerably.

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At the time of third-line therapy, the situation is even worse. This is not an uncommon problem and the prevalence in the U.S.A. is 10 to 15,000 cases. There is no established therapy for patients in second or more relapse.

To make matters worse, their bone marrow is frequently compromised by prior therapy, thus, leaving us with few treatment options. These patients frequently are symptomatic and reduction in their tumor burden will lead to symptom improvement.

The results are dismal. Complete responses are rarely achieved, and survival is very short, as you will see in the next slide.

[Slide.

This graph depicts the survival of patients treated at third line or more. This is

derived from a study we performed at M.D. Anderson during the pre-transplant era and the pre-rituximab era using an ifosfamide/etoposide based regimen known as MIME.

After one year, 75 percent of the patients were dead, and at two years, virtually all except 4 percent were dead. This is a highly lethal disorder. As you will see soon, the patient population we have treated with VSLI is similar to the one presented on this slide.

[Slide.

At this point, I would like to discuss the available literature data on single agents for relapsed aggressive lymphoma. The FDA briefing document contains a table with a large number of papers quoting response rates with single agents and combination regimens for lymphoma.

As you can see from this table, many of those response rates are in the range of 40 percent and as high as 69 percent, which probably strikes you as unusual for a single agent at third relapse.

At this point, I would like to put this

into perspective. Many of these papers were not adequate for comparison to the VSLI studies for several reasons. For example, the first five drugs listed here were tested in less than 10 patients with the correct histology.

One of the drugs, oxaliplatin, listed as having a response rate of 24 percent, was tested in a population which included indolent lymphomas, as well as aggressive, but the response rate was not separated for these two histologies.

Finally, the number of prior therapies was not comparable for the last three agents on the slide.

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This slide is a summary of the previous slide, and in the first three columns, I have listed the reasons why the studies are not comparable to the VSLI studies. There are only 2 of these 11 single agent papers which actually can be compared to the VSLI studies.

Moving down to combination therapies, you see that the situation is very similar, and only 5

of the 35 papers quoted are comparable.

[Slide.

The two single agent papers that can actually be compared to VSLI are Rituxan studies by Rothe and Tobinai. We have added another important study by Coiffier, which was not included in the FDA document.

As you can see in the first row of data, the median number of prior regimens was 2 in all of these papers, but a substantial percentage of patients actually were treated at first relapse, and those are not comparable to the VSLI patients.

As you can conclude from this slide, even in a population with less relapses than ours, the response rate is less than 40 percent, and the time to progression is only 2 to 4 months.

[Slide.

These are the five combination regimen papers that are adequate for comparison to VSLI. The top half represents those with a median number of prior regimens equal to 2, while the bottom have a median number of 3, which is similar to the VSLI

studies.

The response rates range from 39 to 65 percent, but as you can see from the bottom half, the CR rate is very low at third or more relapse. The top three regimens are not commonly used salvage combinations, and neither is ifosfamide, hydroxyurea, and etoposide shown in the last row and all of them are certainly more toxic than VSLI, as you will see later on, that, even though a popular regimen, is not commonly used to third relapse because of its serious myelosuppressive toxicity, which I am sure those of you who have used it are familiar with.

In summary, the regimens shown here are not used commonly by the oncology community with the exception of DHAP, which is used mostly at second line prior to autologous transplant. It is highly toxic and thus rarely used in patients at third or more relapse.

[Slide.

By now, you probably have realized that there exists several unmet clinical needs in the

management of aggressive relapsed lymphomas. Many patients do not qualify for aggressive combination regimens or have failed autologous transplantation, and they need some other alternative.

Some of the characteristics of such patients are listed here. In the past, patients with compromised marrow function were treated with rituximab, which is not myelosuppressive, however, that is no longer an alternative because by the time they get to third line treatment, most of these patients have already been exposed multiple times to rituximab and are resistant to it.

In summary, there is no compelling literature evidence for available therapy after second relapse, and there is a great need for an agent that can provide clinical and meaningful benefit without excessive toxicity, because at this point, we are dealing mostly with palliation, and we should not induce severe toxicity if we are to effectively palliate them.

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I would like now to introduce Dr. Tom

Madden from Inex, who will discuss the pharmacology of VSLI.

Pharmacology

DR. MADDEN: Thank you, Dr. Cabanillas.

[Slide.

As the name indicates, VSLI is a liposomal formulation of vincristine sulfate where the drug is encapsulated within the aqueous interior of small liposomes. These are composed of sphingomyelin and cholesterol, and this lipid composition provides a highly stable bilayer with relatively low permeability.

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The intention with VSLI is to increase tumor exposure to vincristine, and this is achieved through two mechanisms, first, by providing higher drug levels at the tumor sites, and secondly, by providing a mechanism to provide a sustained duration of exposure. The following slides will illustrate these two mechanisms.

[Slide.

Following intravenous administration of

VSLI, the liposomes, being particular carriers, tend to remain within the blood compartment as they are not able to readily extravasate across the continuous endothelial lining present in most normal blood vessels, and this can be illustrated using a window chamber model, which allows visualization of florescently labeled VSLI.

The panel on the left-hand side here shows normal blood vessels, and you can see that the liposomes are constrained within the vessels with very little accumulation seen in the interstitial spaces.

Within tumor including lymphomas, however, the neovasculature tends to be leaky, exhibiting pores or discontinuities. The liposomes in VSLI are of an appropriate size to allow extravasation through these pores with subsequent accumulation in the interstitial spaces.

Again, we can illustrate this using the window chamber model.

As you will see when I start the video, the blood vessels within the tumor vasculature tend

to be smaller, and you will see the architecture is highly chaotic. You will also see that extravasation of the liposomes is apparent and appreciable accumulation occurs in the interstitial spaces.

The period of time followed in both videos is the first 60 minutes after VSLI administration. The VSLI also accumulates preferentially in the tissues and organs of the mononuclear phagocyte system, such as the liver, spleen, and lymph nodes. These are, of course, also sites of lymphoma involvement.

As you are well aware, vincristine is a cell-cycle-specific agent inhibiting mitosis. Studies using lymphoma isolates from patients have shown that only a small fraction of cells, less than 5 percent, are actually in the sensitive G2M phase at any point in time. Therefore, the duration of vincristine exposure is critically important in terms of its activity.

[Slide.

This is illustrated on the slide shown

here. As you can see, the fraction of tumor cells surviving is greatly reduced as the exposure time to vincristine is increased from 1 hour to 24 hours, and I should note that the fraction of viable or surviving cells shown here is represented on a log scale.

[Slide.

The rate of vincristine release from VSLI is therefore a critical factor in terms of its activity, and has been characterized in several nonclinical studies. Vincristine release occurs by passive diffusion across the liposomal bilayer, and similar behavior is seen in the mouse, rats, and in the dog.

Shown here for the rat is the rate of vincristine release in plasma. As you can see, release is slow and sustained with approximately 50 percent of the drug released by 24 hours and essentially complete release seen by 72 hours.

[Slide.

These changes in the pharmacokinetics of vincristine resulting from liposomal encapsulation

would be expected to increase antitumor activity. This was shown in several studies, comparing VSLI with conventional vincristine against a range of human and murine tumor models.

The study illustrated here compares activity in the Namalwa lymphoma model. As you can see, vincristine is active in this model, but VSLI shows much increased antitumor activity.

I should note that this increased activity is seen when VSLI is given at the same dose as conventional vincristine, as will be discussed during the clinical presentation. Patients are administered VSLI at approximately twice the intensity typically used with conventional vincristine.

[Slide.

The pharmacokinetics of VSLI have been characterized in patients, and the slide shown here illustrates plasma vincristine levels following administration of VSLI to published data for conventional vincristine.

As you can see, much higher plasma drug

levels are achieved for VSLI, and these are maintained for a considerable period of time. Again, you will note that the drug levels shown on the y axis are represented on a log scale.

At almost all time points, plasma drug levels are approximately 2 orders of magnitude higher for VSLI compared to conventional vincristine.

In summary, VSLI provides increased exposure to vincristine through higher tumor drug levels and also an extended duration of exposure. In nonclinical studies, this results in increased antitumor activity compared to conventional vincristine.

I haven't presented any data on the safety evaluations conducted for VSLI. These show that it elicits the same toxicities seen with conventional vincristine, and importantly, no new toxicities were observed.

I will now pass the podium back to Alexandra Mancini who will present the clinical results.

Clinical Efficacy and Safety

MS. MANCINI: Thank you, Tom.

[Slide.

There are two trials in the NDA that provide efficacy data in the indicated population. We have supportive data from the first study we did in aggressive NHL, our Phase IIa study.

This was an investigator-sponsored trial at M.D. Anderson Cancer Center, which was a broad-based protocol including lymphoma and leukemia, and there were 92 patients with relapsed aggressive NHL in that study.

Our primary Phase IIb study was an international multicenter study that enrolled 119 patients at 42 centers. These are the two largest trials reported for patients with multiply relapsed aggressive NHL.

Both were single-arm studies and both used similar response criteria. They provided consistent efficacy results in a total of 211 patients, therefore, for brevity, I will focus on the pivotal study only.

[Slide.

A larger safety database was provided that includes 53 patients.

Our clinical development in aggressive NHL is ongoing using combination regimens. We have had several discussions with the FDA, three meetings in fact, regarding our proposed randomized controlled trial that would serve as a post-approval commitment trial.

We received comments from the FDA as part of our special protocol assessment that we submitted, and the revised protocol will be resubmitted shortly. The study will start within a few months.

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Before I present the results of our studies, I will address several issues raised by the FDA in their review that relate to the adequacy of the pivotal trial and its conduct. One must first be assured that the results are reliable before embarking on their interpretation.

[Slide.

The Agency has raised concerns about the low number of eligible patients attributed to the following reasons: numerous protocol amendments and exemptions, a low histologic eligibility rate, and incomplete staging in 19 percent of patients.

Additionally, there have been concerns raised about the Independent Review Panel for efficacy evaluations, specifically with respect to the wording of the response criteria, operations of the core imaging lab, and amendments to the IRP charter.

I would like to provide further clarification on these points for your consideration.

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It is true that there were 9 versions of the protocol, but it is important to note that the study did not begin enrollment until Version 5. As shown on this slide, almost all patients were enrolled under two versions of the protocol, Versions 8 and 9. Therefore, there were really only four amendments after the trial started.

[Slide.

The initial protocol used for patient enrollment required that patients had a CR or CRu to first line chemotherapy, and they also had to have achieved at least a PR to their last line.

We were unable to enroll patients to this narrowly defined population. The trial was open for 6 months, and we had 4 patients enrolled. Therefore, we amended the protocol. We deleted the requirement for a complete response at first line and allowed patients in if they had only at least a minor response.

We also removed any requirement for a response to their last therapy, and in doing so, we now defined a poorer prognosis population.

[Slide.

To further enhance patient enrollment, we added some additional histologic categories shown here, but as you can see from the number of patients, this did not result in significant additional enrollment.

Once again, this defined a poorer

prognosis population, and there were no further changes to eligibility criteria. Importantly, with each amendment, the FDA agreed that the trial population was a suitable population to support an accelerated approval.

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The last amendment changed the schedule to obtain CTs 4 weeks after the first documentation of response instead of the original 8 weeks, and we further clarified the wording that these confirmatory CT scans should be obtained instead of must be obtained as we realized the original wording might be misconstrued as a requirement for confirmation of response.

This was not the intent, as it is not a part of the International Workshop criteria. This protocol amendment was implemented after approximately half the patients in the trial were enrolled and before Inex was unblinded to the study data.

We remained blinded to the data until all patients were enrolled.

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We did allow medically justified exemptions for some patients, but we were always careful to not allow exemptions that would have enhanced the apparent VSLI response rate, and we are prepared to discuss specific exemptions during the question period.

The net effect of the exemptions was enrollment of a patient population with a poorer prognosis.

[Slide.

Correct histologic diagnosis of non-Hodgkin's lymphoma is problematic in clinical practice. For this reason, we included a retrospective central pathology review to confirm eligibility. Nineteen percent of the patients were deemed histologically ineligible by the Central Review, and these were mostly indolent lymphomas.

The FDA excluded an additional 7 patients described as probably eligible by the Central Review. Dr. Randy Gascoyne was the lead pathologist in our Central Review. He is available

to discuss these 7 cases during the question period and why they should be considered eligible.

It is important to clarify that these histologically ineligible patients were not protocol violations or due to the amendments. Enrollment eligibility was determined by the site pathology assessment.

[Slide.

This slide provides a summary of histologic eligibility for several large studies in aggressive NHL. The rate seem in our study, 81 percent, is very consistent with what has been reported in the literature.

Furthermore, the studies listed here were all conducted in newly diagnosed patients where one often has a larger biopsy specimen available for review.

[Slide.

Now, on this next slide, I believe that the comments I was prepared to make are perhaps no longer valid. We have looked ahead at the slides that the FDA is to present, thank you for giving

those to us in advance, and I think that some of these numbers won't match anymore, so please excuse that.

But what we were going to comment here was that in our opinion, some of the categories here listed as reasons for exclusion are not categories that we feel should be used for exclusion from an efficacy analysis.

[Slide.

There was 1 patient who did not have complete CTs at study entry, and, of course, in an eligible patients analysis, they should be excluded.

Having had bone marrow biopsy earlier or having missing LDH at baseline is not a reason, we feel, those missed data points should not be a reason to justify exclusion from an efficacy analysis.

Negative bone marrow and normal LDH are required, of course, at the time one declares a complete response whether or not they were abnormal at baseline. They are a part of the criteria for a

partial response.

The other reason noted here, which was missing neurologic exams at baseline, I don't believe that that was a reason, and FDA will clarify that in their presentation, so I believe that they have removed that category.

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Concerns have been raised that would suggest that the International Workshop criteria were not followed. I would like to clarify that the wording in the protocol did not, in fact, reduce the strictness of the criteria. As excellent as the International Workshop criteria are in providing appropriate guidance for the response determination in this very complex disease setting, there are some situations where the criteria are ambiguous or silent.

The wording clarifications in the protocol were undertaken to uphold the rigor of these criteria and to ensure consistent interpretation in this multicenter environment.

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Before the study was started, we met with the FDA to discuss the protocol Version 5, which contained the clarified wording, and the FDA agreed with the protocol wording and no changes were ever made to that.

With respect to the internal operations of the core imaging lab, the FDA noted correctly that the manual in the NDA was dated one year after the reviews of images began. We had a manual in place before the reviews began, but it was our oversight that this earlier version was not included in the NDA, but we have now provided that to the FDA for their review.

We can summarize, though, that were no changes to the lab procedures during the entire IRP process.

[Slide.

With respect to the amendments to the Independent Review Panel charter, there were no changes to the conduct of the IRP radiology or oncology reviews. Most of the amendments were in place before the reviews began.

A few radiology clarifications were requested by the IRP radiologist, Dr. Scott Gazelle, for situations not previously anticipated, and he is available during the question period to discuss the details.

All images were read in chronologic sequence and they were locked after review, and no changes were permitted.

[Slide.

To summarize the conclusions regarding the study conduct issues, the protocol amendments and exemptions neither contributed to ineligibility, nor favored a positive outcome with VSLI. They, in fact, defined a population with a poorer prognosis.

The histologic eligibility of 81 percent in this study is comparable to what is reported in the literature. Only 8 percent of patients were ineligible for efficacy evaluation due to protocol violations.

Lastly, the Independent Review Panel process was well conducted, therefore, we are confident that we are providing for your

consideration today a well-defined and reliable assessment of objective response in the indicated population and that our pivotal study meets the criteria for an adequate and well-controlled trial.

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I would like to now turn to the presentation of the pivotal study results.

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As agreed with the FDA, some of the key eligibility criteria in this trial were as follows. First of all, this was a population of patients with aggressive NHL that was either from first diagnosis de novo or transformed, and it was required that they had at least received 2 prior combination regimens, one of which had to contain an anthracycline.

We required only a minor response to first-line therapy, which is usually CHOP therapy containing vincristine.

[Slide.

The additional criteria on this slide define a population that would not be eligible for

many clinical trials in that we did not have a maximum on the number of prior regimens patients could have, there was no requirement for response to prior salvage therapies, no upper limit on age, ECOG performance up to level 3 was accepted, a Grade 2 neuropathy was permitted, and as VSLI is hematologically well tolerated, we were able to allow enrollment of patients with low granulocyte or platelet counts, who would not be able to take standard chemotherapeutic agents.

Some of these criteria, particularly the first two, allowed a somewhat heterogeneous population to be enrolled, but this is the population for whom we are seeking an indication.

[Slide.

VSLI was given as a monotherapy regimen in this study. It was given as 2 mg/m 2 without any dose capping, 1 hour infusion every 2 weeks. The protocol specified 12 cycles maximum with the intent to go 2 cycles after a complete response.

What is highlighted now in yellow are points of differentiation from the conventional

vincristine dosing schedule. Conventional vincristine is given at 1.4 mg/m^2 often with dose capping at a flat dose of 2 mg, and it is usually repeated every 3 weeks, so by implementing these changes, we are able to at least double the dose intensity of vincristine.

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The efficacy endpoints in this trial were the traditional oncology endpoints with objective response as the primary endpoint. The primary population for analysis was the intent-to-treat population as defined in the protocol and the stats plan.

The secondary population was based on patients who met the key inclusion criteria and who were evaluated. That is what we call the "per-protocol" population, and we identified 77 patients who met those criteria.

[Slide.

The assessments of response were determined using the International Workshop Criteria. A key point here was that 6 indicator or

target lesions were to be measured carefully throughout the study, and all other disease was assessed qualitatively.

According to these criteria, response does not require subsequent confirmation.

As this was a single-arm study, it was important to use an Independent Review Panel for the primary efficacy assessment. The IRP was blinded to the site's opinion of response, and they also independently chose 6 indicator lesions.

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So, who did we enroll in this study?

[Slide.

In the interest of time, I will discuss only a few characteristics of the study population. The extent of prior therapy was a significant predictor of response in this study. The protocol required a minimum of 2 prior regimens, and we see that 19 percent of the patients in the study had exactly that amount of prior therapy, but the vast majority of these patients had much more prior therapy.

The mean was 3.8, the median was 3, so therefore VSLI was being given predominantly as a fourth- and fifth- line therapy to this population.

[Slide.

Another important perspective that provides context for the interpretation of our results is how these patients responded to their previous therapies. When they were at their first-line therapy, the overall response rate was 92 percent, 50 percent complete response.

By their second line, the response rate had dropped down considerably to 41 percent, and we were now seeing only 20 percent CRs. At their last therapy, which could have been second line, but was usually much further along than second line, the response rate was down to 35 percent with only 13 percent complete response.

I would like to emphasize that three-quarters of the patients were receiving a combination regimen as their last line. Therefore, these data demonstrate that the population in this trial had disease that had become very difficult to

treat.

The median duration of response was 8 months at first-line therapy and had decreased to 5 months with salvage regimens.

[Slide.

Patients were further characterized with respect to the sensitivity or resistance of their disease to their last qualifying therapy. Two-thirds of the patients in this trial had resistant disease, and half of the patients had truly refractory disease, meaning that they did not respond to their last therapy.

Another 17 percent had early relapses within 3 months. Therefore, only one-third of the population had sensitive disease with responses lasting more than 3 months to their last therapy.

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Turning now to the efficacy data.

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The results are very similar in the intent-to-treat and per-protocol populations. For brevity, I will focus on the intent-to-treat

population, which was the primary efficacy analysis. The per-protocol analyses have been provided for your review in Appendix B of the briefing document.

The primary efficacy endpoint was the objective response rate as assessed by the IRP, and these are the results on this slide. The IRP determined that 30 patients were responders. That is 25 percent. We had 8 patients with a CR or CRu, so these were predominantly partial responses in this trial.

Additionally, one-quarter of the patients had stable disease with VSLI therapy.

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Now, on this slide, I provided comparison of 3 different analyses. The first column is the intent-to-treat data that I just shared with you.

The second column is the per-protocol population that we defined of 77 patients, and the response rate is very similar, as is the distribution being predominantly PRs, but still maintaining some complete responses in about a

quarter of the patients with this disease stabilization.

In the far right column, I have presented the FDA eligible analysis, as was shared in their original posted briefing document. I believe they will be updating this analysis today, but this analysis again showed a very similar response rate at 22 percent with about 4 percent complete response.

[Slide.

A key focus of today's deliberations is whether the objective response rate observed in this study is likely to predict clinical benefit. We looked at other available data for the responding patients as we were requested by the FDA to prepare patient benefit summaries to facilitate their review.

[Slide.

We determined that there was evidence of some symptomatic improvement associated with objective response. There were 8 patients who were determined to be complete responses or CRu by the

IRP. Three of those patients were actually asymptomatic at study entry, but the remaining 5 patients who were symptomatic either had resolution of their symptoms or an improvement in their ECOG performance status.

Of the 22 patients called partial responses, 15 of them had improvements in symptoms or ECOG performance status.

I should mention that there was no formal symptom efficacy endpoint in this trial, so this is a summary of baselines signs and symptoms or that resolved after VSLI treatment. Other evidence of possible clinical benefit was presented in the briefing document.

[Slide.

Turning now to the secondary efficacy endpoints, the time-to-event endpoints.

[Slide.

The first one I would like to discuss is duration of response. This was analyzed using Kaplan-Meier method, the usual method, and it is done only, of course, for the 30 responders. The

median was not reached in our analysis, but we were very close at 52 percent probability at the last event of progression or approximately 3 months.

The FDA analysis appears to have used a slightly different definition that included withdrawal due to neurotoxicity as a progression event, but this analysis provides a similar median estimate of about 2 1/2 months.

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The analysis of time to progression is, of course, conducted on all 119 patients. The median here was estimated again to be about 3 months, but, of course, this was heavily influenced by the majority of patients in the trial who did not respond to VSLI treatment, so an additional analysis was done for the responding patients.

For this subgroup, the estimated median time to progression was not reached, but once again, we were approaching the median at 45 percent probability. So, we were at about 4 months.

[Slide.

The overall survival is shown in this

Kaplan-Meier curve. The median was 6.7 months, and at 2 years, we have 25 percent of the patients still alive.

[Slide.

The protocol and stats plan prespecified several subgroup analyses, and there were two factors that were determined to be statistically significant predictors of objective response.

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With 2 significant predictors of response, the most informative presentation is for the 4 subgroups, as shown on this slide. The response rate for patients who had 2 prior regimens was 46 percent, and for the patients who had more than 2 prior regimens, which was a much larger proportion of the patients on the trial, the response rate was lower, at 20 percent.

Within each of these 2 big groups, if we would further subdivide by whether they had sensitive or resistant disease, we see the impact of that factor, as well.

So, we have quite a range of response

rates here, from the lowest being 15 percent, to the highest being 64 percent, and what we can conclude from this analysis is that the overall response rate of 25 percent, that we saw in our study, was very much the result of the relative number of patients in these 4 subgroups that were enrolled in the study.

Had we had more patients in this subgroup, the poorest prognosis subgroup of more than 2 prior regimens with resistant disease, we would have had a lower response rate closer to the 15 percent.

Had we had more patients with sensitive disease in the protocol, we would have been in the 30 to 40, 50 percent response rate.

One criticism of this analysis is that some of the subgroups are very small.

[Slide.

So, on this slide, we are now showing the Phase IIa supportive study alongside the data that I just showed you. The denominators here are for the combined studies, and what is impressive is that the results for the 2 studies are very

consistent for the 4 subgroups. These 2 predictors of outcomes were consistent in both trials.

Therefore, one can be reassured that the estimates for these subgroups are reasonable.

[Slide.

This slide summarizes some other subgroup analyses that are noteworthy as they did not identify significant predictors of response. The response rate was not any lower in patients who had previously undergone autologous stem cell transplant, nor was the response rate affected by age. The median age was 60 years.

Twenty-eight patients on this study were older than 70 years, and this subgroup had a 36 percent response rate, so at least as good as the total population.

Patients who have relapsed after transplant and those who are elderly are particularly in need of an effective therapy that is minimally myelosuppressive.

[Slide.

Returning now to the question of whether

VSLI provides meaningful therapeutic benefit over existing treatments, we have the rituximab publications presented earlier by Dr. Cabanillas on this slide in the first three columns, and now I have listed the results of our Phase IIb study in the two right columns.

The furthest right column has the results for the intent-to-treat population, which had a median of 3 prior regimens, therefore, to provide a better comparator I have pulled out the subgroup of patients who had 2 prior regimens as that is more comparable to what is in the literature citations.

But it is important to note again that these 3 publications for rituximab did include a substantive proportion of patients at first relapse, which we did not have in our study.

Even with a slightly more favor population enrolled in these studies, our response rate, which is shown along this line here, a response rate of 46 percent compares favorably to what was shown with rituximab.

Duration of response was not reported in

the publications, but on time to progression at the bottom of the table, the VSLI is in the same range.

[Slide.

We can also compare to the rate of response demonstrated with rituximab for the patients in our study. There were 20 patients who had rituximab as a single agent therapy as their last therapy before coming into the study.

The response rate to rituximab was 25 percent, and there were no complete responses.

With single-agent VSLI then, as their next therapy, the response rate achieved was 40 percent, and we did see some complete responses in these same patients. Therefore, we are seeing a somewhat higher rate of response.

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I would like to turn now to the safety data presentation.

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The mean number of cycles of VSLI administered was 4.6 with a median of 4, and the dose intensity was very close to the target of 1,

indicating that very few dose reductions occurred on the study. I should say that was 1 mg/m 2/week. That was our target at dose intensity.

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Fourteen percent of the patients withdrew due to associated adverse events, which was mostly neuropathy. It was 13 percent for neuropathy. There were no treatment-associated deaths.

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The dose-limiting toxicity of conventional vincristine and of VSLI is, of course, neuropathy.

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This slide summarizes the number of prior regimens that the patients had that contained neurotoxic agents. Eighty-six percent of the patients had at least 2 prior regimens that contained a neurotoxic agent. Therefore, it is no surprise that 85 percent of the patients entered the study with some level of neurologic deficit.

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Now, on this slide, I am showing the worst grade of neuropathy on study for patients grouped

by their grade of neuropathy at study entry. We did allow up to Grade 2, as I mentioned.

These data are the worst values for any of the 5 neuropathy symptoms that we tracked, as shown in the title. The scoring system here is the NCI CTC scale, which goes from zero, which is normal, to Grade 4 at the worst end.

For patients who entered this study with Grade 1 neuropathy, one-quarter of the patients had no change on study, and about half of them worsened by one grade to a Grade 2 level, one-quarter went to a Grade 3 level.

For patients who entered this study at Grade 2, approximately 40 percent of them did not have any worsening on the study, but half of the patients did worsen one grade to Grade 3. As would be expected, patients who entered the study with worse neuropathy had a higher chance of developing Grade 3 neuropathy.

[Slide.

Numbness in the hands was the symptom that was most adversely affected on this study, and this

plot shows the mean change from baseline to Cycle 6 for this parameter.

We observed a gradual cumulative increase in hand numbness, reaching a peak which was less than one grade, and again, this is the NCI grading system that goes to 4.

This peak was reached after 5 cycles, and the data beyond Cycle 6 don't show any further increase. We are down to fewer numbers of patients on the study at that time.

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Her analysis was done to estimate the dose that would result in Grade 3 or 4 neuropathy if all patients continued to be dosed. The Kaplan-Meier method was used for estimation, and all five symptoms were included. Reaching Grade 3 in any one of these symptoms was called an event in this analysis.

One-third of the patients on the study developed a Grade 3 or 4 neuropathy, but as you can see, they were almost all Grade 3 neuropathies. There were only 3 patients who went to Grade 4.

The estimated median cumulative dose to achieve this was 21.2 mg/m 2, which is approximately 11 doses of VSLI. This is equivalent to approximately 15 doses of conventional vincristine. This is a lot of vincristine for patients who have received previous neurotoxic agents, and it speaks to the safety from the liposomal encapsulation.

[Slide.

With the 25 percent response rate, an important consideration is the risk exposure for patients who will not respond to VSLI therapy. This slide summarizes the magnitude of treatment-emergent worsening in neuropathy from no change up to 3 grades. This are all zeros here. This is presented separately from responders versus non-responders. So these are the grade changes from baseline to worse value, the treatment-emergent changes.

As one would expect, the responding patients who received more drug did achieve bigger changes in their neuropathy, mostly 1 or 2 grade changes, however.

In the nonresponding patients, 55 percent of the patients had no change on study, and one-quarter had a one grade worsening. This group includes stable disease patients, and which includes their minor responses, not meeting the definition of a partial response, and some of our stable disease patients actually were treated for a very long time.

So, I have pulled out a smaller group here in the bottom row, which are the patients who had rapid progression, and we see that 69 percent of the patients in that group had no change at all on study and 19 percent had a one grade worsening.

Because of the gradual development of neuropathy, we are able to avoid significant toxicity in patients who will not benefit from this therapy.

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It is also of interest to compare the timing of the antitumor effect to the timing of the neuropathy, and when we prepared the patient summaries, we observed that the antitumor activity

was evident very early in those patients who would be declared responders, usually within the first two weeks of off the first injection of the drug.

There was evidence of symptomatic improvement, reduced palpable adenopathy or decreased LDH long before we were doing CTs. As shown earlier, the development of neuropathy is gradual and predictable, therefore, in contrast to most other drugs, with VSLI, the physician and patient can make an informed treatment decision before significant toxicity develops.

[Slide.

With respect to hematologic abnormalities, at study entry, we see here at study entry, approximately 80 percent of the patients had some level of anemia, 40 percent have thrombocytopenia. One-third of the patients would not have been eligible for standard chemotherapeutic agents that were myelosuppressive based on the low neutrophil or platelet counts as defined here.

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This slide now summarizes the treatment

emergent grade changes from baseline to worst grade on study for these three hematologic parameters. As shown in this column, about half of the patients for any particular parameter, about half of the patients had no change on study.

Most of the changes were in the 1 grade category. Neutrophils was the parameter that had the most change, and we see 20 percent of the patients having a 3 or 4 grade change, and approximately half of those, so 10 percent of the patients is where it was considered to be treatment related.

With respect to the worse level of neutropenia reported on study, 8 percent of patients had Grade 4 neutropenia and 3 percent had febrile neutropenia. This occurred in the setting of only 2 percent prophylactic filgrastim usage, so this study provides a good estimate of the VSLI effect on neutrophils.

Grade 4 thrombocytopenia occurred in only one patient and 6 percent of patients received platelet transfusions.

Based on all of these data, we conclude that VSLI was hematologically well tolerated in this study.

Dr. Cabanillas will now describe patients who achieved net clinical benefit in this study.

Clinical Benefit

[Slide.

DR. CABANILLAS: The FDA has requested that the company prepare patient benefit summaries to facilitate the review of clinical benefit.

There were 38 patients considered to be responders by either the IRP or the investigator, and summaries were prepared for all of those patients. In addition, there were 5 patients with minor responses who had evidence of clinical benefit.

Therefore, a total of 43 individual patient benefit-risk assessments were prepared.

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Of the 43 patients analyzed for clinical benefit, there were 41 who actually manifested evidence of benefit. I will discuss the findings

for the first two categories noted in yellow here, specifically, symptom improvements and patients who went on to receive stem cell transplants.

Other categories of clinical benefit included durable responses and better outcomes than previously achieved. Some of these will be demonstrated in a few case studies.

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This slide summarizes two of the clinical benefits, improvement in symptoms and improvement in performance status.

Twenty of the 43 cases had improvement in either B symptoms or some other symptom related to lymphoma, 13 patients experienced improvement in performance status. A total of 26 patients had improvement in one of these two categories.

Another clinical benefit we consider important is being able to provide these patients with the opportunity to receive a stem cell transplant.

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Six patients were able to receive

transplants after the VSLI study. Both responsiveness to VSLI and maintenance of a good performance status enabled these patients to receive their transplant. Five of these 6 patients are actually alive, 1 with disease, and 4 with no evidence of disease for two to three years.

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In the pivotal study, we observed some very striking outcomes in several patients, and I wish I could review each one of them, however, in the interest of time, we will only be able to go over three of these patients, but we have also some patients who will be testifying today.

The first case is a 56-year-old lady with primary mediastinal DLCL and associated symptoms. Her response to prior therapy had consisted of a brief PR to CHOP. Upon relapse, she was treated with ESHAP and RICE without response to either. She achieved a CRu of 1 year after 20 cycles of VSLI. Her toxicity consisted of only one episode of Grade 4 neutropenia.

What is striking about this case is that

she was able to obtain a CRu after being refractory to 3 combination regimens including CHOP. She benefited also from resolution of B symptoms and anemia.

[Slide.

This 76-year-old lady with DLCL and IPI of 3 presented with multiple pulmonary metastases and thrombocytopenia of 72,000. Her prior therapy included CHOP and subsequently Cytoxan, VP16, Rituxan.

After 8 courses of VSLI, she obtained a PR of 8+ months, and her platelets normalized. Her tolerance to VSLI was excellent with no Grade 3 or 4 toxicities.

The pulmonary metastases improved, but never disappeared completely. The residual lesions, however, have not changed for 2 1/2 years, suggesting that they are scars, rather than lymphoma.

This patient benefited from a long chemotherapy-free interval still ongoing at 27+ months, which is a longer remission than she ever

experienced with any of her prior therapies.

[Slide.

This third case is a 47-year-old male with advanced DLCL and a mediastinal mass plus bone marrow involvement. Front-line therapy with CHOP failed to induce a response, and second-line therapy with RICE also failed.

After 8 cycles of VSLI, he achieved a PR according to the IRP or a CR according to investigator without serious toxicity. He is alive with no evidence of disease after 30+ months and has not required any subsequent therapy.

Therefore, the investigator's assessment of complete remission was correct.

Most striking about this case is the achievement of a CR in the context of primary and secondary refractory to chemotherapy. The B symptoms and anemia also resolved.

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I would like now to turn our attention to our conclusions about the benefits versus the risks of VSLI.

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Our patient population consisted of patients treated with a median of 3 prior regimens, which translated into 4th and 5th line therapy for most of these patients.

One-third of our patients had received a prior autologous transplant and one-third had low blood counts, which would have made them ineligible for a treatment with a myelosuppressive agent.

Half were refractory to the last qualifying therapy and one-quarter were older than 70 years. Finally, two-thirds had an elevated LDH at time of entry.

In summary the prognostic factors associated with this population are extremely adverse.

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In this study, we have 25 percent overall response rate. In patients treated on second relapse, however, the response rate was better at 46 percent. We consider this response rate to be clinically important for this population.

In fact, I consider this drug to be the most active single agent I have used since we tested a phosphamide back in the 1970s non-Hodgkin's lymphoma. The objective responses usually translated into symptomatic improvement.

The median response duration was approximately 3 months and time to progression was approximately 4 months. This is in the setting of an overall median survival in the range of 7 months.

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Regarding the risks, we can summarize them by stating that neuropathy was the dose-limiting toxicity. Its development is gradual and cumulative, and only 13 percent withdrew because of neuropathy.

Compared to other agents, VSLI is well tolerated with a low incidence of severe myelotoxicity and hospitalizations. In addition, nausea and vomiting, as well as alopecia are infrequent.

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An important point is that the improvement in symptoms and the antitumor response occur early with VSLI. This allows for informed treatment decisions before serious neuropathy develops.

In essence, there is a favorable benefit-risk profile for this population, which has not standard therapy options.

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So, why do we need VSLI? It is an effective and well-tolerated agent for patients on third relapse or later. It offers a therapeutic alternative for patients who do not qualify for aggressive combination regimens or who have relapsed after transplant, as well as for those with a compromised marrow function.

VSLI resulted in benefits for 1 out of every 4 patients with minimal toxicity.

Thank you for your attention during the presentation. We would be happy to answer your questions at anytime.

DR. MARTINO: Thank you.

At this point, I would like the FDA to

present their evaluation of this data.

FDA Presentation

DR. HAZARIKA: Good afternoon. My name is Maitreyee Hazarika, medical reviewer.

This NDA submission is for Marqibo, which is vincristine sulfate liposome injection.

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The indication is for the treatment of patients with aggressive non-Hodgkin's lymphoma previously treated with at least two prior combination chemotherapies.

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This presentation will go through the regulatory issues with this application. Study CA99002 is the major trial submitted. Study DM97-162 is the supportive study. The FDA analysis of the efficacy and safety will be discussed followed by the summary and the issues for ODAC.

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The regulatory issues for this application includes accelerated approval, available therapy, endpoints, adequate and well-controlled trials, and

confirmatory trial requirements.

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Accelerated approval is granted by the Agency if a drug appears to provide a benefit over available therapy, and the benefit is determined by the drug's effect on the surrogate endpoint deemed reasonably likely to predict clinical benefit.

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Because accelerated approval requires an advantage over available therapy, the definition of this term is critical. Available therapy should be interpreted as therapy that is reflected in the approved labeling of regulated products.

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There are exceptions where a safe and effective therapy for a disease exists, but it is not approved for that particular use by the FDA.

In oncology, treatments that are not labeled for use but is supported by compelling literature can be considered available therapy.

The ODAC members will need to use their expertise on what constitutes available therapy for

aggressive non-Hodgkin's lymphoma.

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Initially, FDA-approved drugs were based primarily on clinical data and review of literature. Most of these drugs listed here are used as part of a combination in relapsed patients.

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Within the past 15 years, FDA has approved four biologic agents mainly for the treatment of low grade follicular non-Hodgkin's lymphoma. This is a different indication from the one being discussed here today. Approvals were based on single-arm or randomized, controlled trials. The first three approvals were based on response rates and duration. Intron approval was based on a longer progression-free interval and median survival.

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To determine whether vincristine sulfate liposome meets the criteria for accelerated approval, the ODAC and the FDA must consider not only approved drugs, but also the published

literature. There are many known approved combination therapies used for relapsed aggressive non-Hodgkin's lymphoma, which also includes high-dose chemotherapy with stem cell transplantation.

Some examples are shown here. The combinations used have overall response rates of 30 to 88 percent with complete responses of 18 to 53 percent.

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Many single agents are also used that are not specifically labeled for non-Hodgkin's lymphoma indication. Based on published literature, overall response rates varied from 37 to 69 percent and complete responses from 13 to 33 percent.

In both the combination and the single agent reports shown here, these may not be the exact population. Patients may have received between 1 to 3 prior therapies and may have mixed histologies.

Nevertheless, we will be asking the Committee whether any of these constitute available

therapy.

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Previous recommendations have been to use complete response as the endpoint in this disease. Two important questions should be in the Committee's mind for this application. Should FDA consider partial responses to be reasonably likely to predict for clinical benefit in relapsed, aggressive non-Hodgkin's lymphoma? If so, would responses of the magnitude and duration seen in this study predict for clinical benefit?

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There are a few key regulatory points to consider for the present application. The study should use a design that permits a valid comparison with a control to provide a quantitative assessment of drug effect.

The method of selection of subjects should provide adequate assurance that they have the disease being studied.

The methods of assessment of subjects' response should be well-defined and reliable.

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Since 1999, the Agency has had around 20 meetings with the sponsor on various issues. In those meetings, FDA has advised the sponsor that response duration was of interest. FDA advised the sponsor for the need for a confirmatory trial, and FDA has emphasized the endpoint of durable complete responses.

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At the March 2003 ODAC meeting, the Committee reinforced the Agency's recommendation that the postmarketing studies be ongoing at the time of accelerated approval. The FDA expects that confirmatory studies to demonstrate that treatment with the drug is associated with clinical benefit will usually be underway at the time of accelerated approval, although that is not a specific requirement.

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Study CA99002 is the major trial submitted. It is a multicenter, open-label, single-arm Phase II study with a primary endpoint

of response rate, which included complete response, complete response unconfirmed, which is a complete response with a residue in mass, and partial responses.

119 patients were enrolled. VSLI was given at 2 mg/m^2 intravenously over 1 hour every 2 weeks.

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Patients had relapsed, aggressive non-Hodgkin's lymphoma, who had received at least 2 prior combination therapies including 1 prior anthracycline-based therapy.

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Histologies included aggressive de novo and transformed lymphomas, and included diffuse large B-cell lymphoma and peripheral T-cell and anaplastic lymphomas.

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According to the Central Pathology Review, only 75 percent patient histologies were identified as definite eligible, 30 patients were probable eligible or ineligible. The majority of the

ineligible patients had low grade histology on biopsy. Two patients had slides missing for Central Pathology to review.

FDA evaluated only the definitely eligible patients. Definite eligible have the histology for the indication proposed for VSLI.

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These are the reasons for exclusion from the FDA efficacy analysis. There were 30 patients with histology not definitely eligible by Central Pathology Review. Eight patients did not have baseline indicator lesions measurable by the independent radiologist.

A durable disease was defined as at least 1 bidimensionally measurable lesion with clearly defined margins that were greater than 2 centimeters in the largest dimension by CT scan or physical examination.

Five patients did not receive 2 or more prior combination chemotherapy from the time of diagnosis of transformation. Two patients did not have a washout period of 4 weeks, and 12 patients

did not have complete baseline staging with CT scan or bone marrow biopsies, or had bone marrow biopsies done more than 2 months prior to the study drug administration.

That is a total of 40 percent patients were considered ineligible for the trial by the FDA.

The briefing document gives slightly different numbers, but the results do not change significantly.

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There were other study conduct issues, such as bone marrow biopsies done between 3 to 8 weeks prior to entry. Missing full set of CT scans at one or more visits, missing scans for tracking the disease, and missing baseline neurological examinations. These patients were included in our efficacy analysis as we felt that they did not impact on the response rate.

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The FDA analysis used 61 percent of the enrolled patients who met the critical eligibility

criteria. That is, they had relapsed, aggressive non-Hodgkin's lymphoma, had received 2 or more prior combination chemotherapies, including 1 prior anthracycline-based therapy, and had required baseline scans and bone marrow biopsies.

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The response criteria used was based on the International Workshop to standardize response or non-Hodgkin's lymphoma. There were 4 categories based on physical examination - lymph nodes, lymph node mass, and bone marrow biopsy, complete response, complete response unconfirmed, which included a residue mass or indeterminate bone marrow, partial response, and relapse or progression.

The normal lymph node size was based on the abnormal node size at diagnosis. A lymph node greater than 1 cm was considered compatible with involvement by non-Hodgkin's lymphoma.

These criteria do not require response confirmation. Most international cooperative groups require a confirmatory evaluation for the

response classification. Although it was agreed to use these criteria, FDA emphasized that duration of response must be examined and described.

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The sponsor made some modifications to the International Workshop, such as defining the normal lymph node size and nodal mass size to be 1.5 cm, and using indicator lesions that were a minimum size of 2 cm in at least one dimension.

The FDA analysis of response used the sponsor modifications.

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Prior to any patient enrollment, amendments included a statement which required response confirmation by repeat assessment at 4 weeks following the first documentation of response.

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The sponsor's analysis of response rate included patients with tumor size reduction documented on at least 1 occasion.

In addition to the same response rate, the

FDA analysis was also done on confirmed response rate where tumor size reduction was confirmed at least 4 weeks later.

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On analyzing response rate documented on 1 occasion, the sponsor found 4 complete responses, 4 complete responses unconfirmed, which to remind you are complete responses with a residue of mass, and 22 partial responses, for an overall response rate of 30 patients or 25 percent.

The FDA analysis on the evaluable patients found 1 complete response, 3 complete response unconfirmed, and 11 partial responses, for a total response rate of 21 percent.

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The FDA also did an analysis on confirmed response rates with a greater than or equal to 4-week confirmation, and found zero complete responses, 2 complete responses unconfirmed, and 9 partial responses,, for a total response rate of 15 percent.

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In the sponsor's analysis, the duration of response has been estimated using the Kaplan-Meier procedure. Patients who did not have documented progression were censored at the time of treatment cessation, and the sponsor's analysis of duration of response, 67 percent of the responders were censored.

Any attempts to interpret a response duration where two-thirds of the patients are censored is of questionable value. The sponsor's median duration of response was reported to be greater than 85 days. In the FDA analysis of 11 confirmed responders, the median duration was 85 days.

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In the sponsor's analysis, out of the 20 censored patients, reasons for treatment cessation included neuropathy, relapse, underwent bone marrow transformation, completed study, withdrew consent, thrombocytopenia, and unknown reason.

Forty-three percent of the responders in the sponsor's analysis did not have repeat scans or

physical examination or progressed before a repeat scan was done. Thirty percent of patients discontinued within 30 days of initial response.

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Patients completed a median of 4 cycles of therapy. The dose intensity was 96 percent of planned. The most common cause of dose delay was due to neuropathy followed by hematologic toxicity.

Neuropathy was also the most common cause of dose reductions. Thirteen percent of the dose reductions were at least 0.24 mg/m2.

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The commonest Grade 3 or Grade 4 adverse events were peripheral neuropathies, both sensory and motor, which occurred in 60 percent of patients, followed by myelosuppression in 45 percent of patients. Other adverse events were fatigue and constipation.

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Study DM97-162 was submitted as supportive evidence. It was a single-center, open-label, single-arm study in patient with relapsed lymphoma

and acute lymphoblastic leukemia.

The primary endpoint was response rate. 132 patients were enrolled, 116 had a diagnosis of lymphoma, of which 97 patients had aggressive lymphoma.

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There was no independent review of pathology or radiology. Selected CT scans were reviewed retrospectively. There was incomplete documentation of bidimensional measurements.

Case report forms were not used prospectively. Standardized response criteria for non-Hodgkin's lymphoma was not used.

Therefore, the use of the study for support is questionable.

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The sponsor reported the response rate in the aggressive non-Hodgkin's lymphoma population as 29 percent. There was nor duration of response assessed.

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In summary, the submission is multicenter,

single-arm Phase II study in patients with relapsed, aggressive non-Hodgkin's lymphoma submitted for accelerated approval based on the endpoint of response rate.

In the major study, 72 patients met the critical eligibility criteria.

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The FDA analysis found the response rate documented on at least 1 occasion to be 20.8 percent with 1.4 percent complete responses. The confirmed response rate was 15.3 percent with zero confirmed complete responses.

The FDA analysis contains only patients who have aggressive relapsed histologies.

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The study conduct raises doubt regarding the method of assessment of response. The duration was short and not adequately evaluated. The use of the supportive study is questionable for support. There is no confirmatory trial underway.

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We bring this application to the ODAC

Committee for the consideration of several issues. The first issue is the available therapies for relapsed, aggressive non-Hodgkin's lymphoma.

Drugs considered under accelerated approval must demonstrate an advantage over available therapy. The Committee needs to consider not only the magnitude of the response rate, but the data which indicates that this response rate is comprised primarily of partial responses.

The Agency believes that the duration of any response rate must be considered in assessing the potential clinical relevance of any claimed benefit.

Finally, the Committee should consider if the sponsor has demonstrated in this single-arm trial that VSLI represents an improvement over available therapy, keeping in mind the activity of multiple drugs and combinations in aggressive non-Hodgkin's lymphoma.

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This is the review team for the application.

Thank you for your attention.

DR. MARTINO: Thank you. At this point, ladies and gentlemen, we will move on to questions from the Committee to either the sponsor or the FDA, and also please know that we have chosen to not allow you a break after the questions as several of us need to leave, and I want to give the group the opportunity to at least have their questions asked and answered.

Dr. George.

Questions from the Committee

DR. GEORGE: I have a question. Maybe it's for Dr. Pazdur, but it has to do with accelerated approval again. The more I learn about it, the more subtle it seems.

This has to do I think with this application because of the available therapy issue, the issue of appear to provide some improvement over available therapy.

This is not, of course, the same thing as proving it has any advantage over available therapy, and it just has to do with accelerated

approval, because if you were to get full approval later, you don't have to prove that it is superior or in any way compared to available therapy.

So, I just want to be sure that that is correct, and maybe some clarification on what would be meant by "appear to be superior" or an advantage over available therapy.

DR. PAZDUR: Let me over the regular approval is for clinical benefit, and therefore, we are looking at different endpoints. We would be looking at a survival benefit. We would be looking at a very durable CR rate here.

But for accelerated approval, we do want an improvement over available therapies. Remember, the whole purpose of accelerated approval, which came to us from really the AIDS arena, you know, decades ago, or about 15 years ago, was an effort by the Agency to get out therapies that were novel, that were an improvement over available therapy.

So, it isn't appears to be, it should be, in our interpretation, and provides is the correct word--thank you, Grant--an improvement over

available therapy here.

Now, just from a historical perspective, you know, our first approval or one of our first approvals, getting back to this available therapy, was in colon cancer, a disease that I am very familiar with, and many of you here are, too, for irinotecan.

There, in 1995, there was no irinotecan, there was no oxaliplatin, there was no Avastin, there was no Erbitux, nothing like that existed. All you had was 5FU and leucovorin, and that was it.

Now, it was very easy to answer that question, because nothing existed and there was complete consensus in the community that any therapy was going to be better than nothing basically.

That is why we felt initially very comfortable going ahead with this. Similarly, in lung cancer, where you had patients progress on a platinum-containing combination, on a Taxotere-containing combination, we feel very

comfortable looking at single agent ERISA, and we approved the drug.

In therapies where there has been, you know, activity in available therapy, for example multiple myeloma, when we approved Velcade, for example, we had durations of responses that were over a year, so it was very obvious to us that you didn't need a randomized trial here.

That is a basic, trying to get away from the nuances of drug regulation, what we are looking for in a sense is should a randomized study be done, and that is the clinical issue here, is there enough evidence that you have from the literature that you feel that there is compelling evidence that there is available therapy that would warrant a randomized study.

The issue also is "compelling" is a very vague word, it is like beauty, it's like sexy, it's in the eyes of the beholder. So, it is very difficult to establish that, and when we looked at the literature, we found it very confusing, and that is why we decided we would ask your opinion

regarding this, because when you go back, it is very hard unless you did a actual meta-analysis of all of these reports to find out exactly what therapies patients had, et cetera.

So, it is an area of ambiguity in a sense, what is available therapy.

DR. MARTINO: Dr. Hussain.

DR. HUSSAIN: I had a question regarding the comments about symptomatic improvement. Were the data on symptoms collected prospectively and systematically? I am really curious. I deal with solid tumors and we would consider a 10 percent high-grade neuropathy as an unacceptable rate of neuropathy.

So, I am curious about your comments about how this drug is so well tolerated, yet, you have a 60 percent Grade 3 or 4 neuropathy, which does not really speak for a good quality of life in a setting of this kind of disease.

MS. MANCINI: Yes, I will address your first question regarding how the symptoms were collected. Can I clarify, are you asking about the

symptoms of neuropathy or the symptoms of disease?

DR. HUSSAIN: I believe the doctor was asked about quantifying clinical benefit, and we saw a slide that showed there were improvements in performance status and symptom improvement, and so my question is, did you actually go back and look in the charts and see that the doctor mentioned something, or there was systematic collection of the symptoms prospectively.

MS. MANCINI: I can answer that question then. As I commented, we had no prospective symptom endpoint in this trial, so therefore, these are soft data. What we have is what was reported as baseline signs and symptoms, so as part of collecting adverse event data. We would watch what happened to that as the patients were treated, so you could see as it gets better basically, and as it is resolved.

So, it is not the same level of evidence we would normally have for a formal efficacy symptom endpoint, but the reason we summarized that data was we were asked to look to see was there any

evidence to support that the patients who got partial responses particularly had other clinical benefit.

So, it is soft data. It is the level of data, however, that you would experience in your clinical practice, the patient complains of tumor pain, neck pain, et cetera, and then it goes away, so it is at that level.

DR. PAZDUR: If I could just add to that because I think I was the person that instigated this question. We don't put any credibility or very little credibility in a unblinded single-arm trial as far as interpreting symptoms.

One of the reasons I just asked this, was there any kind of supplemental information that could give some credibility to a response rate, because a response is, one, you know, even when we talk about a complete response rate, is it a single mass going down versus multiple masses, is there something that might bolster this up, but the level of proof that we would require to make any labeling claims about that in any product would not come

from a single-arm, unblinded trial.

MS. MANCINI: If i could return to your second comment, then, I would just like to clarify. If we could back in the primary presentation, please, to the slide--excuse me while I flip to it, to the safety presentation--let's go to Slide 71, please.

I may have gone quickly over this in the presentation. There are two factors to consider when we look at the tolerability of our drug. One is how did the patients come into the study and what happened from there.

So, just as a point of perspective, 86 percent of them had had at least 2 prior regimens containing a neurotoxic agent, so 85 percent came in with some level of neuropathy.

The next slide, please, 72. This is the analysis that shows what happened to them by their worst grade at study entry. So, when you look at the people who get to Grade 3, they are mostly coming from patients who started some neuropathy.

So, the incremental toxicity that they

have endured is what we are trying to summarize here. So, for patients who came in with a Grade 2 neuropathy, half of them did worsen to Grade 3. That is a one-grade change. Had they not come in with Grade 2, they wouldn't have gone there probably. So, in patients who came with no neuropathy, we don't see that high a proportion going to Grade 3.

I can also share with you the perspective of if we go to, again in the primary, it is just a couple of slides further, Slide 75. I think this is the data that you were referring to--Slide 74, I am sorry, my eyes are not good.

It is correct to say that a third of the patients on this study got to Grade 3 or 4 neuropathy, and mostly Grade 3, but as I mentioned earlier, the withdrawal rate due to neuropathy was only 13 percent, therefore, Grade 3 neuropathy was not a reason to stop treating in many patients.

I do have some additional data if you would like to know what happened to these 37 patients, what the treatment decisions were. Would

you be interested in that? Okay.

If we go to Slide 739, please, in the backups. This is now going to summarize all 37 patients who ended up with a Grade 3 or 4 neuropathy on study.

The first point is that 10 of those patients had a simultaneous declaration of progressive disease, therefore, there was no further treatment decision to be made for those patients.

So, of the 27 remaining patients, 11 withdrew for neuropathy or withdrew consent, so to be conservative, we are taking the 7 and the 4, and saying 11 patients probably withdrew due to neuropathy, but 16 patients continued with VSLI therapy. So, just over half of them chose to continue despite getting to a Grade 3.

The next slide, 740, please. This shows you for those patients who continued, for the 16 patients, 8 of them had 1 additional dose, and I have a footnote here to say why did they stop, it is not because they weren't tolerating it again, it

is because 7 of them had progressive disease after the next cycle.

So, the reason to stop treating in this study was almost always disease progression. There are patients who were at Grade 3, but continued, got 3 or 4 more additional cycles.

So, we conclude that although we did want to present the total Grade 3/4 neuropathy as being clinically important, it did not always trigger a decision to stop treating.

DR. MARTINO: Dr. Wilson.

DR. WILSON: I would like to get some better idea about how the patients were evaluated. Of course, PR and CR per se, In the absence of a meaningful length, is not really worth much. The overall length of response is somewhere in the 3-month arena.

What did the protocol state in terms of how often patients had CT scans done? The documentation says that CTs were required on study every 4 weeks, but in those patients in whom therapy was actually stopped, were CT scans also

done every 4 weeks, and for those who didn't have it done every 4 weeks, was this factored in, and were those patients censored?

MS. MANCINI: Thank you for that question. That gives me an opportunity to clarify a point in that in our duration of response analysis, if I could just have Slide 266, please, just to demonstrate this point.

The duration of response was calculated in a classic manner in our study. Start of treatment is over here on the left, and then the first formal evaluation of response was after about 6 to 8 weeks on study.

Then, response was considered to be continuing until you either had documented progression or you were lost to follow-up, the patient was lost to follow-up while still in response. This happened very seldom.

So, if a patient stopped being treated in here because of neuropathy, that did not matter. We continued gathering the CTs. Now, the schedule for CTs was originally every 8 weeks in the

protocol. We then amended it after about half of the patients had been enrolled to say after the first evidence of response, please get another set of CTs 4 weeks later, and then we are back to the every 8-week schedule.

DR. WILSON: So, I think it is fair to say that with a median of approximately 3 months, that many of these patients, if you were only obtaining scans every 8 weeks, the true median, had you been doing it on a more frequent basis, might have even been shorter?

MS. MANCINI: I will ask Dr. Cabanillas to comment on that in a moment. Many of the progressions were declared based on the clinical evidence. We had physical examinations, clinical visits every 2 weeks on the study.

DR. CABANILLAS: I would like to also show the Kaplan-Meier curve, Slide No. 270, please, because it is true that many of these responses were short, but as you will see from this slide, those are these patients that relapse early, but there are a number of patients that actually did

enjoy longer disease-free survival.

This is an IRP review. The IRP met at one point, and they don't keep on meeting to update the curve, so we don't have obviously a prolonged duration here, but we do have some patients, and I mentioned a few of them, and we have some that are here today that will also show you that they were actually some of these patients that had very long remissions.

So, it is true, that if you look at these patients that they had short remissions, but we also have to keep in mind the other side of the coin, which are the ones that did have long remissions.

The other point that I would like to make is that, as you know, Wyndam, there has been some controversy regarding the use of CT scans in lymphoma, and there is one study in which 39 patients were evaluated with the CT scans to determine whether they relapse or not. Actually, those were 39 patients who relapsed, I am sorry, those were 39 patients who relapsed, and only 2 of

them were picked up by CTs, by routine CTs.

Most of them were picked up because the patients developed symptoms or the LDH went up, or physical examination showed the abnormality, so even though intuitively, you might think that, yes, doing more frequency, these might have detected earlier relapses, I think that in real life, that is not really what is happening.

DR. PAZDUR: Fernando, could you put that slide back up, and tell us how many patients were censored there or still on study?

MS. MANCINI: Yes, that's Slide 270. This is the IRP analysis, and the circles are the censored data. In the IRP analysis, there were two-thirds of the patients as Maitreyee presented.

DR. PAZDUR: Two-thirds were censored.

MS. MANCINI: In this analysis, yes.

DR. PAZDUR: And did the rest progress?

MS. MANCINI: Yes, or continued.

DR. PAZDUR: How many continued?

MS. MANCINI: I am sorry, I am saying it the wrong way, excuse me. Censored is continuing,

the response is continuing at the last time that they were evaluated. When they are censored, there is no data for the patient beyond that point, but they have not been called a failure, they have not been called a progression.

DR. WILLIAMS: But many of those patients will never get another evaluation, right?

MS. MANCINI: That's correct.

DR. WILLIAMS: How many patients actually still are on study and could contribute to ongoing data versus how many are censored because of neuropathy, or they went off study, et cetera?

MS. MANCINI: This is an Independent Review Panel determination. The study is over, so there is no further data coming, but I can show you Slide 275, please. Because we have continued to follow, as part of the survival update, those patients who were still in response, and the reason the other curve had this line here was because of the censoring, we all understand that.

This is now the investigator duration of response, which again the median was not different,

but you do see that there were some patients that had longer durations.

DR. MARTINO: Dr. Perry.

DR. PERRY: This is for the sponsor. I am just sort of a country doctor who doesn't do a lot of lymphomas, but it seems to me that this turbo vincristine is not going to be fairly compared against a lot of other agents.

What happens if you go back and look at vincristine itself, what kinds of responses do we see in duration of responses if we go back to, say, how in 1972, I think that is the kind of comparison I would like to see. I think you are making a bad comparison for yourself if you are not going back to the original, because I can't imagine this drug is going to have, from what you presented, is going to have much of an impact as a single agent. It is going to be used in combination to replace vincristine.

So, if that is the case, does it do compared to vincristine?

MS. MANCINI: That is very difficult to

do. The vincristine is a very old drug and the literature from that time does not provide us the data we would need to be comparing durations of response.

Even the types of disease, as it is described back in the 1960s, it is impossible to compare to some of that old work. We have been able to compare on a safety basis better, but not very well on the efficacy basis.

We do have perspective, there was work done in the early days by Dr. Don Jackson with infusional vincristine, attempting to achieve what we achieve with the liposome in terms of the continued exposure, and we certainly can compare our information to that. I will ask Dr. Cabanillas to do that. There is no good efficacy comparison, unfortunately.

DR. CABANILLAS: While you find it, let me introduce a topic. Dr. Jackson made a study with infusion of vincristine as a single agent a long time ago, and he had some interesting findings.

He treated 25 patients with a variety of

NHL types. He used a 5-day continuous infusion at 0.25/m 2 after a bolus of 0.5, and he repeated the courses every 3 weeks.

The interesting thing is that he had 48 percent neurotoxicity, and the GI toxicity was the most serious toxicity, which included severe ileus. Hematological toxicity was minimal. Of course, during those days, there were not too many agents that you could offer to the patients, so many of these patients were actually being treated at first relapse, so it is not strictly comparable to what we are showing. We are showing really 4th and 5th line treatment.

He showed that there was an ability to deliver high cumulative dose of vincristine with the low GI toxicity with VSLI. That's his impression when we showed him our data, and he thought that the absence of ileus was highly unusual because that was a very common complication when he used the high dose infusion of vincristine.

Also, the ability to proceed to transplant following monotherapy, he found also to be highly

unusual.

Now, I think that is a very important question.

DR. PERRY: Slide 805, response rate.

DR. CABANILLAS: That is the problem. The response rate, it's a mixture of different histologies treated at first relapse, so it is really impossible to compare with ours.

Do you remember exactly what the response rate was?

MS. MANCINI: It is not literature that we can compare on efficacy other than we did meet with him to get his own impressions, and that is what we are sharing with you here.

I think the best data that we can share, that is the only data that we can share that is head to head comparison, is actually preclinical data. There is no efficacy publications of singe-agent vincristine. It is always used in combination.

If you would like we can show you some preclinical data.

DR. MARTINO: Is there someone in the Committee who actually has the answer to that question?

DR. WILSON: Actually, they are right that it was a mixed group, but keep in mind, at least for the intent-to-treat study here, it was a mixed group, as well. I believe one-quarter of the patients were not felt to have a de novo large cell or a transformed large cell.

If I recall that paper right, the response rate was around 30 percent, and I also want to say that one of the things that he did in that paper was to take patients who he considered to be a failure using bolus vincristine, and I just want to reiterate that I think the patient population in the study was very, very different from what we are dealing with here, but I do think that it did give the first hint early on that perhaps changing exposure schedule may give you a better therapy.

DR. MARTINO: Thank you.

DR. CHESON: We just got the Jackson abstract up.

MS. MANCINI: Thank you.

DR. CHESON: Nodular PL, diffuse histiocytic, duration of response up to 16.4 months, median 4.4. Complete response and histiocytic lymphoma and partial in 8 patients, so 9 out of 25 responded, 36 percent. You said 30, I was over saying 40, so 40 percent response rate lasting a median of 4.4 months with a variety of histologies including diffuse large B-cell, diffuse mixed, diffuse everything.

MS. MANCINI: Did they comment on other significant predictors of the number of prior therapies they have had or refractoriness of the disease?

DR. CHESON: This is just the abstract. All had received prior vincristine by conventional bolus. It doesn't say.

MS. MANCINI: That is the difficulty we have with interpreting the data. In our own analyses, these were very significant predictors of outcome, and therefore, it is very hard, as we have all seen, it is very hard to compare to the

literature.

DR. CHESON: But even your best patient group, it was only around the same response rate.

DR. CABANILLAS: It was 46 percent response rate on patients treated after second relapse. These are not first relapse patients. The minimum acceptable for this study, the VSLI, was that the patient had to have at least 2 relapses, so these are not really comparable, but the 46 percent, I think actually compares favorably with anything in the literature including Rituxan.

I think that it is important to point out that vincristine is a cell-cycle activation as you all know, and that is why, even after long exposure to vincristine, it might actually result in a higher response rate.

I think that might also explain why Jackson's results are somewhat better than you would expect, and also the fact that some patients were refractory to vincristine, responded to it, and I think that is what we are seeing also. We had some patients that were clearly refractory to

CHOP, and yet they were able to go on to respond even, some even with a complete remission.

DR. MARTINO: Thank you.

Dr. Brawley, do you still have a question?

DR. BRAWLEY: Yes. Again, at risk of being politically incorrect, and without making any allegations against anyone, would the academic presenters be willing to disclose any potential interest they might have in the company including such things as stock ownership, honoraria, or are they salaried by the company?

I am also interested in did the company salary the investigators at the various sites that put people onto the trial.

DR. CABANILLAS: I think that is actually a very politically correct question. Let me explain my interest in the company. When we did the Phase IIa study at M.D. Anderson, Dr. Ceres [ph] was the PI on that study, and he realized that being able to give the drug every 2 weeks at a high dose constituted a novel way of delivery vincristine, so in the name, representing M.D.

Anderson, he applied for a use patent, which has been issued to M.D. Anderson, and which we will also share with M.D. Anderson. I am not a salaried employee of the company, and, of course, I do charge consulting fees.

MS. MANCINI: None of the investigators on our trials are salaried.

DR. CHESON: You don't know about stock ownership, I suspect.

DR. CABANILLAS: I don't have any stocks, and I don't have any stock options either.

MS. MANCINI: Inex is a small pharmaceutical company in Canada. We are not traded in the U.S. We are on the Canadian stock exchange, Toronto stock exchange, and people are free to buy stock if they wish. We do not track their participation in the Canadian market.

DR. PAZDUR: I would just like to stipulate that submitted to the IND was the financial disclosure, which did list Dr. Ceres and Dr. Cabanillas, I think it was that the patent was going to be allowed, or something like this, plus

the royalties to be paid to M.D. Anderson.

We did go back and check the informed consent at M.D. Anderson, and it did, in our estimation, provide adequate explanation and adequate patient protection to the patients that were enrolled on the study.

DR. MARTINO: Thank you.

Dr. Reaman.

DR. REAMAN: I just have a question about the retrospective histopathology review. You cite the incidence of ineligible patients, about 19 or 20 percent, to be similar to previously reported studies, some of which were actually done 12, 20 years ago, none of which looked to demonstrate efficacy of a single agent in a specific disease.

Can you explain why the retrospective review was performed and why those ineligible patients were then included?

MS. MANCINI: Yes, I will begin briefly and then I would like to ask Dr. Gascoyne to comment on what is the current finding in lymphoma.

Just to begin, why did we include a

retrospective review. We understood that getting a correct histologic diagnosis in clinical practice, in routine clinical practice, it is difficult to get right, and Dr. Gascoyne will speak to that more eloquently than I can.

Therefore, we built into the protocol that there would be a retrospective review. It was not the basis for allowing a patient to be enrolled because we could not get a real-time pathology assessment. This was an international trial. So, we use the site pathology to allow patients to be enrolled, and they were allowed to be treated. Even if they were subsequently determined to be histologically ineligible, we did not withhold treatment for them.

I should also comment that all of the patients were considered to be histologically eligible by the treating sites, so what we are dealing with here is the current situation lymphoma, and I would like to ask Dr. Gascoyne to comment further.

DR. GASCOYNE: The first comment I would

make is I am slightly biased, because as a pathologist, and someone who has been doing lymphoma for 20 years exclusively, I personally think it all starts and end there with an accurate diagnosis.

We spent the last 20 years trying to determine that lymphoma is not one disease, it is about 35 diseases, and I think to continue to mix apples and oranges in any kind of trial is a mistake. So, I quite frankly applaud them for asking us to be involved in a study where we review the pathology.

I think the issue of path exclusion speaks to an issue that is even bigger than this trial, and it is a problem with what is going on out there in the community and the acceptance of expertise.

So, I think all of these things need to be looked at. We excluded cases that we felt were low-grade lymphoma, and I could sit up here and go through the reasons why that occurs. I noticed that the FDA was not willing to accept 7 cases that we have looked at very seriously, and I will tell

you that in current trials, I am currently, and have been for 5 years, the co-chair of the Eastern Cooperative Oncology Group from the point of view of lymphoma although I am a Canadian who lives on the West Coast, which is a bit of a funny mix.

The kind of criteria we apply to those ongoing current types of trials are what we applied here. So, I don't think we were any more or less rigorous as we applied those criteria. The cases that we accepted were based on FNAs and needle core biopsies, follow-up biopsies, but you have to remember that those were not diagnostic biopsies in patients with newly diagnosed lymphoma.

We are talking about patients in a multiply relapse setting. To even get a few cells at the end of a fine need aspirate is lucky. We use that information in combination with growth fraction and other types of ancillary studies in order to arrive at a diagnosis.

Do I have confidence in those 7 patients that you decided to exclude, that we left in, the answer is yes, I would confidently stand here or

anywhere else and say that those patients deserved to be in the trial, and to have been included as being consistent with the aggressive histology lymphoma.

DR. WILLIAMS: Can I just ask why you used the word "probably" then instead of "definitely?"

DR. GASCOYNE: Because in studies like that, we don't have architecture basically, so you are talking about cytological detail, and when we had to combine that, a few of those cases, if you go back and look on the additional data, we went back and were able to actually retrieve the original pathology.

So, they didn't look like discordant even based on an aspirate, and thus we re-reviewed some of those diagnoses. I remember one of the cases in particular we had said it's a needle, it's kind of crushed, it is hard to interpret, but it was accompanied by a growth fraction of 80 percent. When we got the older pathology and there was primary mediastinal large B cell lymphoma, we were willing to accept that, in fact, that represented

aggressive disease.

That is not what I would call out of line with current practice. In fact, those kind of techniques are being used much more frequently here in the United States than they are in the country that I come from.

DR. MARTINO: Dr. Cheson.

DR. CHESON: Well, now that I am on, I have got two questions, one for Randy. So, you used other than morphology and growth fraction, I presume. You immunophenotyping and all that stuff, as well.

DR. GASCOYNE: In the actual diagnoses, we had information that came from the hospital of origin, so what we were trying to determine was their eligibility as aggressive lymphoma, so in many of the instances, of course, we had phenotype available, either flow cytometric or paraffin section immunostains.

But the particular example I was citing, we actually were aware that there was a growth fraction, and that was provided in terms of a Ki-67

stain. That was labeling at 80 percent. That is not the labeling presented that one sees in so-called indolent lymphoma, and I think most people in practice nowadays would accept that as a reasonable conclusion based on that material, that that, in fact, was aggressive lymphoma.

But the ability or the desire here to use fine needle aspiration and needle core biopsies, as you know, is a serious matter, but you have to keep it in the context that we are not dealing with diagnostic biopsies, where it also is used far too frequently.

DR. CHESON: My other question is more for the sponsor, and I guess I can guess what the answer is. Do you have any information on whether these patients were treated with other things after liposomal vincristine and what the responses were to subsequent therapies, and what these other therapies were?

MS. MANCINI: No, unfortunately, once they were off study, we don't have the downstream therapy. We do know of those 6 cases that went on

to stem cell transplant, we do know the outcome for those patients, and that is what Dr. Cabanillas has presented.

We collected that data as part of the survival update, but we do not have all the other therapies.

DR. MARTINO: Dr. Bishop.

DR. BISHOP: Related to what your last statement was, the stem cell transplant patients, and going back to your time to progression slide, am I correct that there are only 5 patients on that slide who were greater than 4 months time to progression?

MS. MANCINI: No, no, there is more than 5.

DR. BISHOP: Those were just the censored.

MS. MANCINI: Those were censored, yes, there is definitely more. The line was flat at about 50 percent. We were right at the median there.

DR. BISHOP: So, you are estimating about 10 patients?

MS. MANCINI: Fifteen.

DR. BISHOP: Among those, does that include the transplant patients?

MS. MANCINI: Transplant patients would have been censored in that analysis at the time they went to transplant.

DR. MARTINO: Dr. Wilson.

DR. WILSON: This is a question for both Randy, as well as the sponsor. It is a little unusual, in my experience, to do an intent-to-treat for a Phase II study. A number of cooperative group studies were shown in which it was shown that only 80 percent of the patients were eligible based on histology, and yet when those Phase II studies are usually published, those 20 percent are actually not included, so I wasn't quite sure why that was done like that.

But specifically, Randy, I, too, feel that we shouldn't be fixing apples and oranges, and I think that the response to an agent like this, in a low grade lymphoma, is going to be very different from a de novo large cell.

I guess my question is, number one, do you really think it is fair to be mixing de novo large cell with those patients who have histologically transformed low grade, both, number one, because the biology of the histologically transformed is very, very different.

Even though it may look like a high grade lymphoma, it certainly may not clinically act like one, and finally, you have some nodes that are low grade and some that are high grade, so it is very difficult to know if it's a low grade node shrinking or the high grade.

DR. GASCOYNE: I can address the last part of the question. I mean you certainly know yourself that when you are treating patients and one site blows up, it wouldn't be uncommon for you to do a needle aspirate or a needle core at that site, and make a determination that that previous lymphoma has, in fact, transformed. We don't biopsy all the sites and all the patients.

From the old data from the seventies, from the stage and laparotomy data that came out of

Stanford and other centers, we know that there are discordant histologies. I would agree with you those biologies are different.

I wasn't involved in the design of that part of the study. I was simply asked to apply vigorous criteria to a histologic central path review and deem which patients were eligible based on the criteria.

I think we applied that in a uniform way, the same way I do for ECOG and the same way I do for British Columbia, and so I don't have any problem, and I am feeling comfortable about those data.

DR. WILSON: So when you did score somebody as a histologically transformed low grade, they would have been essentially what we now term as follicular Grade 3B?

DR. GASCOYNE: No. We tried to determine in any setting in which we had tissue, of course, we wanted to know architecture, so we wouldn't have accepted that as transformation, and specifically that is in the protocol that actually Grade 3B

would not have been included.

So, these are patients that we had to have evidence that they were diffuse large B. It is quite true that there were some fine needle aspirates and some needle cores in there, in which we attempt in some situations to actually do some additional immunostains in the way of looking at FTCs, et cetera, to know whether there is any underlying follicular elements.

So, I am happy that those cases that we looked at, particularly in regards to looking at if they are only cytologies, looking a proliferation rate, that I don't think Grade 3B is associated with an 80 percent proliferation site, so I think we can feel relatively comfortable that those were probably cases of diffuse large B cell lymphoma that represented transformations.

DR. CABANILLAS: I want to make a comment regarding your question also, Wyndam, because you are absolutely right, that the low grade or indolent lymphomas respond differently to VSLI, but the way they respond differently is they respond

less well because when we did the Phase IIa study at M.D. Anderson, we found out rapidly that the low grades were not really responding well, and that is the reason why the next trial was done exclusively with aggressive lymphomas.

It makes sense from a scientific standpoint you would expect that they would respond lower, because their S phase is lower, so they are turning over less rapidly and exposing them to a long duration of concentration of VSLI might not really make any difference.

DR. WILSON: So, that would be consistent with the Taxol data, as well, where it is also hitting the microtubules where the higher grades seem to do better with it.

MS. MANCINI: I would like to add just to clarify, you asked a question about the intent-to-treat analysis and why we presented that, and if I could go to Slide 429, please. I would like to also, while we are pulling up that slide, comment that we did look specifically in response to a question from FDA at the discordant lymphoma

cases where they had a mixed presentation to see if we could conclude which parts, which types of histologies were responding, and it was always clear-cut. The patient either didn't respond and therefore it was not an issue, or it was such a dramatic response that all of the disease was responding consistently.

This slide shows you, on the far right, was the intent-to-treat analysis that was in the main presentation. This now shows the per-protocol population, and the ORR is the 27 percent, which is very similar to the ITT.

Now, if we talk about those patients who were histologically ineligible, based on Randy's review, it was 23 cases, the response rate was still the same in this trial. People who were excluded from our per-protocol population for other reasons had a slightly lower response rate.

Open Public Hearing

DR. MARTINO: Are there other questions? If not, we will move on to the next part of the program, which is the open public hearing. Before

we do that, I need to read a statement.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of this Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the 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 had with the sponsor, with 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 today's meeting.

Likewise, the FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationship. If you choose not to address this issue of

financial relationship at the beginning of your statement, it will not preclude you from speaking.

Ms. Clifford will now announce the ladies and gentlemen who have asked to speak.

MS. CLIFFORD: When I call your name, if you would please approach the microphone in the back in the audience, please.

Our first speaker is Helen Smith.

MS. SMITH: Good afternoon. My name is Helen Smith from Greenbrae, California near San Francisco.

I would like to thank you for the opportunity to speak at this meeting. I would also like to thank Inex Pharmaceuticals for covering my costs to attend this meeting.

I am a patient of Dr. Jennifer Lucas, Merin [ph] Oncology where I am being followed for my non-Hodgkin's lymphoma. I was diagnosed with non-Hodgkin's lymphoma in 1999. I remember it was in June when I first noticed I became tired very easily. I was usually very active.

After my diagnosis in December '99, I

participated in a cancer vaccine that was being conducted by Dr. Levy at Stanford University Medical Institute. They took one of my lymph nodes to make the vaccine and then I started a course of CHOP.

At the end of CHOP, I was given the vaccine. My cancer did not completely go away. Later, I had a second round of CHOP. The CHOP did not make me sick, but I did lose my hair and wore a wig for a while and felt very tired.

They also gave me medicine to prevent my blood count from going too low. My CT scans indicated that I had a lymphoma in my chest and in October of 2001, I agreed to begin the trial with VSLI.

I was treated with VSLI during the first part of 2002. I had 8 cycles of treatment and during my first treatment I had a fever, but after that I was fine for the later injections. I did get some tingling in my fingers and numbness in my feet, and had difficulty with buttons.

Today, two and a half years later, I am

functioning quite well, although I do get tired easily. I have not had any more cancer treatment. I have not missed any of my tenpin bowling sessions, and I use a heavy 14-pound ball, so my fingers are fine. My only problem is my bowling average has fallen from 150 to 121.

Thank you.

DR. MARTINO: Thank you.

Next, please.

MS. CLIFFORD: Our next speaker is Virginia McCormick.

MS. McCORMICK: Good afternoon. My name is Virginia McCormick and I am from Sparta, Tennessee, and I think you for the opportunity to speak at this meeting today. I thank Inex Pharmaceuticals for covering my costs to attend this meeting and for all the help that they have given me.

I am a patient of Dr. Deng [ph] at the M.D. Anderson Cancer Center in Houston, Texas, where I am followed for my non-Hodgkin's lymphoma.

Let me begin by telling you that I was

diagnosed with non-Hodgkin's lymphoma in 1999. The first year I took CHOP. The chemo made me weak and nauseous at time, and, of course, I lost my hair. This took several months because most of the time my white cells would get too low and they couldn't do the chemo, and I would have to go back home and wait a week and then go back.

When I finally finished the treatment, this was about six months later, the lymphoma had returned, and I took other treatment, such as Rituskin [ph], and this didn't work. During this time, I had several bone marrow biopsies to see if it had spread to my bones, and I was thankful that it had not.

At this point, they wanted to do a bone marrow stem cell transplant using my own cells, and my stem cells were harvested and frozen, and I went into the hospital, and for the first week I took high-dose chemo and then they gave me my stem cells back. Again, I was very weak and sick at times.

I was in the hospital for over a month and within a few months after this, the lymphoma was

back again. I asked my doctors if there was anything else that could be done there. I was told that it would be too dangerous to do further treatment because it could do some damage to my main organs or possibly death.

At this time, my husband and I decided to go to M.D. Anderson Cancer Center in Houston, Texas. We just refused to accept the alternative. At M.D. Anderson, my doctor, Richard Champlin [ph] told me I could do a bone marrow transplant using a donor.

So, I asked what my options were, and he told me that they were having 30 percent survival rate. So, I told him this was better than what I had, because I didn't have any.

So, out of 6 of the blood donors, half of them were a perfect match. So, Dr. Champlin introduced me to Dr. Deng, who gave me a new treatment, an anticancer drug called liposomal vincristine or VSLI. This helped me a great deal and I was able to receive my bone marrow transplant.

The VSLI was an easy treatment for me to take. I went into the hospital for one-hour treatments, which they would watch me for a couple hours afterwards, and then I could leave the hospital.

The VSLI made my fingertips numb and the bottom of my feet were numb, but my hands are okay now, and my feel are getting better. The VSLI, with it, I didn't feel weak or sick or anything, and my hair didn't come out. Since this treatment, I feel normal again, I feel better than I have in 6 years.

I can go to church, I sing in the choir. I do my own shopping, and I play with my first little grandson, who is 3 years old, and which I might not have been able to do if it had not been for VSLI.

When I was asked by Dr. Deng if I would be interested in going to Washington, D.C. to speak at this meeting, I thought, wow, this is an opportunity of a lifetime to help so many people, like it has helped me.

So, I am a living example that VSLI does work and I just praise God that I have been cancer-free for over two and a half years.

Thank you.

DR. MARTINO: Thank you.

Our next speaker, please.

MS. CLIFFORD: Barbara Cruse.

MS. CRUSE: Hi. My name is Barbara Cruse and I live in Sugarland, Texas, outside of Houston.

I would like to thank Inex for inviting me to speak at this meeting, and they have covered our expenses to be able to come.

My cancer journey began in June of 1997 when I found a lump. I was diagnosed with Stage I large B cell aggressive lymphoma. I had surgery to remove the tumor, then 6 rounds of CHOP and 25 treatments of radiation.

On Christmas Eve 1999, my doctor told me that I had a recurrence of the lymphoma. in January of 2000, I began treatment at M.D. Anderson Hospital for the lymphoma preparing for a bone marrow stem cell transplant using my own stem

cells.

I received 3 rounds of chemotherapy preparing to rid my body of the lymphoma. I was admitted into the hospital in May for 7 days of intense chemotherapy to prepare for my transplant. I spent 5 and a half weeks in the hospital.

Fifteen months later I had a relapse again. Dr. Fayad, my lymphoma doctor, at M.D. Anderson was researching an exciting new trial, which was the VSLI Phase II clinical trial. I was accepted into the trial and began treatment in September.

The treatments were done in an infusion suite at the hospital and lasted 4 hours per session. I had no side effects during the first 3 treatments. The good news, after 4 treatments, I was restaged and I had a 96 percent reduction of my tumor. The bad news, severe neuropathy in my hands and feet.

In November I had 2 more treatments preparing me for my second bone marrow stem cell transplant using my brother's stem cells. I was

admitted to the hospital on December 13th and received 3 days of chemo and then had my transplant. I did so well with this transplant that in two and a half weeks, I was released from the hospital.

As I mentioned earlier, the down side of the VSLI is the neuropathy. I was not able to drive for a year and I needed help with daily activities. I had an EMG to determine how much nerve damage I had and to see if there was anything that could be done to help me.

There is no drug that works for neuropathy. I was told that all the previous chemotherapy treatments that I had had, had contributed to my neuropathy.

Finally, in March of this year, I began going to a doctor and receiving acupuncture of the neuropathy, which I have seen remarkable improvement. This summer when I had my checkup with Dr. DeLema, my bone marrow doctor, we talked about my treatment options and if I had it to do over, would I choose the VSLI, and I told him

honestly yes, I would choose it even with the neuropathy.

In my cancer journey, I am one of the lucky patients who survived with the help of this very important drug VSLI. Thank you for this opportunity to share my story.

DR. MARTINO: Thank you.

Are there any final questions from the panel to either the FDA or the sponsor?

Seeing none, I would like to ask Dr. Pazdur, do you mind if I give the group a 5-minute break only, because Dr. Martino needs one? Thank you. It is 5 minutes, however, ladies and gentlemen.

[Break.]

Committee Discussion

DR. MARTINO: The final portion of this meeting is the discussion of the Committee itself, and that needs to be focused to questions that have been posed to the Committee from the FDA that relates to this application.

We have four questions, each of which will

require a vote at the end of the discussion that pertains to the specific question. When we vote, I will ask each of you to state your name as well as your vote each time, please.

The first question I will read to you.

Review of the oncology literature suggests that there are single agents and multiple agent therapies capable of producing substantial response rates, including reasonable CR rates, in relapsed, aggressive non-Hodgkin's lymphoma.

Does the Committee believe that these therapies constitute available therapy for relapsed, aggressive non-Hodgkin's lymphoma previously treated with at least two combination chemotherapy regimens?

Dr. Cheson, I am going to ask you actually if you would speak to this issue. Are there prior therapies, either single-agent or multiple-agent, that you feel would be an alternative?

DR. CHESON: As you know and as was shown, there are very few drugs that have been recently approved for the treatment of lymphoma, but there

are a whole bunch of other drugs out there, which are used regularly in a variety of histologies of lymphoma, some which have been around for a long time and others which are relatively new.

I think that there are clearly a variety of other single agent--it depends on whether you go along with the company's date or the Agency's assessment of the data, but there are quite a number of other drugs out there that can give you response rates in the range of 30 percent or so lasting three or so months, be it etoposide, be it gallium nitrate, be it a variety of other drugs.

There are some new drugs out there. Even the radioimmunotherapeutics, since there are two, I won't go and mention any names, there is only one that has been used for aggressive lymphoma, and that has been associated with a 43 percent response rate in patients who have failed a median of two to three prior regimens.

So, yes, there are a number of other agents out there with different safety profiles, some which appear to be, you know, like the

radioimmunotherapeutics have more marrow suppression, don't have neuropathy, so they are limited, but there are other drugs out there, and it is quite a list of them that can give you 20 to 30 percent response rates.

DR. MARTINO: Are there other thoughts on this issue? Are there alternative therapies for these patients, and might those alternatives constitute a control against which a randomized trial might be done?

Dr. Wilson, do you want to speak to that, please.

DR. WILSON: Well, I guess I would just reiterate what Bruce said, that is that there really is a list of agents out there, both in this range. I think it important to note that the population of patients has a huge impact.

I think we all know that. I do laud the group for having broken the patients down, but as it stands, the response rate of this drug seems very much in the middle of the pack for many other agents.

In terms of what would you compare this to, I think there are numbers of agents you could, and I guess I would like to think about that before commenting on how to do a comparative study.

DR. MARTINO: Do you feel that, in fact, if you were asked to choose a comparator, that you could come up with one? I am not asking you to tell me your choice, I simply want an answer to whether you think that you could.

DR. WILSON: Well, if you wanted to come up with a single agent, I think the answer is yes. I think that, as Bruce points out, there are agents with different toxicity profiles. I think one drug that comes to mind that one could think about would be etoposide.

The down side to that is that a hematologic toxicity can be limiting for it, but I think that if you didn't take tremendously pretreated patients, that I don't think hematologic toxicity would be limiting for it, and I think that that would weigh off against the neurological toxicity associated with a Vinca alkaloid.

DR. MARTINO: Dr. Pazdur, do you want to comment?

DR. PAZDUR: One does not have to specify a single drug here, and, in fact, as I stated in my opening comments, there have been situations where pharmaceutical sponsors have had varying combinations or various drugs, and in a randomized study, you could randomize to a treatment arm, might have several treatments, kind of a treatment de jure, as long as there were agreement by the investigators that that was something that they would consider a reliable and reputable treatment.

The stipulation is you would have to win against that treatment arm.

DR. MARTINO: Are there other comments to this question? If not, we will now turn to the vote, and we will start with Bukowski on my right, please. Please state your name and your vote, the question being: Do we believe that there are alternatives for this patient population?

DR. BUKOWSKI: So, the name is Bukowski, and the answer is yes.

DR. CHESON: The answer is yes.

DR. BRAWLEY: Yes.

DR. REAMAN: Yes.

DR. MARTINO: Yes.

DR. MORTIMER: Yes.

DR. PERRY: Yes.

DR. HUSSAIN: Yes.

MS. HAYLOCK: Yes.

DR. GEORGE: Yes.

MS. KRIVACIC: Yes with a stipulation that I don't know if there is potent, if you will, or I guess show what has been shown here today, so there is a lot of conflicting data between the FDA's information and the sponsor's, so I am a bit conflicted with this question, as well.

DR. BISHOP: Yes, with the stipulation I can't think of an outstanding agent for patients with a lack of hematologic reserve.

DR. WILSON: Yes.

DR. MARTINO: Our total is a unanimous yes, although we have two members who have some uncertainties.

The second question is: Previously, the Agency has stated that the primary relevant endpoint for aggressive non-Hodgkin's lymphoma were rate of durable complete response and survival. Partial responses were not considered predictive of clinical benefit.

In this setting of relapsed, aggressive non-Hodgkin's lymphoma, does the Committee agree that durable CR should generally be the primary endpoint for approval?

So, the issue again is CR's versus PR's, or lesser degrees of response.

I would like to hear some comments on this question, please. Dr. Perry.

DR. PERRY: I think part of the problem here is the definition of complete response. There are complete responses and there are complete responses. It depends on how far you want to go. Do you do a warm autopsy to biopsy everything within the abdomen or do you simply say a CT scan is evidence enough, or a PET scan or a gallium scan, and what number of biopsies and how many PCRs

do you do.

Just saying "complete response" in these days doesn't mean as much as it used to when we had more primitive techniques and were smarter. We knew much more than we do now.

So, I think there are partial responses that are probably now the equivalent of old complete responses, and I think some of them are helpful.

DR. WILSON: I do think that PRs are a relevant endpoint, but I think a PR in the absence of a duration means little in a disease like this. So, I know the question is written based on previous ways in which this data was looked at, but I think that a PR that lasts for a reasonable length of time is a reasonable endpoint, but PR alone, I do not.

DR. MARTINO: I share that feeling completely. I don't think PR, in and of its own, I mean a PR can be extremely fleeting and doesn't always correlate with anything related to the patient's behavior or the patient's well being. It

is often an x-ray event and primarily makes the doctor feel good to be able to talk into a room to say you have a response, and then not have to do much more than that.

So, I completely agree that the issue of durability and/or reduction of symptoms probably are much more meaningful events.

Dr. Cheson.

DR. CHESON: As we discussed in the response criteria paper, PRs in the setting of relapsed and refractory disease are interesting to identify drugs with some activity to pursue further, but in and of themselves, I agree with you that unless they have some durability, they are rather meaningless, and I guess Dr. Perry has stepped out, but not only are all CR's not all CR's, but with the advent of PET technology, for example, a lot of PR's turn out to be CR's, so we are getting more sensitive measures of this, but a true PR in the relapsed, refractory setting generally bodes ill, and probably wouldn't even be transplanted by many centers, these with a good

conscience.

DR. MARTINO: Dr. Pazdur, did you want to comment?

DR. PAZDUR: I just wanted to reiterate something that Bruce said. Here again, we are not talking about drug screening. We are talking about drug approval, and these are not necessarily the same thing or they should not be the same thing obviously.

So, there has to be a different level that one is saying that they are going to accept between something that is of interest to take to another step in another development, and then saying, well, this drug is ready for prime time here for general use with all of the ramifications that that has associated with it.

DR. MARTINO: For me, this is really a problem that I have with this entire accelerated approval process. I have sat on this committee for about three years now, and it almost occurs to me that we are looking for what is the least amount of data to be convincing, and I think that is the

wrong approach, but that is what I see that we do, especially with accelerated approval, is what is the least amount that you can show me, to which I will then give you a reward for that.

I actually think that as a medical community, we have to rethink what our objectives are and what our purpose are. They should be much grander than that, and I think you are either trying to shut me up or you want to say something.

DR. PAZDUR: The only thing I have to say, Silvana, is go, girl, go.

[Laughter.]

DR. MARTINO: But in all--

DR. PAZDUR: Let me finish my comment, though. That was just starting there.

When we have a meeting, such as this, we have a litany of sponsors that come in and pose the question to us. What is the lowest response rate that you will take? What is the fewest number of patients that you will take? And, in fact, we actually have a euphemism regarding these meetings, and it is called the "How long can you go?"

I think that that really represents a clarification, and this is one of the reasons why we have been discussing this and emphasizing the accelerated approval commitments that these patients have.

The purpose of accelerated approval was not accelerated drug company profits. It was accelerated access to people that had desperate illnesses, that needed the therapies, and we were allowing basically a surrogate to be used to get these therapies out early to these patients that needed it.

It wasn't a license to do less, less, less, and less to a point now that we may be getting companies that are coming in, well, what is the lowest. It shouldn't be what is the lowest. It is what is a sufficient amount to give patients and physicians a real understanding of what their drug will do.

Granted, we realize that there is a need to get these drugs out, but we also have to have a data package that we can understand and will make

labeling a strong process here. That is why our commitment really is to get these trials ongoing, these confirmatory trials, so it is very important to us.

DR. MARTINO: The fear that I personally have, as I have treated patients over the past 25 years, is that we, as a medical community, and that "we" does include the pharmaceutical industry, really in my observation have aimed for a lower and lower behavior of drug, and in that process, if we keep rewarding such behavior, we will see more and more of it.

There is nothing new in the universe. That is the way life works. So, we do have to separate what our responsibilities are and to whom are these responsibilities.

Dr. Bukowski.

DR. BUKOWSKI: When I think about this, I think about the issue of unmet need as the main factor that sort of leads me to think about how and whether an agent should be considered for approval in a particular area, and I think that to be

somewhat foremost in our minds.

I mean it may not be necessarily the issue of how low can you go, but is there anything else available in the area that can be utilized, and I think that is very, very important, because clearly, there are many situations where there are unmet needs, where new agents may well have a very minimal or modest response rate or modest activity, but still these may be useful, and I think the issue is, is getting those agents out to patients in a very timely basis, with subsequently then doing the appropriate studies to demonstrate the clinical benefit associated with the agent.

DR. PAZDUR: Ron, that is specifically why have the better than available therapy or an improvement, or a situation where therapies do not exist, but it has to be a real clinical situation, it cannot be a contrived situation.

A couple of years ago we had a company that wanted to develop a drug for leukemic patients on a respirator, and the reason why patients were on the respirator was because they received the

drug on the NDA, which was kind of ridiculous.

So, it has to be a real situation, a really clinically relevant situation, not a contrived situation.

DR. MARTINO: Dr. Brawley.

DR. BRAWLEY: Dr. Martino and Dr. Pazdur are to be praised for their speaking of truth this afternoon. I just want to add one thing. When we teach our graduate students the development of drugs, we teach them things about like how one can look at data and actually think there is benefit, but when one probes further, one finds that there is not a benefit to that drug, there is actually a net harm to the drug, and this is actually frequently the reason why we need randomized clinical trials.

I personally have been burned by clinical studies that ultimately showed that beta carotene increased the risk of lung cancer in smokers, and did not decrease it, and I was one of the people who said it's just a vitamin, how can it be harmful. There are numerous examples in the

medical literature.

Now, we have heard today from some patients who told us about some significant toxicities that they are living with, and now we have to make a decision is this drug beneficial given those significant toxicities, and I think we have not heard about some significant toxicities.

I will finish by saying I am very worried, while I look at the FDA data versus the company's data, I am very worried, not that there were individuals who called responses because they wanted to make money, I am worried that there are doctors out there who saw patients who called responses because they really wanted to see responses in their patient. They were hoping against all hope that they could do best for their patient, but we have to remember there are some significant discrepancies in data here.

DR. WILSON: We are looking at No. 2, and we are asking is a PR of a certain length a reasonable endpoint, but I think we should all recognize that this is a unique circumstance. This

drug is known to be active. This is a drug that is active, and the activity level is well within that which has been seen before when it has been given as either a single agent or as a continuous infusion.

So, I think the bar is perhaps a little bit even different than is it active. I think the question is, is it active in a safer way, is it active in a way that gives it significant additive value.

DR. MARTINO: Other comments? Yes, Dr. Hussain.

DR. HUSSAIN: It is just basically what everybody said. I guess as doctors, you look at things and you try to be objective, and to me, objective with a patient benefit means you either make them live longer or live better, and to look at a scan, and a scan that goes down from a 6 cm mass to a 3 cm mass, I would like to ask the lymphoma doctors, has there been any precedent in any drug, in lymphoma, in these kinds of settings where a PR actually translated into a meaningful

thing as in patients, when tested prospectively, as in patients living longer, quality of life improved, or any direct benefit other than an image benefit.

DR. CHESON: Well, there is that old statistical conundrum of the responder/nonresponder, and the CR's always do better that the PR's, and the PR's always seem to do better than the nonresponders. However, as we all know, there are flaws in that sort of analysis.

Having some response confers some benefit, but the magnitude of the response, you know, and it depends what kind of response, was there associated relieving of an obstruction, was there associated decrease in symptoms going along with it, but as you have said before, just shrinking something by 50 percent is not necessarily going to translate into a meaningful clinical benefit unless there is some durability of this and there is some associated clinical benefit along with it.

DR. MARTINO: I think at this point I would like to call the question to a vote. Again,

the important words to this question are does the committee agree that a durable CR should generally be the primary endpoint for approval, not PR, CR, and the word durable.

We will start with Dr. Bukowski on my right, please.

DR. BUKOWSKI: Yes.

DR. CHESON: Yes.

DR. BRAWLEY: Yes.

DR. REAMAN: Yes.

DR. MARTINO: Yes.

DR. MORTIMER: Yes.

DR. PERRY: Yes.

DR. HUSSAIN: Yes.

MS. HAYLOCK: Yes.

DR. GEORGE: Yes.

MS. KRIVACIC: No.

DR. BISHOP: Yes.

DR. WILSON: Yes.

DR. MARTINO: The total is 12 Yes, 1 No.

The next related question. Would high rates of PR and long PR duration be reasonably

likely to predict clinical benefit, and thus potentially support an accelerated application? If so, please describe the PR rate and duration that would be convincing.

Who would like to speak to that, please?

DR. CHESON: If I can reiterate something I said before, about PR being a PR, we have a paper in press in JCO in which we integrated PET scanning into the International Workshop Criteria, and what you see is that initially, there is a modest difference--although this was in upfront patients with large cell lymphoma--there was a modest difference between the time to progression or progression-free survival between the CR's and the PR's.

Once you throw in PET scanning, the difference becomes absolutely enormous, so it depends how you measure these PR's. If you have a PR that, indeed, is really a CR in disguise, then, lo and behold, they are going to do quite well, and so I think you have to look at this in the context of what are you calling a PR, how are you defining

a PR, because that is going to make a big difference.

DR. MARTINO: I personally would be leery of answering the question with a number and a duration, because I think the issue then, for me, has to do what is the quality of life during that time.

A PR that achieves improved quality of life for some length of time is valuable, but it would have to be accompanied by some true measurement of quality of life for reduction in symptoms. In and of its own, it would not impress me very much.

DR. CHESON: And not just substitution of one set of symptoms for another.

DR. PAZDUR: Perhaps this question is not a voting question, but more of a discussion question.

DR. REAMAN: I think the other discussion issue is whether or not there are alternatives. I mean if there are, in fact, other options, should we really be discussing this in any great detail.

DR. BISHOP: The only thing I counter the Chairperson's comments is that you can apply those same criteria to a complete response. Yes, we found that when you want to have a complete response, and if you don't have quality of life and everything else, then, should you count a complete response that way, so I really don't think that is a fair criteria.

I mean the only things that we have to go on is improved survival, yes, we would all like quality of life, but there is other things that as we heard testify, that people are willing to live with neuropathy, for one, and yet if that gives them opportunity to be with family and friends, I just don't think that is a fair criteria.

So, the duration is difficult to define, but I don't think that is a fair criteria that you have to have quality of life to go along with it.

DR. MARTINO: I think your point is extremely well taken, and for me, what it reminds me of is that even a CR may not be that meaningful, which again gets to this issue of what is the point

of accelerated approval for me.

DR. PAZDUR: Here again, I think one of the answers, and maybe when we wrote this question it perhaps needed a bit of clarification, is there any PR rate in duration that one would accept.

I think perhaps in this situation, one may have to take a look at a randomized study if one is even going to contemplate this, or is it a situation, in a single-arm trial, that one would accept a PR rate in a very refractory situation.

DR. WILSON: Without getting into numbers, I mean I personally think yes, that there are numbers of PR's, and there is durations that I think would convince most people that that would be accompanied by clinical benefit assuming that you didn't have collection of quality of life issues.

So, I think the answer personally to No. 3 is yes, I think reasonable people can sit down and hammer out where those numbers should lie. It is probably beyond the scope of today.

DR. MARTINO: The problem that I see with this is that when one looks at response rate, and

practically all tumors, what you primarily deal with is PR, and CR rates are few and far between, and that is a fact of life for all of us that deal with oncology.

So, invariably, these applications do come down to not arguing over is the CR rate high enough, but rather it really comes down to the issue of PR, whether we accept PR's as valuable or not, because 90 percent of the time, that is actually what you are getting pretty much in any application that I have seen brought to this committee.

DR. PERRY: Could I move we table the question?

DR. MARTINO: Rick, are you comfortable that you have heard enough?

DR. WILLIAMS: It is a basic question for us, because we will have sponsors come to us, and let's say there is no available therapy in a situation, you know, the lymphoma situation, let's say that is true, they will ask can we do a single-arm study, and if we get a high enough

response rate, might we get accelerated approval.

Now, I don't have a sense. We have always categorically said CR's are nothing, but we have primarily been looking at tumors in an earlier setting, we never really had this question, but now we are getting the question a lot.

So, I think it is either the possibility, as you suggest, Wyndam, I think that perhaps, I mean you never know, a very high PR rate with a long duration, it is conceivable, or perhaps it is not, we will say what we have said in the past.

That is, you know, really I am going to look at CR's, because you certainly can evaluate in a single-arm study, the PR rate and the PR duration, so there is no problem evaluating it, and you may well say that this is way beyond what you can do with anything out there, but the question is do we think it is reasonably likely to predict benefit. That is the essential question we would have to ask.

DR. PERRY: I think the question differs upon what tumor you are talking about. For

melanoma, we would take just about anything. For Hodgkin's disease, we want very high standards indeed. I think that is not a question we can settle here this afternoon in this committee, at this particular time, when we are trying to discuss another drug. That is why I move to table, because, as I understand it, it is not suitable for discussion.

DR. PAZDUR: As far as endpoints, we will be discussing endpoints in other meetings as far as our ongoing endpoint project, we are going to be having a hematology symposium on this perhaps this year, so we will table that.

DR. MARTINO: Dr. Brawley.

DR. BRAWLEY: I would make a plea for PR with quality of life criteria, and that probably means that you are going to have to end up looking at a randomized study, but if I were to see PR's and better quality of life in a particular drug A versus the leading drug in the treatment of that disease, I would vote for it.

DR. MARTINO: Dr. Reaman.

DR. REAMAN: I would also like to clarify from statements that were made earlier, about PR's being indicative of activity and useful in screening, we are only talking about PR being an acceptable endpoint for accelerated approval, correct, with a guarantee or with a plan for definitive studies in place.

DR. MARTINO: Dr. Bukowski.

DR. BUKOWSKI: But clearly, there are PR's that have long duration, and I think we have to keep that in mind, where we will see refractory settings where PR's develop that are of long duration, and that has to be a consideration in our deliberations.

I think we need to consider all these alternatives.

DR. PAZDUR: Ron, in my comments initially, for example, with Velcade, we had a duration of a year, so we were quite happy with that. You know, you didn't have to do a randomized study here. But in the context of the disease that we are talking about here, with the multiple drugs

that are available, to have somebody come in with a single-arm trial with just PR, unless it was some eye-popping results, I would discourage people, and I think the tone of this whole conversation has been a randomized study, so you have available therapy even if you have to develop the drug in a combination regimen before you first take it out into a randomized setting might need to be done.

DR. BUKOWSKI: I agree with that, Rick, and I purposely said durable as the modifier here, and I think that has to be a part of it if you are looking at a single-arm study. Clearly, the randomized trial is the best way to do this.

DR. MARTINO: I think maybe we can sort of summarize by saying that the Committee doesn't have a strong feeling that response rate alone, without some other bit of meaningful information, that that alone is not probably adequate for an accelerated approval.

Dr. George.

DR. GEORGE: A couple of comments. One is I think it has been implied or even stated, and

something I agree with, you can't prove clinical benefit from studies like this, these single arms, so that you have to do something else.

The point I would like to make is you can design such studies, so you could come up with numbers here if you make certain assumptions, such as, for example, as you do in ordinary studies, you hypothesize certain differences you want to pick up.

You could do the same thing here if you said the only possible benefit is going to be in those that have responses of some kind, and then you can take it from there and say, well, if that is true, then, what kind of response rates would you have to have to even have a chance of finding a clinical benefit in studies of a certain size.

In other words, a complete response or a partial response, has to be at least a certain level or you will never pick it up with a reasonable size study.

There are ways to get at these numbers, and if will depend on the disease, of course, but

it is not just sitting around the table saying, well, what kind of duration of response or percentage of responders could lead us to a favorable conclusion. You could actually put numbers on it.

DR. PAZDUR: No. 4 is the approval question.

DR. MARTINO: So, we will move on to that last one.

It reads: Do the partial responses at the rate seen and for the duration reported for this agent predict clinical benefit in relapsed, aggressive non-Hodgkin's lymphoma?

Do you want to expound at all on what clinical benefit means? I am reminding you of earlier today when we had an issue of what is the meaning of this, what is the exercise at hand here.

DR. PAZDUR: I think since we are talking about accelerated approval, this question should be reasonably likely to predict clinical benefit. Here again, this is a predictor of clinical benefit. Clinical benefit has been something that

is tangible to the patient, an improvement in survival, as Maha said, an improvement in disease-related symptoms, something tangible to the patient.

So, what we are asking is does the partial response rate and the duration, with all the problems that we have discussed with this, is this reasonably likely to predict clinical benefit.

DR. BRAWLEY: You are not asking is the drug active? You are asking a different question.

DR. PAZDUR: Correct. This is an approval question. We assume that the drug has some response rates here. There is no argument with anybody on that. This is an approval question.

Is it reasonably likely, with the data that you saw, does this predict clinical benefit, i.e., an improvement in survival, disease-related symptoms, et cetera, something tangible to the patient?

DR. BISHOP: Does that response include comparison to currently available treatments?

DR. PAZDUR: We have already answered that

in a sense.

DR. BISHOP: No, I look at this question different than that. This is asking does this have benefit. You said this is in regard to approval, and your opening minutes comments for accelerated approval strictly assigned a demonstration of clinical benefit, and you listed the four things - survival, amelioration of symptoms, advantage over available treatments.

DR. PAZDUR: That was advantage over available treatments is what you need to show for--

DR. BISHOP: So, that is a definition of clinical benefit in this question.

DR. PAZDUR: It is a requisite for accelerated approval.

DR. WILLIAMS: You have already basically, by answering No. 1 the way you did, probably ruled out any possibility of approval if we went along with that advice, but you would also have to answer No. 4.

DR. MARTINO: Can I just make it very simple? I think what the question is about is with

what we have heard today, and the discussions that we have undergone today, do you believe that there is enough substantial data to give approval to this drug, so that it is available for someone to use tomorrow.

DR. PAZDUR: Accelerated approval.

DR. MARTINO: It is that issue. Do you think the data is good enough that you now want the world to have it tomorrow, or do you think the data is not of such magnitude. It is an issue of magnitude, not is there a whiff of response. That is the question.

Again, we cannot confuse the issue of is there any activity, is there any value. It is not the minimum requirement here. We cannot be aiming for what is the lowest. That cannot be our goal here. If it is, I am done with this group as of this moment if that is our goal.

Dr. Bukowski, you are up first.

DR. BUKOWSKI: No.

DR. CHESON: No.

DR. BRAWLEY: No.

DR. REAMAN: No.

DR. MARTINO: No.

DR. MORTIMER: No.

DR. PERRY: No.

DR. HUSSAIN: No.

MS. HAYLOCK: No.

DR. GEORGE: No.

MS. KRIVACIC: No.

DR. BISHOP: No.

DR. WILSON: No.

DR. MARTINO: The vote is unanimous to Question No. 4. It is No.

DR. PAZDUR: Thank you for your time and interest.

[Whereupon, at 4:03 p.m., the meeting was concluded.]

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