DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

NDA 21-824

ZARNESTRA (TIPIFARNIB)FILM COATED TABLETS

TIBOTEC THERAPEUTICS, A DIVISION OF ORTHO BIOTECH, LP PROPOSED INDICATION FOR THE TREATMENT OF ELDERLY PATIENTS WITH NEWLY DIAGNOSED POOR-RISK ACUTE MYELOID LEUKEMIA (AML)

Thursday, May 5, 2005

8:00 a.m.

5630 Fishers Land
Room 1066
Rockville, Maryland

P A R T I C I P A N T S

ADVISORY COMMITTEE REPRODUCTIVE HEALTH DRUGS

Silvana Martino, D.O. - CHAIR
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Alexandra M. Levine, M.D.
Joanne E. Mortimer, M.D.
Michael C. Perry, M.D.
Gregory H. Reaman, M.D.

Johanna M. Clifford, M.S., RN, Executive Secretary

CONSULTANTS AND GUESTS

Consultants (voting)

Susan O'Brien, M.D.

Patient Representative (voting):

Arthur Flatau

Acting Industry Representative (non-voting):

Roger Porter

Guest Speaker (non-voting):

Frederick Appelbaum, M.D.

FDA PARTICIPANTS

Qin Ryan, M.D.
Ramzi Dagher, M.D.
Robert Justice
Richard Pazdur, M.D.
Robert Temple, M.D.

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. MARTINO: Good morning, ladies and gentlemen. I'd like to begin this meeting.

The topic before us this morning is the drug Zarnestra, presented by Tibotec. And the proposed indication is for the treatment of elderly patients with newly diagnosed poor-risk myeloid leukemia.

Introduction of Committee

The first order of business is I would like the members of the committee to introduce themselves. And I'd like to start with Dr. O'Brien, please.

I need you all to use your microphones, please.

DR. O'BRIEN: I'm from the leukemia department at MD Anderson.

DR. CHESON: Bruce Cheson, head of Hematology, Georgetown University Lombardi Cancer Center.

DR. GEORGE: Steve George, Duke University

Medical Center.

DR. BRAWLEY: Otis Brawley. I'm a medical oncologist and epidemiologist at the Winship Cancer Institute of Emory University.

DR. MORTIMER: Joanne Mortimer, medical director, UCSD Morris Cancer Center.

MS. HAYLOCK: Pamela Haylock, oncology nurse and doctoral student at UTMB, Galveston, Texas.

MR. FLATAU: Arthur Flatau, I'm the Patient Representative.

DR. REAMAN: Greg Reaman, pediatric oncologist, Children's Hospital, Washington, D.C.; George Washington University in the Children's Oncology Group.

DR. LEVINE: Alexandra Levine, head of hematology at University of Southern California, Norris Cancer Center.

DR. MARTINO: Silvana Martino, from the Angeles Clinic in Santa Monica, California, main medical oncologist.

MS. CLIFFORD: Johanna Clifford, Executive

Secretary to the ODAC.

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

DR. PORTER: Roger Porter, retired both from the NIH and Wyeth, now a consultant.

DR. BUKOWSKI: Ronald Bukowski, medical oncologist, Cleveland Clinic, Cleveland, Ohio.

DR. DAGHER: Ramzi Dagher, Division of Oncology Drug Products, FDA.

DR. JUSTICE: Robert Justice, Acting Deputy Director, Oncology Drug Products, FDA.

DR. PAZDUR: Richard Pazdur, FDA.

DR. TEMPLE: Bob Temple, Director, OD-1.

DR. MARTINO: Next, I'd like Ms. Johanna Clifford to read the conflict of interest statements for the members of the panel, please.

Conflict of Interest Statement

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

Based on the submitted agenda all financial interests reported by the committee participants, it has been determined that all

interest in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest, with the following exceptions.

In accordance 18 USC 208(b)(3), full waivers have been granted to the following participants: Dr. Stephen George, for consultant for a competitor, which he received less than $10,001 per year; Dr. Ronald Bukowski, for consulting with a competitor, which he receives less than $10,001 per year. Pamela Haylock has been granted waivers under 208(b)(3) and 21 USC 505(n) for her spouse owning stock in a competitor. The stock is valued from $25,001 to $50,000.

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.

In addition, we would like to not that Dr.

Frederick Appelbaum, FDA's invited guest speaker, is participating as a representative of the Fred Hutchinson Cancer Research Center. He has no financial interest in, or professional relationship with any of products of firms that could be affected by the committee's discussions.

With respect to the FDA's invited industry representative, we would like to disclose that Dr. Roger Porter is participating in this meeting as the industry representative, acting on behalf of regulated industry. Dr. Porter is a private consultant to industry.

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

With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with

any firms they may wish to comment upon.

Thank you.

DR. MARTINO: Thank you, Ms. Clifford.

And, next, Dr. Richard Pazdur will provide some opening remarks to this meeting.

Opening Remarks

DR. PAZDUR: Thank you, Dr. Martino.

First of all, I'd like to say Feliz Cinco de Mayo to everyone.

[Laughter.]

For everybody that's lived in Texas, such as Susan and myself--

VOICE: Muchas gracias.

DR. PAZDUR: De nada.

[Laughter.]

This is a big day in the State of Texas. And I just want to bring that up.

I have some enjoyable issues to do to start out here, and that is to thank two members of our committee that will be retiring. And I use that word "retiring" in quotations, because, because of their expertise, we probably will be

inviting them back--both to sit on ODAC special committees, as well as to serve as special consultants to us during the process that we evaluate drugs outside of the ODAC committee.

The two individuals that will be leaving the committee are Stephen George and Otis Brawley.

Stephen George is, obviously, from Duke University in North Carolina, and has served on the ODAC Advisory Committee as the committee statistician from July of 2001, to June of 2005. In addition to his committee participation, Dr. George has visited the FDA and he's given numerous presentations to us on various statistical issues, and has served as a consultant to us on many NDAs and IND matters. So we really appreciate Dr. George's efforts--on this committee and also behind the doors here--in helping the FDA. And we look forward to working with you, as you leave the committee, on a continuing basis.

So I have this beautiful plaque here that I'd like to present to you.

[Applause.]

Thank you very much.

DR. GEORGE: Thank you. Thank you.

DR. PAZDUR: And the gentleman that is

sitting right next to him, Dr. Otis Brawley, is professor of hematology and oncology and epidemiology, and is the Associate Director for Cancer Control at the Winship Cancer Institute at Emory University.

He's an international authority in the field of health disparities research and prostate cancer. He's served on the committee from July of 2001 to 2005. Like Dr. George, Otis has been involved with many of the behind-the-scenes efforts at the FDA; consulting with us on numerous applications, considerations of Phase I and Phase II trial designs, and Phase III trial designs also.

We really have appreciated Dr. Brawley's work with us. And here, again--this is not to say goodbye, but just as a transition to another role with us in the FDA. Thank you very much.

[Applause.]

Hasta luego, he said. Okay.

[Laughter.]

Recuerdos a todos--regards to everyone.

I'm just going to make a few short comments about this application, because I think that the speakers will probably address all of the salient points, and I think we could bring up any

regulatory issues relatively succinctly during our presentations, and also in our discussions.

Basically, what we have here is a single-arm study in a patient population where there has to be discussion that there is no other available therapy for this patient population--or the results are so impressive here that we need to consider the approval of the drug.

We're going to be asking basically the question: does this drug deserve full approval? Okay? And one of the reasons why we're asking this is that we have accepted basically a situation where complete response rates have equated clinical benefit. Okay? We believe that this is an established surrogate for survival. And, in addition to that, we believe that application in a

complete response rate would have a reduction in transfusion requirements and other supportive care products. So this is meaningful clinical endpoint, an established surrogate for clinical benefit.

So, with that in mind, I'd like you to proceed with the discussions, and I'll turn the discussions--the presentations--over to Dr. Martino.

DR. MARTINO: Rich, before I let you sit down, please, I just want to be sure that I'm clear that, in fact, the application is seeking for full approval, and not accelerated approval.

DR. PAZDUR: Correct--yes.

DR. MARTINO: Because, when I reviewed the material, I came to this with one view, and then when the question was presented to me, I realized that it was full approval.

DR. PAZDUR: Correct.

DR. MARTINO: So I just wanted to be sure that that is what you mean.

DR. PAZDUR: And this is the area that I want to clarify here. The issue here is: we look

at complete response rates. And, here again, that's not only the response rates but response rates of a sufficient magnitude--okay? So we look at both of these parameters: the response rate and the magnitude. If that is sufficient, one should conclude that this would be an established surrogate for clinical benefit. Okay?

DR. PERRY: Do we have the option of recommending it for accelerated approval and not for full approval? Or is this simply "yes" or "no."

DR. PAZDUR: Yes--we would entertain any topics or discussions regarding that.

DR. PERRY: So we've got three options then: yes, no--

DR. PAZDUR: Correct. But we'd like to firsts discuss that endpoint of full approval. And then, if you want to deviate from that, let's please have a discussion of what. Okay?

DR. PERRY: Okay.

DR. MARTINO: Are there other questions for Dr. Pazdur at this point? Ladies and gentlemen?

Okay.

Turn the microphone on, please.

DR. PAZDUR: They're right there in the plastic box.

DR. MARTINO: A practical question, there. Thank you.

At this point, I would like to turn to the Tibotec representatives to present their data. And Dr. DeLap, if you would please introduce your subsequent speakers, as well.

Sponsor Presentation - Tibotec Therapeutics

DR. DeLAP: Thank you. Madam Chair, members of the committee, colleagues and guests--good morning. I'm Dr. Robert DeLap, Vice President of Regulatory Affairs at Johnson & Johnson Pharmaceutical Research.

We are pleased to be here today to present data generated in National Cancer Institute and company-sponsored studies on the efficacy and safety of tipifarnib in poor-risk AML, and our application for approval of tipifarnib for use in a patient population that is not well served by

existing AML therapies.

Our application proposes that tipifarnib will be indicated for the treatment of elderly patients with newly diagnosed, poor-risk acute myeloid leukemia, based on durable complete remissions that were observed in the CTEP-20 study.

As noted in the agency's briefing materials for today's meeting, complete remissions have been used as evidence of patient benefit to support approval of new treatments for AML. Thus, the consideration today is the use of these data to support the approval of tipifarnib for this indication.

Elderly patients with AML obtain less benefit from the intensive induction treatment regimens used in younger patients, and the risks of severe treatment toxicities and treatment-related mortality rise with increasing age. Since risk-benefit considerations for intensive-induction treatment are often not favorable in these patients, new treatments are clearly needed.

In the clinical research to be discussed

today, tipifarnib has demonstrated meaningful efficacy in elderly patients as described in our proposed indication, with a well-characterized safety profile in outpatient treatment.

[Slide.]

Tipifarnib was originally synthesized in the Johnson & Johnson Pharmaceutical Research laboratories. Clinical investigations began with solid tumor studies in 1997. Based on mutual interest in this compound, the company and the NCI entered into a Cooperative Research and Development Agreement in 1999.

Pre-clinical evidence of activity against leukemias led to clinical research in AML, with initiation of the CTEP-1 Phase 1 study in 1999. Complete clinical remissions observed in CTEP-1 led to further research, including the CTEP-20 Phase 2 study in myeloid malignancies.

Following consultations between the company, the National Cancer Institute and the FDA, CTEP-20 was subsequently amended and expanded to focus on evaluating the efficacy and safety of

tipifarnib in elderly patients with newly diagnosed poor-risk AML.

Considering the unmet need in this patient population, tipifarnib has recently received orphan designation for AML, and has been granted fast-track status by FDA.

The NDA for tipifarnib was accepted into FDA's Continuous Marketing Application-1 pilot program, which has allowed for expedited submission and review of these data.

[Slide.]

This slide summarized the study program for tipifarnib in poor-risk AML.

Following the CTEP-1 study, the INT-17 study evaluated tipifarnib in patients with relapsed or refractory AML.

Today's discussions will focus on the CTEP-20 study, as this is the study that has evaluated efficacy and safety in the patient population of interest for today's discussion.

The AML-301 study, in patients greater than 70 years of age with newly diagnosed leukemia

is evaluating the effect of tipifarnib versus best supportive care. And that study is designed to establish the magnitude of the anticipated survival benefit, and is actively enrolling patients.

The ongoing CTEP-50 study is an iterative trial being conducted under NCI supervision, which is evaluating alternative dosing regimens in elderly patients with newly diagnosed leukemia.

Finally, the AML development program also includes related studies, not shown on this slide, in maintenance of remission and use in combination with other agents. Those studies are briefly noted in the company's background materials for today's meeting, but will not be included in our presentation today, as they represent work in progress in other AML settings.

[Slide.]

The CTEP-20 study focused on patients who have generally not been represented in AML clinical trials, and are not well served by intensive-induction chemotherapy regimens. The median age of the elderly patients enrolled in this

study was 75. Most of the patients had antecedent myelodysplastic syndromes; 49 percent had unfavorable karyotypes; the remainder had intermediate karyotypes. No patients with favorable karyotypes were enrolled.

Overall, 90 percent of patients had two or more risk factors, considering age, antecedent myelodysplastic syndromes, unfavorable karyotypes, or evidence of organ dysfunction. These are patients who would be expected to have poor tolerance for standard AML treatments, and would be much less likely to benefit from existing treatments.

[Slide.]

As you will see in today's presentation, tipifarnib demonstrates a favorable benefit risk for a more fragile patient population that generally does not receive standard AML therapy. Evidence of meaningful clinical efficacy has been observed, with a 15 percent rate of durable complete remissions in the planned analysis.

Treatment safety has been well documented,

with more than 1,000 patients in monotherapy studies. This includes a total of 409 patients in the AML studies, CTEP-20 and INT-17, as well as patients exposed at lower doses in solid tumor studies.

Tipifarnib produces predictable and reversible myelosuppression with continued daily dosing, but it is myeloablative, and the incidence of life-threatening, not-hematologic toxicities has bene low.

Patients in the CTEP-20 study were able to spend much of their time outside of the hospital. Thus, tipifarnib can serve as an oral out-patient treatment for these patients.

[Slide.]

Our agenda today includes three additional presentations. In a few moments I will turn to Dr. Richard Stone, from the Dana-Farber Cancer Institute, who will discuss the problem of AML in elderly patients.

Dr. Alain Thibault will then review the clinical data provided in our new drug application,

focusing on the CTEP-20 study, which has provided data on the efficacy and safety of tipifarnib in elderly poor-risk patients with newly diagnosed AML.

Finally, Dr. Alex Zukiwski will summarize benefits and risks of tipifarnib treatment in this patient population.

We are joined today by medical experts to contribute to the discussion, and to help address specific questions. These include Dr. Karp, who served as principal investigator for the CTEP-20 study; Drs. Sekeres and Stone, who have special expertise in AML and have experience with the use of tipifarnib; and Dr. Wright, from the NCI's Cancer Therapy Evaluation Program. Unfortunately, Dr. Albitar from Nichols Institute, who provided an independent review of bone marrow slides in the CTEP-20 study, and had planned to be with us today, could not be here because of a family emergency.

This concludes my introduction. I will now turn the podium over to Dr. Richard Stone who will discuss the problem of AML in elderly

patients.

Thank you.

AML in Elderly Patients

DR. STONE: Dr. DeLap, thank you very much.

Members of the panel, guests--I'll be spending the next few minutes discussing the following topic: AML in the older-age patient represents a therapeutic area of significant unmet need. And this is particular true for those subjects who have an inferior prognosis compared to the average.

[Slide.]

Now, AML in the older population is not uncommon, and the number of cases will be increasing over time. This is clearly a biologically and therapeutically distinct disease compared to AML which may occur in younger adults. And the reasons for this distinctive character are: number one, it's an intrinsically resistant disease to chemotherapy; and number two, there are markedly inferior outcomes to available chemotherapeutic agents compared to younger adults.

Some subgroups of patients who are older adults with AML have a markedly worse than the average prognosis which, I think you'll see in a

minute, is quite poor to start with. As such, many patients who are older with AML are not offered and/or refuse the standard cytotoxic induction and post-remission therapy. As such, an efficacious, relatively non-toxic approach would be welcomed by patients and leukemia doctor's alike.

[Slide.]

There are approximately 12,000 new cases of AML each year in this country. Approximately 9,000 people die of this disease.

In contrast to what might be the case if you look at a tertiary care cancer center, the median age of AML is at least 68. The incidence increases markedly as people get older. For example, if you're 50 years old you have a 1 in 50,000 chance of having AML. If you're 70, you have a 1 in 7,000 chance.

[Slide.]

This next slide graphically depicts the

marked increase in the incidence of AML that occurs as people get older. And it's particularly striking once you get to the sixth, and particularly seventh, decade of life.

[Slide.]

Moreover, as I think everybody is aware, the demographics of our population are changing to the fact that we're getting to be older as a country. And, as such, the number of cases of AML in this age cohort--or the number of cases total--will be increasing over the next few decades.

[Slide.]

Now, this slide depicts the situation that was true in the 1980s, when chemotherapy was applied the same way to younger adults and older adults with AML. This is data taken from cooperative group trials on both sides of the Atlantic, and this required the patient to get to a center where they could get chemotherapy. So, as I'll come back to, it may not be representative of what really happens in the community.

Nonetheless, this slide makes the important point that the therapeutic outcome in older adults is much different than younger adults.

For example, if you're over age 65, your chance of achieving complete remission is only 45 percent, compared to 70 percent in younger adults with AML.

If you achieve remission your chance for staying in remission is only about one in five, compared to about 45 percent of younger adults.

And what's particularly striking to me as an oncology and a leukemia doctor taking care of these patients, is the treatment-related mortality rate is about one in four, and the early death rate is much lower in younger adults.

The overall survival--about 10 percent, walking in the door. And these are people that could get chemotherapy--compared 1 in 30 younger adults.

The median survival of older adults who present with AML and go on clinical trials is only 10 months--which I think we'd all agree is not someplace we'd like to be.

[Slide.]

There are two major reasons--as I indicated--for this inferior outcome. The first general category is decreased host tolerance. Of course, being older, these patients have a higher incidence of having co-morbid diseases such as

diabetes and vascular disease. Perhaps because of that, and for just general aging features, they have a decreased ability to clear chemotherapy, which obviously could contribute to increased toxicity.

Thirdly, it's been shown in multiple studies that the ability to recover from myelotoxic chemotherapy is diminished in older adults, and they have a longer period of neutropenia and thrombocytopenia--which leads to an enhanced rate of chemotherapy-induced complications.

[Slide.]

At least as important, if not more so, is the fact that the leukemias which arise in older adults are intrinsically resistant, biologically. This fact of increased intrinsic resistance is

manifested by, or associated with, these features: number one, there's an increased instance of what's called "unfavorable chromosomal abnormalities" in older patients, such as the loss of the long arm of the entire chromosome-5 or -7' problems at 11q23, and complex cytogenetic abnormalities. These are the same type of abnormalities that occur in people who have myelodysplastic syndrome, and/or people who had prior chemotherapy for other cancers.

There's an increased incidence of antecedent--either known or suspected--hematologic abnormalities, most particularly myelodysplastic syndrome.

There's an increased likelihood of expression of genes which encode drug resistance, most notably the MDR-1 protein, which is a chemotherapy efflux pump, as well as other ones like MRP, LRP, MSH-2.

[Slide.]

Now, this combination of biological and host factors, and the inferior outcomes, led to a slight change in the approach of cooperative groups

in the 1990s, where separate clinical trials were designed for older adults compared to younger adults with AML.

This is a representative list of trials conducted in the 1990s in cooperative groups in Europe and in America. And even though these trials evaluated different novel therapeutic strategies, such as the use of growth factors, different chemotherapeutic drugs, and drug-resistance modulating drugs, the results are very stereotyped from trial to trial. There are other trials out there which I could have picked, such as the recently published MRC trial, but that was largely a little bit younger patient population.

The median age is 68 in all the trials. The complete remission rate is about 40 to 50 percent. And, again, the toxic death rate--and this is the 1990s--is in the 20 percent range throughout all the trials. And, again, all the trials--median survival, nine to 10 months.

And I want to stress one very important

point: it's that these--the patients who went on these trials were, number one, deemed to be chemotherapy candidates. They got to a center that was participating in a cooperative group trial. They had to meet the eligibility criteria for these trials--which varied from trial to trial, there were subtle differences. Most of these trials did not allow people with secondary AML; that is AML that occurred myelodysplastic syndrome, or after prior chemotherapy to go on. Some did. Some of the trials had a lower boundary of age 60, some 65, some 55.

And so those are kind of the best results one can get with chemotherapy.

[Slide.]

The situation in the community is certainly much worse. That's number one.

Number two is: if you look into the subgroup analysis of these trials, you can find some important facts which suggest that you can identify patients that even have a worse prognosis than the average. For example, if you have prior

myelodysplastic syndrome, your chance of remission is 24 percent compared to 52 percent if you don't. If you have one of those poor cytogenetic abnormalities that I mentioned, 21 percent likelihood of remission, compared to 55 percent if you don't. And these data were taken from the SWOG trial.

This data from the recently published ECOG trial says that if you're over age 70, you've got a 29 percent of going into remission, compared to 51 percent for those younger than age 70. However, only 13 percent in this trial were above age 75.

Only 5 percent of those in the Lowenberg trial were above age 80, and in those people the chance for remission was only 14 percent.

So, number one, you can find bad prognostic factors within these groups and, number two, the number of patients who are really old who go on these trials is low.

[Slide.]

Community data is shown in this slide which suggests that if you're over age 65 and you

present with AML, your median survival may be only in the several-month range, compared to the another 10 months we saw for the people who went on those chemotherapy trials.

[Slide.]

So, given this sort of dismal outcome with chemotherapy, the value of chemotherapy in this age population is debated, particularly in those who have poor prognosis features.

There have only been a couple of randomized studies--and these were done in Europe in the 1980s--which tried to compare early aggressive chemo versus less intensive approaches. And they both showed a small increase in survival for early intensive chemo, but there was no associated quality of life studies, and cost, in terms of up-front mortality was quite high.

These issues are reflected in the National Cancer Center Network guidelines--it's a consensus panel of AML experts--which acknowledges that standard induction chemotherapy is an option, but clinical trial with either new agents or biological

agents is the preferred approach even for those people who have good performance status who are over age 60 and present with AML.

[Slide.]

How do people make this difficult decision between a treatment which has a 25 percent toxic death rate and a low cure rate, versus supportive care? It's a very difficult decision. My colleague Dr. Sekeres, when he as at the Dana-Farber, tried to study this by a prospective patient-doctor questionnaire, and among the findings from the study are that, number one, patients consistently inflate the chance of cure, compared to what is stated in medical record predicted by the physician; number two, despite documentation in the medical record that the doctors discussed multiple treatment options with the patients, the patients said, no, they didn't discuss this with me. That may be because there really aren't too many options, and the options seem to be so stark that people feel they don't really have any.

[Slide.]

What happens in the community? This slide suggests the choices people make.

First of all, if you're in the younger cohort of the overall older cohort, you only choose chemotherapy about half the time. As you get older, the chance of choosing chemotherapy is quite low.

What are the consequences of this decision? Well, if you choose to get chemotherapy, you're going to spend significantly more time in the hospital than if you choose supportive care.

What's even more important than that is you don't get any bang for the buck, because the percentage of time you spend in the hospital, compared to the total amount of time that you have left is still higher if you choose chemotherapy. So you don't seem to reap any benefit in that regard.

[Slide.]

So I think it's quite clear that the efficacy of standard chemotherapy is reduced in the

older adult with AML compared to the younger adult. The therapy is poorly tolerated. There is clearly a high therapy-related mortality rate. No trials that I know about have really addressed the quality of life cost of chemotherapy.

If there is a small improvement in survival with chemotherapy, it's quite likely to be offset by an increase in hospitalization and other negative QOL factors. And it's moot for many patients, because two-thirds of patients who are older than age 65 don't choose chemotherapy as their primary treatment modality.

So non-chemotherapeutic approaches, besides supportive care, which may have efficacy and low toxicity, are badly needed.

[Slide.]

In summary, it's clear that AML in the older adult is a biologically and clinically distinct entity. Even in the so-called "best" patients who go on chemotherapy trials, the chance for treatment-related death with induction chemotherapy is actually greater than the chance

for cure. In those poor prognosis patients who have--in the older part of this group--who have prior MDS, adverse cytogenics, the advisability of chemotherapy must be considered very low.

Patients and doctors are often choosing a non-intensive approach, but currently there is really no such therapy in this category which offers and appreciable chance for remission.

So I'd like to thank you for your attention. And I'll be happy introduce Alain Thibault from Johnson & Johnson Pharmaceutical Research & Development to talk about CTEP-20.

Clinical Data

DR. THIBAULT: Thank you, Dr. Stone.

Good morning. My name is Alain Thibault. I'm responsible for the clinical development of tipifarnib worldwide.

I will first describe key features of tipifarnib, then I will present the results of CTEP-20, which was a trial sponsored by the Cancer Therapy and Evaluation Program of the National Cancer Institute. These data are presented in

support of our application for the approval of tipifarnib in the treatment of newly diagnosed elderly patients with poor-risk AML.

[Slide.]

Tipifarnib is a selective and competitive inhibitor of the enzyme farnesyl transferase. The enzyme processes more than a hundred proteins intracellularly--some of which are shown here, and many of which are involved in signaling pathways linked to the control of cell growth. Other extensive research has been conducted. To this date, the specific pathways associated with the anti-leukemic activity in AML are still the subject of ongoing research.

[Slide.]

Tipifarnib is an oral treatment. So, after oral administration, plasma and bone marrow concentrations rapidly exceed the IC50 of AML cell lines as determined in vitro. Tipifarnib is metabolized in the liver by several pathways. The major metabolites are biologically inactive. Tipifarnib is not a substrate from drug efflux pump

encoded by the MDR-1 gene.

The diversity of metabolic routes may explain why tipifarnib has demonstrated a low potential for drug interactions in several pharmacology studies that have been carried out to date.

[Slide.]

The recommended dosing regimen is 600 milligrams po BID, given for 21 days in four-week cycles. This was established by a classical dose escalating Phase I trial conducted in 34 patients with poor-risk leukemias, most of whom had AML.

The 21-day administration is required to maintain sustained inhibition of the target so as to maximize efficacy. And the seven-day rest period is required to reduce the incidence of peripheral neuropathy, which had been observed when continuous, uninterrupted dosing was used.

The 600 milligram BID dose is associated with consistent farnesyl transferase inhibition; plasma and bone marrow concentrations that exceed the IC50, and acceptable patient tolerability.

[Slide.]

Let's now turn to the description of the study design. I'll first describe the rationale in

design, then I'll go over demographics, indices, characteristics. Then we'll go over efficacy and safety.

CTEP-20 was part of a research agreement established between Johnson & Johnson and the National Cancer Institute. This was a single-arm study. It was conducted at six sites across the United States, and Johns Hopkins University was the coordinating center.

From the very beginning, the aim of the investigators was to study tipifarnib in patients with poor-risk myeloid neoplasms--I'll go over them in a few minutes. And this was a very critical feature of the study from the very outset--that study of patients with poor-risk myeloid disorders.

[Slide.]

So--newly diagnosed patients, with high-risk MDS--myelodysplastic syndrome--chronic myelomonocytic leukemia, and acute myeloid leukemia

were initially enrolled. Specifically regarding AML, the diagnosis of AML was based on WHO criteria. No prior therapy for AML was allowed--with the exception of hydroxyurea, which could be used to control counts prior to the patient's entering the study.

With respect to age, the study initially enrolled patients age 18 to 65, with risk factors such as unfavorable cytogenetics, prior MDS, or prior exposure to chemotherapy. On the other hand, patients aged 65 and above could enter the study with or without risk factors. These were the initial age requirements for AML patients.

The patients had to have approximate status of 0 to 2 on the ECOG scale. And this was chosen because it would enable them to receive treatment in the outpatient setting.

[Slide.]

After consultation and discussion and input from the FDA in July of 2003, the study protocol was amended: it was amended to focus on a more homogeneous population of elderly patients who

had AML, who were not candidates to receive intensive induction chemotherapy because the associated risks were felt to outweigh the benefits.

Therefore, after this amendment, the age requirements were raised. Patients aged 65 to 74 had to have a prior history of MDS, while patients 75 years or older could enter the study in the absence of other risk factors.

So these are the patients that Dr. Stone described as commonly excluded from trials that are commonly reported in the literature.

[Slide.]

The primary endpoint of the study was complete remission, assessed by the investigators.

Duration of CR, partial remission, hematological improvement, and overall survival were evaluated as secondary endpoints. Then the safety profile was characterized.

[Slide.]

The study applied standard morphologic criteria of complete remission, which are listed

here.

To achieve a complete remission, a patient had to demonstrate less that 5 percent leukemic blasts in the bone marrow; full recovery of peripheral counts--without, obviously, circulating blasts or any evidence of extramedullary AML.

[Slide.]

Partial responses were defined as: complete recovery of counts in the presence of residual blasts--5 to 19 percent, following at least a 50 percent decline from baseline values. Then, hematology improvement was defined as partial recovery of peripheral counts, with the same bone marrow context.

So these responses can be viewed as broad indicators of anti-leukemic activity, even though their correlation with survival is not well established.

[Slide.]

Treatment with tipifarnib as an outpatient monotherapy regimen--to ensure patient safety all patients were monitored weekly for toxicity. All

patients had a bone marrow aspirate and biopsy performed prior to study entry. And this procedure was repeated at the end of each treatment cycle.

Unless they had dose-limiting toxicity, patients continued to receive tipifarnib in a cyclical fashion until disease progression or relapse.

The only exception concerns patients who achieved a complete remission. These patients had the option to stop treatment after three additional cycles, and then be re-treated at the time of relapse. And I will go over the outcome of this maneuver, as well.

[Slide.]

In response to adverse events, the investigators could individualize treatment using three strategies: either dose reductions, treatment interruptions within a cycle, or treatment delays between cycles.

Each cycle was to include a minimum of 21 days of tipifarnib. The minimum rest period was seven days, which could be extended by a maximum of

35 days if needed. The total cycle duration could not exceed 63 days.

[Slide.]

So let's go over the details of the population right now.

So, CTEP-20 started as a study of tipifarnib in high-risk MDS, CMMD and AML. Of the 171 patients that were enrolled, 158 were considered to be poor-risk AML patients. The 137 elderly poor-risk patients were strictly defined in the final protocol--as I outlined earlier. And from now on, the presentation will focus on the 136 patients who were actually treated.

The 61 patients aged 65 to 74, with prior MDS; and the 75 patients aged 75 or more make up a unique population.

[Slide.]

The median age of the patient population is 75 years. The male to female ratio is similar to that of the general elderly AML population, and appears to reflect the higher incidence of MDS in men.

The major of patients were Caucasians--or White. Among the seven non-Caucasians, three were African-Americans, two Asians, and two were

Hispanics.

Most patients were symptomatic, either from AML or from pre-existing co-morbidities.

[Slide.]

Now, using the age-specific incidence of AML that Dr. Stone referred to earlier, if we use this as a comparator, CTEP-20 appears to be more representative of the general AML population than what is found in most other trials, in that the median age of the CTEP-20 patient was 75 years old. And this exceeds that of the major cooperative group studies by approximately 10 years.

[Slide.]

Now, we know that many issues underlie the assessment of AML patients, especially in the elderly. The chance of cure, the risk of toxicity, the need for hospital stays all have an impact on treatment options that are offered to these patients. This has been reviewed by Dr. Stone.

What this slide lists are the clinical reasons given by the investigators--the six principal investigators of this study--for including the patients on the trial rather than administering intensive chemotherapy to them.

Age and the presence of risk factors were

most commonly invoked. Patient preference over physician preference of experimental treatment over chemotherapy played a minor role.

[Slide.]

Now, the clinical rationales I've just reviewed can be more objectively described in terms of the risk factors that are classically associated with poor outcome from chemotherapy So the CTEP-20 patients had, by design, one of the highest prevalence of risk factors ever reported in the literature. Prior MDS was documented in 82 percent of the patients. Forty-nine percent of the patients harbored unfavorable cytogenetics, such as deletion of chromosome-5 or -7. The other patients had intermediate karyotypes. Patients with favorable karyotypes, such as inversion-16, were

not enrolled on this study.

All in all, 41 percent--this number is not on the slide--had both MDS and unfavorable cytogenetics.

Now, in terms of increased morbidity risks, 55 percent were age 75 or older--more than half; and 61 percent had evidence of organ dysfunction. This was manifested by two or more active medical conditions other than the AML, on either history, physical examination or laboratory findings.

[Slide.]

Looking at the number of risk factors per patient is also very interesting: 44 percent of the patients had two risk factors; 35 percent had three; 11 percent had four of these risk factors. So, overall, 90 percent of the trial population entered with two or more risk factors on this trial.

[Slide.]

The full spectrum of leukemic burden was represented also in this study. The median bone

marrow blasts count at diagnosis was 46 percent. All patients met the WHO criteria--as I mentioned--except for one, who was nevertheless included because he was clearly evolving from MDS. This patient, who did not achieve a CR was excluded by the FDA. But, for the sake of this presentation, I'm reporting the results based on the investigator's assessment.

[Slide.]

The majority of the patients were severely myelosuppressed--as would be expected--prior to study entry. The median neutrophil count was 636, with 61 percent having Grade 3 or 4 myelosuppression at the time of entry. Fifty-six percent of the patients had a similar degree of thrombocytopenia, with a median platelet count value of 41,500.

[Slide.]

So, in summary, the 136 patients accrued to this study represent a population with a high incidence of risk factors, and they routinely do poorly with available treatment.

So, it is in this context that I'd like to review the efficacy of tipifarnib for the next few minutes.

[Slide.]

Complete remissions were documented by the investigators at the research sites in 20 patients, for a complete remission rate of 15 percent. The associated 95 percent confidence interval ranges from 9 to 22 percent.

Partial remissions and hematologic improvements were documented in 10 additional patients. So, in total, tipifarnib reduced the leukemic burden of 30 patients, or 22 percent of the study population.

[Slide.]

In general, the data shows consistency across risk groups. And this is what we illustrate here on this slide.

For example, the complete remission rate in the 111 patients with prior MDS, secondary AML, was 16 percent; and the response rate in the patients aged 75 years or more was 12 percent.

[Slide.]

The complete remissions were documented at four of the six sites. No single institution accounts for the majority of cases.

[Slide.]

And as a specific quality control feature

of the study, the complete remissions were sought to be confirmed by the investigators, even though the primary endpoint of the study was achieving a CR.

So what this slide shows here, is that the primary endpoint of the study was complete remission, and that of the 20 patients who achieved a complete remission, 17 were confirmed by repeat bone marrow biopsy at one month. The three that were not confirmed include one patient who relapsed early, one patient who died while in CR, and one patient who refused further follow-up with bone marrow biopsies--and I will go over them in some detail for you.

[Slide.]

Patient 318 was an 81-year-old man with 90

percent blasts at baseline. He achieved a complete remission but had evidence of early relapse by peripheral counts on day 58.

Patient 336 was an 80-year-old man who achieved also a CR following one cycle of tipifarnib at the recovery of counts at the end of the cycle. Upon re-treatment with a second cycle, he developed drug-induced myelosuppression. This was complicated by neutropenic fungal sepsis, and then the patient died in CR on day 67.

And, finally, patient 508 was a 79-year-old man with 90 percent blasts at the time of study entry. He entered a CR which was established by bone marrow biopsy. He then refused further bone marrow assessments, but was maintained in CR by continuous treatment for 121 days, based on peripheral counts.

[Slide.]

Another aspect of the quality control measure was an independent review which was performed by Dr. Albitar. This reviewer was blinded to patient outcome.

This review involved a retrospective collection of the baseline diagnostic bone marrow slides from the 136 patients, and in addition, the

key aspirate slides which were obtained from patients on treatment. This included slides from 18 of the 20 patients who achieved a CR, so that the independent reviewer had access to a large proportion, although not all, of the CRs.

So his findings are summarized on this slide.

[Slide.]

As a result of his review, all 18 CRs--this is the first bullet--all 18 CRs that were available for him were agreed upon, for a concordance rate of 100 percent.

The reviewer--and this is the second bullet--the reviewer also agreed that 15 of the 16 confirmed CRs that were available for his review--there were 17 by the investigators, 16 available. And therefore, from his review of the 16, he verified that 15 were indeed maintained at one month.

The one disagreement is in the patient on whom there was agreement that he achieved a CR, but there was a disagreement as to the number of blasts in the follow-up period. The investigators assessed as less than 5 percent, and the independent reviewer assessed it variously between

6 percent and 9 percent. Both agreed on the time of relapse.

[Slide.]

Now, most patients who achieved a complete remission on this study had more than one risk factor. These complete remissions, but also partial remissions and heme improvements were documented regardless of the number of risk factors present in any given patients. And so the overall rates of anti-leukemic activity ranged from 19 percent to 29 percent, irrespective of the number of risk factors. There is no trend that can be identified.

[Slide.]

On this Kaplan-Myer plot, the x-axis is labeled in days. The complete remissions were

durable. They range from 33 to 376 days, with a median duration of 220 days. This is slightly more than seven months.

The 95 percent confidence interval around this is 154 up to 275 days.

Duration of complete remissions was calculated starting from the first documentation of CR until time of relapse. And the dots represent patients that were censored at the time of clinical cut-off, or the time of death, if they were still in CR.

[Slide.]

Now, turning your attention to survival, on this Kaplan-Myer plot, and on the one that will follow, patients were censored at the time of clinical cut-off or last follow-up. 131 patients have complete follow-up, and five patients had follow-up--at least partial follow-up.

The median survival of the patients who achieved a CR was 433 days. This is in excess of a year. Two patients were alive at two and three years, respectively. And these data suggest that

complete remissions are indeed associated with survival benefit in this patient population.

This potential effect on survival is being investigated in a 301 trial that Dr. DeLap described at the beginning of this presentation.

[Slide.]

Finally, the overall survival of the 136 patients is depicted here. The median survival was 164 days, or approximately five to five-and-a-half months.

[Slide.]

The information collected by the investigators concerned tipifarnib administration, obviously, but also treatment administered after failing the first course of treatment.

This slide shows the re-treatment of patients who achieved a CR--seven of the 20 patients who achieved a CR chose to stop after three cycles. They were re-treated with tipifarnib at relapse. One of these seven patients achieved a second complete remission of similar duration to the first one: approximately six months.

So these data suggest that patients may remain sensitive to tipifarnib at the time of relapse.

[Slide.]

The use of chemotherapy after tipifarnib in the 136 patients was also recorded. The majority of the patients went on to receive palliative care only.

Only 12 patients, most of whom were less than 75, were able to receive intensive chemotherapy, usually anthra-cycline plus Ara-C.

[Slide.]

So, in summary, tipifarnib is active in elderly, poor-risk AML. The CTEP investigators documented a 15 percent complete remission rate, which is the primary endpoint of the study.

Most of the complete remissions were confirmed at one month by the investigators, and verified by the independent reviewer. Complete remissions were durable, lasting 220 days, or 7.2 months. The median survival of patients with complete remission was 433 days, or 14.2 months.

[Slide.]

This enters the final section of the presentation, which concerns safety.

In terms of drug exposure, the median treatment cycle duration was 38 days. 47 percent of the patients received two or more cycles. So

this includes patients with complete remissions, partial remissions, and hematologic improvement--but also several patients who maintained stable disease for s several months.

[Slide.]

The need for treatment interruptions or delays explained the median cycle duration of 38 days which I just presented. Those reductions were implemented in 35 percent of the patients. Reductions were implemented in approximately half of the patients who received two or more cycles, such as the patients who achieved a CR.

The most common reason for dose reductions were related to myelosuppression, gastrointestinal, CNS--and, rarely, renal or dermatological signs and symptoms.

Patient age did not appear to have an impact on the tolerability.

[Slide.]

So, as expected in a population with AML, the adverse events were common: 61 percent of the population experienced drug-related adverse events. These were mostly related to myelosuppression--in the background of, of course, severe myelosuppression.

In contrast, only 10 percent of the patients were withdrawn for drug adverse event. And adverse events were also associated with a low mortality rate. Only nine patients in whom an adverse event--of the nine patients, actually, in whom an adverse event led to death, only one was assessed by the investigators as related to tipifarnib.

[Slide.]

To go into more details, a majority of patients experienced Grade 3 or 4 myelosuppression by peripheral count assessments. Fewer patients went on to develop clinical adverse events in the

form of sepsis or bleeding complications.

And, as I mentioned, approximately two-thirds had Grade 3 myelosuppression at the time of study entry, and so the overall incidence has to be interpreted in this context.

[Slide.]

Turning our attention to non-hematologic adverse events--that is, events excluding myelosuppression and its complications--the overall rate of life-threatening or Grade 4 events was low: 2 percent. Most events were reversible following treatment interruption.

The GI tract was most commonly involved. Nausea, diarrhea, vomiting were most often mild to moderate. The incidence of drug-related mucositis was only 3 percent. This is what this shows--5 percent, and 3 percent if we consider Grade 3 or 4 in severity.

Now, given that mucositis is a major contributor of morbidity and death in myelosuppressed patients, this is probably the most important--the most important safety advantage of

tipifarnib in this older population.

[Slide.]

Rare adverse events affecting the renal and CNS systems were documented. Few reached Grade 3 or 4 severity. All these adverse events were managed appropriately by protocol-defined treatment interruption and dose reductions. Many appeared in the context of sepsis, and were of short duration. Rapid ejaculation, the median duration of CNS events was two to three days.

[Slide.]

Very few patients--as we show here--were removed from the study because of these events.

Indeed, the adverse events that led to the termination of treatment were varied. No one AE appears to be a major contributor. The most common causes were elevation of serum creatinine and skin rash, both of which were reversible.

[Slide.]

This study did not have a specific module collecting data on quality of life as we would have. So, hospitalization data provides a valuable

perspective on the safety profile and the patient tolerability of this drug. And what it suggests is that outpatient treatment of this elderly population is feasible.

Up to 40 percent of the patients received their full course of treatment as outpatients. The majority of patients who were hospitalized were hospitalized only once or twice.

The median duration of combined hospital stay was 15 days--all hospitalizations. And this represents 14 percent of the patients spent on study.

[Slide.]

Finally, few patients died from adverse events on this study. No single cause appears to account for the majority of cases, most of which appear related to a complication of AML.

In the opinion of the investigators, only one death from neutropenic fungal sepsis was related to tipifarnib.

[Slide.]

So how can we best summarize CTEP-20?

First of all, CTEP-20 was a study of patients with significant unmet medical need, determined by the advanced age, and the high prevalence of risk factors which are associated with poor patient outcome.

In this patient population, tipifarnib induced as a monotherapy a 15 percent complete remission rate that was both durable and independent of risk factors.

The safety profile of tipifarnib allowed outpatient treatment. This might be due to a very low rate of life-threatening non-hematological toxicity, especially when one considers mucositis.

So, consequently, the time spent in hospital represented a small fraction of the total study time: approximately 14 percent. Only one death was attributable to tipifarnib.

This concludes my review. And Dr. Alex Zukiwski will deliver the closing presentation for Johnson & Johnson.

Benefit/Risk

DR. ZUKIWSKI: Thank you, Dr. Thibault.

Good morning. I'm Alex Zukiwski from the Oncology Development Group at Johnson & Johnson Pharmaceutical Research and Development. I'm going

to conclude the presentation today with a summary.

The proposed indication is: tipifarnib is indicated for the treatment of elderly patients with newly diagnosed poor-risk acute myeloid leukemia. The basis of this approval is complete remissions-- an accepted efficacy endpoint in AML which has been shown to correlate with overall survival.

[Slide.]

It is evidence that elderly patients with poor-risk AML have limited therapeutic options. As noted in Dr. Stone's presentation, select elderly patients should be considered for chemotherapy, although older patients do not do as well as younger patients. These patients who receive induction chemotherapy were described as having the best ability to tolerate and benefit from such treatment.

In the United States, approximately

two-thirds of the patients greater that 65 years of age do not receive IV chemotherapy. This is due to an unfavorable benefit-risk. These patients have risk factors which predispose to decreased efficacy, including antecedent hematological disorders such as myelodysplastic syndrome, and also have unfavorable cytogenetics.

They also have factors which predispose them to increased toxicity, such as co-morbidities and compromised performance status.

As indicated in the NCCN guidelines, options available for this under served patient population include investigational studies, low-intensity chemotherapy, and--unfortunately for many of these patients--it is simply best supportive care.

[Slide.]

The patients enrolled in CTEP-20 were felt not be well-served by standard induction chemotherapy. And this represents a unique patient population which is not well represented in the literature. For example, the CALGB and ECOG studies

mentioned in Dr. Stone's presentation enrolled patients who were good candidates for induction chemotherapy, and many of these studies excluded those patients with prior myelodysplastic syndrome.

The median age of the CTEP study population was 75 years, and 90 percent of the CTEP-20 patients had two or more risk factors which predisposed them to decreased efficacy and increased toxicity from conventional anti-leukemic therapies.

[Slide.]

The complete remission rate in this very difficult to treat patient population was 15 percent by investigators' assessment. As per the key academic investigators involved in the CTEP study, this response rate is meaningful in a patient population that is often excluded from AML studies, and many times receives palliative care only.

Of the 20 complete remissions as assessed by the investigators, the independent reviewer was able to confirm and verify 15 complete remissions

for quality control purposes. While the other five cases could not be verified for a variety of reasons, there is evidence of substantial anti-leukemic activity in these five patients.

The median duration of complete remissions was 220 days, and complete remissions were observed across all risk groups.

The exploratory analysis of survival--as outlined by Dr. Thibault--is encouraging, and will be further examined in an AML study specifically designed to evaluate a survival endpoint.

[Slide.]

The anti-leukemic activity observed in the CTEP-20 study has to be considered in the overall treatment context as presented by DR. Stone. Even in the "best" patients who can receive induction chemotherapy, individual risk factors which were very prominent in the CTEP-20 study have a negative impact on complete remission rates.

As shown in this slide, a reduction of complete remission rates by approximately one-half is observed in patients with prior myelodysplastic

syndrome, unfavorable cytogenetics, or advanced age--with even the most effective chemotherapeutic agents.

The early death rates in these trials, which includes the more younger and fit patient populations, is approximately 20 to 25 percent, with the majority of these deaths associated with bone marrow aplasia and severe mucositis.

[Slide.]

Now, to put the CTEP-20 study into context.

These are patients which experienced AML investigators felt were not the best candidates for combination chemotherapy. They had an 83 percent incidents of myelodysplastic syndrome; a 49 percent incidence of unfavorable cytogenetics, and a median age of 75.

What would be the anticipated complete remission rate in this patient population with combination chemotherapy?

The anticipated early death rate in this patient population with combination chemotherapy

would most likely be at least double the 12 percent early death rate observed in the CTEP-20 trial.

[Slide.]

In the patient population studied in CTEP-20, advanced age, with its associated co-morbidity co-morbidities, and the underlying disease complicates any treatment efforts.

Despite this, a management and predictable safety profile was observed in the patients treated with tipifarnib. Adverse events were managed with supportive care measures. As the scheduled treatment was for 21 days, dose modifications--including dose interruptions and dose reductions--could be quickly implemented to address any emerging toxicities.

Forty percent of the patients did not require hospitalization. And for those who were hospitalized, the median duration was approximately 15 days. The limited time spent in hospital is an important feature of this outpatient treatment.

Twelve percent of the patients died on study within 30 days of the first dose of

tipifarnib. And only one treatment-related death was reported by the investigators during the study. This data indicates that tipifarnib has been shown to safely treat a unique elderly patient population.

[Slide.]

In conclusion, the application under review is focused on a difficult to treat patient population for whom an unmet medical need exists, and alternative treatments are required. Approximately one in seven to one in nine of the patients treated with tipifarnib developed a durable complete remission.

This novel targeted therapy is administered as an oral tablet which allows for flexible outpatient dosing. As presented here today, there is a positive benefit-risk evidence with tipifarnib treatment.

Approval of tipifarnib for this orphan indication will provide a new treatment for elderly patients with poor-risk AML. These patients are currently not well served. Standard induction

chemotherapy has a high degree of toxicity and a lower degree of efficacy in this patient population.

This concludes the sponsor's presentation.

DR. MARTINO: Thank you.

Ladies and gentlemen, I will not allow questions until we have also allowed the FDA and Dr.

Fred Appelbaum to present. So those of you that have questions please know that that will be your opportunity.

Dr. Ryan, representing the FDA, will present next.

FDA Presentation

NDA 21-824, Zarnestra

DR. RYAN: Good morning. I'm Qin Ryan, medical officer in the Division of Oncology Drug Products. I'm here today to present the main findings from our review of Zarnestra NDA 21824.

[Slide.]

My presentation will cover the relevant regulatory background; clinical development

overview and proposed indication; CTEP-20 study design, efficacy and safety findings.

[Slide.]

First, the relevant regulatory background.

In oncology, clinical benefit has been defined as a longer life, a better life or an effect on an established surrogate for either.

In acute leukemias, durable complete remission--CR--has been considered evidence of benefit.

In some cases where leukemia CRs were of uncertain duration, CR was considered a surrogate reasonably likely to predict clinical benefit.

[Slide.]

Here are some examples. As first-line indications for acute myeloid leukemia --AML--both idarubicin and daunorubicin were regular approvals based on demonstration of durable remissions in randomized trials. In addition, idarubicin also demonstrated a survival advantage in two comparative studies.

In the case of gemtuzumab, accelerated

approval was granted for patients aged 60 or older with CD-33 positive disease who are not candidates for second-line cytotoxic chemotherapy. Approval was based on a pooled complete remission rate from three single-arm studies. Of 277 patients enrolled into these three studies, 157 were 60 years or older. Although relaxed free survival was evaluated, the ratio of remission could not be reliably ascertained, as 45 percent of patients who achieved remission also received additional anti-leukemic therapy.

[Slide.]

Next, I will discuss the clinical background for this NDA.

Patients with newly-diagnosed AML, if not treated, will progress rapidly to a fatal outcome. The standard induction therapy for newly diagnosed AML, such as 3+7 regimen of cytarabine and daunorubicin can be expected to achieve 60 to 75 percent complete remission. And the treatment-related death rate, less than 10 to 20 percent in adult AML patients younger than age 60.

[Slide.]

One follow-up study indicated that 30 to 40 percent of patients in this age group will

survive three years or more. However, clinical outcome would depend on multiple factors. Unfavorable outcome is usually associated with multiple poor-risk factors, such as poor performance status, organ dysfunction, or significant co-morbidity, older age, unfavorable karyotype, prior MDS, disease resistance or patient intolerance to cytotoxic therapy.

Although the incidence of adult AML increases with age, the chance for patients to receive treatment decreases.

[Slide.]

Menzin, et al., analyzed a data base of over 2,600 AML patients aged 65 or older, identified by Medicare claims. Overall, only 30 percent of those patients received some form of chemotherapy. Asa shown here, the percentage of patients receiving chemotherapy decreased drastically with increasing age.

[Slide.]

Menzin, et al., also estimated survival for these patients. As indicated by the curve with diamond points, the median survival for all identified patients was two months, with a two-year survival of 6 percent.

[Slide.]

Compared to younger adults, elderly AML patients usually present with other risk factors, such as poor performance status, organ dysfunction, co-morbidity, unfavorable karyotype, prior MDS, and drug resistant disease, as mentioned before. The less tolerant to standard induction therapy the elderly poor-risk AML patients are, the more likely they are to be a therapeutic challenge.

[Slide.]

One review pointed out that treatment-related mortality in elderly patients with poor-risk AML may be as high as 25 percent, and the complete remission rate may be less than 50 percent.

In a study of AML patients at least 80

years of age, the mortality rate at one month as 48 percent, and the complete remission rate was less than 30 percent.

Few elderly AML patients are expected to live free of disease after standard cytotoxic chemotherapy.

[Slide.]

Next, I will discuss the clinical program.

Zarnestra is a farnesyl transferase inhibitor. It is formulated in film coat 100 mg tablets. In the CTEP-20 study, Zarnestra was tested as first-line AML induction therapy. It was administered hourly with food, at a dose of 600 mg twice daily for 21 days, followed by a rest period of seven to 42 days.

[Slide.]

Zarnestra is being proposed for the treatment of elderly patients with newly diagnosed poor-risk acute myeloid leukemia.

[Slide.]

Eleven studies relevant to safety and dose findings have been submitted in this NDA. Among

those, the studies relevant to efficacy and safety in AML are summarized here. The most relevant population for the proposed indication is a subgroup of subjects in Study CTEP-20, accounting of 79 percent of CTEP-20 enrollment.

The studies INT-17 and CTEP-1 are less relevant to the proposed indication. Therefore we will focus our discussion on CTEP 20.

I will now go over the CTEP-20 study design in the next few slides.

[Slide.]

This open-label, single-arm, multicenter study which opened on October 10, 2001, was originally designed to assess the efficacy and safety of Zarnestra in subjects with previously untreated, poor-risk hematologic malignancies. After enrolling 110 patients, Amendment 6 was implemented on September 16, 2003. The target population as redefined as subjects either 75 years or older with newly diagnosed AML, or 65 to 74 years of age with AML arising from prior myelodysplastic syndrome.

[Slide.]

The original primary objective was to determine response rate, which included CR and PR.

As mentioned, after the 6th Amendment, the primary objective changed to determining the complete remission rate in elderly subjects with previously untreated, poor-risk acute myeloid leukemia.

Secondary objectives were to determine the progression-free survival, overall survival, duration of response, and safety profile.

[Slide.]

After Amendment 6, the major inclusion criteria can be described as follows: untreated newly diagnosed AML patients, 75 years or older, or 65 to 74 years of age with prior MDS.

Our eligible subjects should have pathologic confirmation of AML showing equal or more than 20 percent marrow or peripheral blasts. Patients must have an ECOG performance score of zero or one-- which was changed from the original zero to two--with adequate renal and liver function.

Patients with the following conditions were excluded: hypoleukocytosis despite leukopheresis or hydroxyurea; acute promyelocytic leukemia; previous anti-leukemic chemotherapy other than hydroxyurea; disseminated intravascular coagulation, or leukemia involvement of the central

nervous system.

[Slide.]

Leukemia assessments were conducted at baseline and the end of each cycle, ranging from 29 to 64 days. This included medical history, physical examination, bone marrow aspiration and biopsy, CBC and chemistry.

The criteria for response assessment were based on NCI-sponsored workshop on definition of diagnosis and response in acute myeloid leukemia.

Per protocol, CR is defined as marrow showing less than 5 percent myeloblasts, with normal maturation of all cell lines; an ANC of at least 1,000 per micro liter; a platelet count of 100,000 per micro liter; absence of blasts in peripheral blood; absence of identifiable leukemic

in the bone marrow; clearance of disease-associated cytogenetic abnormalities; and clearance of any previously existing extramedullary disease.

In addition, CR must be confirmed four to six weeks after initial documentation; at least one bone marrow biopsy should be performed to confirm CR.

Subjects who achieved a complete remission could receive additional Zarnestra treatment until disease progression, or receive up to three additional cycles and stop.

Re-treatment with Zarnestra was allowed. Subjects with progressive disease at any time during the Zarnestra administration were withdrawn from the study. The first follow-up occurred 30 days after treatment termination for subjects who did not have a documented progression, or had not started subsequent therapy; every 90 days after documentation of progressive disease or start of subsequent therapy.

In the next few slides, I will discuss the CTEP-20 patient population efficacy data.

[Slide.]

Of the total 171 patients enrolled in CTEP-20, 158 of them had AML. At the time of

clinical cutoff, 157 AML subjects were treated with at least one cycle of Zarnestra. Of those, 136 were elderly subjects with poor-risk AML, and are most relevant to the proposed indication.

Please note that one of the elderly subjects with poor-risk AML was excluded from FDA's efficacy analysis, but not safety analysis. The reason for this exclusion was that this patient's baseline blast count was less than 20,000 per cubic milliliter, as assessed by both the investigator and the sponsor's central review. This patient did not respond to Zarnestra treatment.

This resulted in 156 evaluable patients in the all-treated AML population, and 135 patients in the elderly poor-risk AML population.

Two thirds of subjects had a performance status of one, and a quarter of them had a performance status of zero. There were approximately 10 percent of patients who were

enrolled before Amendment 6, with a performance status of two. As per investigators, all 136 patients were ineligible for standard chemotherapy for at least one reason.

Of patients aged 75 or older, 96 percent were considered ineligible due to age, whereas in the 65 to 74-year-old group, approximately 50 percent of patients had age or other risk factors as a reason for ineligibility.

[Slide.]

Based on the sponsor-provided data, risk factors in the CTEP-20 elderly poor-risk AML population are summarized by category and number.

Eighty-two percent of patients had prior MDS; more than half of the patients were older than 75 years, or with poor organ function as defined by the sponsor; and two-thirds of patients had unfavorable karyotypes; 44 percent and 35 percent of patients had at least two or three of these risk factors, respectively. About 10 percent of patients had either one or four risk factors.

Complete responders were initially

assessed by the site investigators. The sponsor appointed an independent reviewer to reassess the complete remissions. FDA requested all available bone marrow slides of CRs from the sponsor, and reviewed them with an FDA-appointed hematology consultant.

[Slide.]

The assessment of CR by the study investigator, the independent reviewer, and FDA are summarized here. Of the three unconfirmed CRs, the FDA and independent reviewer agreed with the investigator that two could not be confirmed due to death and disease progression. FDA also agrees with the independent reviewer that on CR by investigator assessment was unconfirmed due to insufficient data. In addition, slides of two subjects were not available for response assessment by the sponsor's independent reviewer or FDA consultant.

[Slide.]

FDA agrees with the sponsor-appointed independent reviewer's assessment of complete

remission; that is, 15 subjects were confirmed complete remission from the FDA-identified elderly poor-risk AML patient subgroup.

FDA assessment of the confirmed complete remission rate is 11.1 percent, with a 95 percent confidence interval of 6.6 to 18 percent.

[Slide.]

Based on FDA exploratory subgroup analysis, patients older than age 74 have a lower tendency to achieve complete remission than do patients age 65 to 74, with a rate of 6.7 percent versus 16.4 percent, respectively.

In addition, of the 25 patients older than 74 years with de novo AML who enrolled in CTEP-20, only one patient achieved complete remission with confirmation.

Less responders were seen in subjects with unfavorable karyotypes.

[Slide.]

The FDA has explored the duration of confirmed CR as a secondary endpoint of study CTEP-20. Per protocol, no anti-leukemic therapy

other than Zarnestra was given to patients who achieved a response until after disease progression and removal from the study.

At the time of cut-off, progression of disease or death occurred in seven of 15 patients, giving a median remission duration of 275 days, with 95 percent confidence interval of 127 to 376 days.

Next, I will discuss the CTEP-20 safety data.

[Slide.]

In CTEP-20, all of the elderly poor-risk AML patients received at least Zarnestra during first cycle; 47 percent of them were treated for a second cycle, and 20 percent received a third cycle.

The median duration of these cycles was 36 to 38 days. The mean intensity for the first cycle was 749.4 mg per day, which is approximately 63 percent of the planned 1,200 mg per day dose.

The calculated dose intensity may not reflect true drug exposure, since the Zarnestra

exposure measurements were primarily based on the pharmacy dispensation record. A patient medication diary was not planned for CTEP-20.

[Slide.]

Ninety-eight percent of CTEP-20 subjects experienced adverse events. The most frequently reported non-hematological adverse events were diarrhea, fatigue, nausea, skin rash, fever, anorexia, constipation, vomiting and dyspnea. Dizziness, and ataxia or abnormal gait were the most frequently seen nervous system adverse events. In addition, confusion was the most commonly seen psychiatric adverse event. This may be related to age and hospitalization.

The most common dermatological and infection-related adverse event were neutropenia, with or without fever; purpurea, thrombocytopenia, anemia, bacterial infection, candida and other fungal infections.

The most frequent metabolic disturbances were increased creatinine, hypokalemia, and hyponatremia.

Of 136 subjects, 21, 47 and 56 subjects had at least one adverse event leading to treatment termination, dose reduction, and temporary

interruption of Zarnestra, respectively. The top three adverse events leading to changing treatment were neutropenia, increased creatinine and rash.

FDA agrees with the sponsor that 113 subjects, or 83 percent of the elderly poor-risk AML group, experienced Grade 3 or 4 adverse events. The most frequent treatment-emergent Grade 3 or 4 adverse events were secondary to myelosuppression, including neutropenia, with or without fever, infection, thrombocytopenia, and anemia.

Other frequent severe adverse events were fatigue, rash, dyspnea, confusion, diarrhea, and hypokalemia.

[Slide.]

Thirty-one of the 136 elderly poor-risk AML subjects in CTEP-20 died, either within 30 days of treatment termination, or within 30 days of receiving the first dose of medication. The death rate within 30 days of the first dose was 12

percent. Based on the sponsor-provided data, we verified the sponsor's summary and agree that 19 of 31 deaths were due to disease progression, and nine of them were due to adverse events. The deaths due to adverse events were 7 percent with causes such as cardiac failure and various infections.

One death due to adverse event was thought to be drug-related by the investigator. This was a patient who had a neutropenic fever, fungal infection, and renal dysfunction.

There were three of 31 deaths attributed to adverse events or progression of disease on subsequent treatment, after patients progressed from Zarnestra, which the sponsor categorized as "other" cause of death.

[Slide.]

Eighty-one subjects, or 60 percent of the total 136 patients, were hospitalized during the study. Fourteen percent of the subjects received Zarnestra treatment in the outpatient setting completely.

The median total duration of

hospitalization was 15 days. Ten subjects required at least three hospitalizations during the study period.

[Slide.]

In summary, durable complete remission has been accepted as an endpoint supportive of regular approval in AML. Zarnestra efficacy findings should be considered in the context of a poor-risk AML population and the toxicity profile observed. Although the remission rate does not compare favorably with that reported with cytotoxic therapy, the one-month's mortality and treatment related date rate of 12 percent and 7 percent, respectively, compare favorably with the greater than 25 percent treatment-related death rate reported in the literature for patients age 60 or older, with or without other risk factors, who had adequate organ function to receive chemotherapy.

We will have one question for the committee to discuss: does the risk-benefit analysis support regular approval of Zarnestra for the treatment of elderly patients with AML?

Thank you very much for your attention.

DR. MARTINO: Thank you, Dr. Ryan.

At this point, ladies and gentlemen, we

have one additional speaker, and that is Dr. Fred Appelbaum, who will present via videoconference at a quarter to the hour.

So, at this point, I'm going to give you about 15, 20 minutes of a break, and we'll be back here at 10:45 for his video presentation. We will take questions subsequently.

[Off the record.]

DR. MARTINO: Back on the record.

The next presentation is Dr. Fred Appelbaum. He's going to speak to us via videoconference. He is the Director of Clinical Research at Fred Hutchinson Cancer Center. And I don't know if we are actually ready to go.

Ms. Clifford? Are we ready to go with Dr. Appelbaum?

MS. CLIFFORD: I think so.

DR. MARTINO: I someone going to clue him in? Or shall Dr. Martino simply say: "Action."

AML in Older Individuals

[Via videoconferencing]

DR. APPELBAUM: I couldn't hear anything you were saying. Can you see my slides?

VOICE: [Off mike.] [Inaudible.]

You won't be able to follow the pointer,

is that right?

Well, thank you for inviting me to say a few words about AML in older individuals. I was asked by the FDA just to provide a general background. I am not speaking particularly about this product or any of the information that was presented about the product, but rather just a global picture of AML in the elderly. Some of this was probably already gone over this morning, so I will be relatively brief.

[Slide.]

The problem of AML in the elderly is a substantial one because the disease, as you can see from the first slide, in terms of incidence, goes up quite rapidly once patients are in their sixth decade. Before that, it is relatively uncommon.

But once patients pass the age of 50, the incidence of AML goes up quite markedly.

The problem of AML in the elderly--or the older individual--is different than AML in the younger individual for two primary reasons. First, the patients are different and, secondly, the disease is different.

In terms of patients being different--well, older patients are older. And, with that comes an increased incidence co-morbidities and decreased performance status.

[Slide.]

This next slide shows you a typical picture of patients that were entered onto a protocol for patients with AML above age 55, using a standard induction regimen of daunomycin and Ara-C.

As you can see from the performance status and the age, patients under age 60, a relatively small proportion of them--about 8 percent--will have a very poor performance status of 3 or greater; whereas once patients are over age 75,

that incidence at least doubles.

Yet, even on those over age 75, at least 60 percent--on this Southwest Oncology Group Study, which was the last one performed--had a performance status of zero or one, indicating relatively good performance.

These statistics almost certainly understate the problem of decreased performance status in the elderly, because these are patients that the doctors chose to enter onto the trial. And it may be that, particularly among the elderly, there's a substantial proportion who were not entered onto the trial because of decreased performance status.

I know of no easy--or no way, in fact, at all--that we can get data which truly reflects the performance status on a population basis of the elderly patients with AML. This is almost certainly an underestimate of the difficulty.

[Slide.]

The next slide shows, I think, a very important principle that hasn't been talked

about--or it hasn't been published, to my knowledge, quite in this way--and that is the very great interaction between performance status and age. So that this looks at patients, again, treated with a standard induct of Daunomycin-45 x 3 and Ara-C, and a chance of dying within the first month of being entered onto study, based on the performance status and age.

So that older patients--that is, those that are over age 70, have a relatively low chance of dying within the first 30 days if they have a good performance status--only 9 percent, which is not substantially different than what you'd see in patients even under age 50.

Yet once patients get older, and their performance status goes done, then you see a marked interaction. So that if you're both over age 70 and have a performance status of 3, the chance of dying within the first 30 days is 62 percent, which is very, obviously, substantial. So there's this interaction which is--both of performance status, because the younger patients don't have that high

chance of dying, even with a poor performance standard. That's only 17 percent. So you can see there's this interaction with both age and performance status, which are cumulative.

[Slide.]

This, of course, reflects what would happen with the overall complete response rate--I'm sorry, this slide simply shows what I just told you, but in a different graphic form. That is performance status and age being cumulative in terms of the chance of early death, with 62 percent--that's in the back right, versus a very low chance, in the front left, if you are young and have a good performance status.

[Slide.]

This clearly reflects--on complete response rates, which are shown in the next slide, so that if you're over age 70 treated with standard chemotherapy and have a good performance status, you have a relatively good chance--50 percent or greater--of getting a complete response. But if you're older and have a poor performance status, it

deteriorates to, in this study, 29 percent. Whereas if you're younger and have a poor performance status, the interaction doesn't seem to be as great. The numbers in these individual cells get fairly small with a total n of 500.

So, the first way that AML in the elderly or the older patient differs is that the patients are older, they tend to have a poor performance status, and a poor performance status is a clear bad prognostic factor for getting a CR and for early death.

The second way that AML in the older patient differs is that is biologically is different from AML in the younger patient--in general; not in each specific case, but as a population it differs.

AML in the older patient is more often preceded by myelodysplasia. It is a less proliferative disease. It's more frequently associated with unfavorable cytogenetics, and it more often expresses multidrug resistence.

And I'll show you data about each of

these.

First, as far as "preceded by myelodysplasia"--and here one has to be careful about the definitions. If one takes a strict definition of having a documented hematologic disorder preceding the diagnosis of AML by at least three months, generally this is seen in about 15 to 18 percent of patients who are over age 55, and seen in about half that number in patients who are less than age 55.

[Slide.]

As far as "less proliferative" is concerned, that's shown on the slide you now have in front of you. And this is a large number of patients--about 900 patients on three sequential studies--and it just shows that the white count, at diagnosis for AML, in patients who were less than age 55 is about 17,000, but it goes down to about 12,000 when you're over age 75. And the percent blasts if you're less than age 55 tends to be higher, at 39 percent; but if you're over age 75 it drops to about 26 percent--not marked differences,

but there is a biologic difference here which suggests that AML in the very old patient tends to be a less highly proliferative disease.

[Slide.]

The next slide shows the marked difference in cytogenetics as patients age in AML.

The blue bars at the very top are the percent of AML patients with unfavorable cytogenetics, according to age. So that if you're less than age 55, about 21 percent of patients will have unfavorable cytogenetics, using the SWOG--or Southwest Oncology Group--criteria for cytogenetic risk group--which is very similar, but not quite identical, to the MRC's definition.

If patients are over age 75, the incidence of unfavorable cytogenetics increases markedly from 21 percent to 52 percent; and, conversely, the dark bar at the bottom, the percent with favorable cytogenetics--that's 8;21, inversion 16, or 15, 17, then that drops from 20 percent in patients who are less than age 56, to only 4 percent if you're over age 75.

The particular cytogenetic abnormalities which are seen more frequently as one ages are shown on the next slide.

[Slide.]

And they are of marked increase in the incidence in the loss of -5, or part -5, on the long arm, or loss of -7 or part of 7 on the long arm, where either one of these was seen in either 6 to 8 percent in patients age less than 56, but if you're over age 75, you see this in a three or four-fold higher incidence, with 26 or 22 percent, respectively.

Similarly, a loss of the short arm of 17 is seen in only 2 percent less than age 56, and greater than 11 percent in those age greater than 75. And all those p-values you can see are .0001.

Conversely, as I've already mentioned, inversion 16, and 8;21s drop as you get older, among the favorable cytogenetic risk group.

It is, I think, just intellectually interesting to speculate why we see this particular differences with age. We don't, in fact, know the

answer.

Some have argued that AML in the elderly is more the result of multiple cytogenetic or mutational [technical difficulty] a myelodysplasia with a subsequent alternations.

An alternative hypothesis is that our stem cells get older, and getting a leukemia stem cell is a bad thing to do and the disease, therefore behaves differently in the elderly. And there is some data for each of those arguments.

[Slide.]

MRK is one way of measuring multidrug resistance. It may not be the best. It's a simple, reproducible one. But whether one uses MRK staining, or one uses actual drug efflux, which is cyclosporin inhibitable, in either way that you measure it, you will find that, as patients age, there is a higher incidence of multidrug resistance.

In this--which included about 600 patients--if you were less than age 56, about 33 percent would have a bright MRK staining. If you

were over age 75, it's about twice that number.

[Slide.]

Now, if you take all of these possible changes, and you look at the likelihood of getting a complete response, in univariate analysis--this is a study that we did in the Southwest Oncology Group--in univariate analysis you can see that these make a big difference in outcome. AML, if you have a secondary AML--that is, secondary to primary myelodysplasia; this isn't treatment related, which is another kind of secondary AML. But this is secondary to primary myelodysplasia--the CR rates are half as much as if you have a de novo disease, if you are CD34 positive in some, but not all studies, in this one, that seemed to give a lower incidence of complete response rates.

As I obviously mentioned, MRK staining--if you have a bright, you have half as much chance of getting a CR as if you're negative.

Unfavorable cytogenetics--again, about half as much a chance of getting CRs as if you have

intermediate or favorable. And functional drug efflux, like MRK staining, also predicts for CR rates.

[Slide.]

Now, this is in univariate analysis. When we looked in multivariate analysis, we found three factors-- and that's shown on the next slide that predicted for complete response rate: and that is whether you had secondary AML; if you had unfavorable cytogenetics, and then if you had MDR1 expression--either by functional drug efflux or MRK staining. And each one of these were independently significant in this multivariate analysis.

And if you had all three factors present, you had almost no chance of getting a CR; that is, if you had secondary AML, with unfavorable cytogenetics and MDR1 expression, the chance of CR was 11 percent. But even if you're over age 65, if you had none of the three factors, you'd have an 81 percent chance of getting a complete response--much like you would expect in a younger patient with AML.

[Slide.]

Now, we're not the only ones that have seen this. This has been seen by others. One of

the largest studies of treatment of AML was the MRC AML 11 Study. It looked at three different preparative regimens: a classic daunomycin-Ara-C and 6TG regimen, versus the daunomycin-Ara-C VP-16 regimen, versus a mitoxantrone-Ara-C regimen--and then also randomized to giving G-CSF after induction. And they also had a randomization and consolidation of two, versus six, cycles.

The study itself isn't what I"ll be talking very much about, since none of these factors had a major impact on outcome. But I would--just to look at this study-- which was published in Blood in 2001--for the general principles of treatment of AML. And, as I said, this was a large study--it will show on the next slide--with over 1,300 patients. And they had ages between 56 and up to above 90 years old.

[Slide.]

As I said, in the Southwest Oncology

Group, we see about a 15 to 18 percent incidence of secondary AML, which is exactly what the MRC study saw. And they had a 4 percent incidence of treatment-related disease. Ours was a bit higher in SWOG--about 6 percent. But these are very typical numbers for AML in the older individual.

[Slide.]

In their study, they had a 62 percent complete response rate. They had a 7 percent death in incomplete response. They had a relapse rate of 78 percent, and they had disease-free survival at five years of 15 percent.

These results are fairly typical of most studies of chemotherapy for patients over age 55.

As I have tried to make the point--and will make it again--

[Slide.]

--oh, this shows you the outcome by treatment group. And, as you can see, there is essentially no difference among the three groups, with a median survival that is between nine and 11 months, and a five-year survival which is down

around 15 percent on these studies.

Now, the point I've tried to make repetitively is that AML in older patients is a very heterogeneous disease.

[Slide.]

And this shows you--the next slide shows you--what the MRC found. And they found essentially the same thing that we had previously reported in SWOG--and other have reported, as well--and that is that cytogenetics, age, whether you have primary or secondary disease, performance status and--in their hands--also white count at diagnosis were powerful predictors. And you can see, with a large study of over 1,300 patients, how powerful these are. Those p-values are 10-14 or 10-6, or 10-7--so that's a lot zeros, suggesting that these are very powerful predictors. So that unfavorable cytogenetics--both for complete response rate and overall survival--is a bad fact; having a high white count likewise gives you a low chance of CR or overall survival. As you age, things get worse. If you have secondary disease

and if you have a poor performance status--the same things that we had previously reported.

[Slide.]

So, in summary then, using conventional chemotherapy, if you take a large cohort of patients that are over age 60--or 55, depending on the particular study--complete response rates of 50 to 60 percent can be expected; a median survival of 9 months can be also expected in this cohort of patients; and perhaps 10 to 15 percent may continue to be alive after four to five years.

However--and this is the most important point--the patient and disease-related factors very greatly, among this population, and heavily influence treatment outcome. In my mind, particularly important in considering any patient group are age, performance status, primary versus secondary presentation, cytogenetics and the MDR status.

And these facts have been relatively unchanged over the last several decades because our therapies for AML in the elderly haven't changed

very much over the last several decades. And there clearly is a need for new and effective agents for this patient population.

I'd be happy to answer any questions about this relatively brief and perhaps superficial presentation.

Thank you.

DR. MARTINO: Fred, Thank you. And ladies and gentlemen, it is my understanding that we are able to handle some questions to Dr. Appelbaum--from a technical perspective. So, if there are questions to him directly, this would be your opportunity.

Dr. Mortimer?

DR. MORTIMER: Yes, Fred--this is Joan Mortimer. I wonder if you could just make a comment on the role of growth factors. I presume that since you didn't talk about it in the MRC trial that there is no advantage or disadvantage to the use of growth factors?

DR. APPELBAUM: In the MRC trial there was no advantage or disadvantage for the use of growth

factors. There have been--as you know, probably better than anyone on the planet, Joan--I think at least a dozen studies of the use of growth factors after chemotherapy for AML in older individuals.

And the vast majority of those studies show that the use of growth factors shorten the duration of neutropenia quite consistently by five to seven days. They are more variable in whether that shortening of neutropenia changes the risk of significant infection; and only, as I'm aware, two studies showed a change in survival or complete response rate. The majority of them showed no effect on CR rates or survival, but did show an important shortening of the period of pancytopenia--that's after induction. And then after consolidation, the results are a little more consistent that you shorten neutropenia and decrease the incidence of infections--again, with no change in survival.

DR. MARTINO: Dr. Brawley, you're next.

DR. BRAWLEY: Yes, Otis Brawley here.

Dr. Appelbaum, in the studies that you

presented, and all the data that we've reviewed, it seems like the goal is always to get a complete remission, as if the complete remission is a surrogate for patient benefit in terms of increased survival.

Has anyone ever tried any studies that look at the possibility of a drug that might sort of suppress a smoldering factor, where the goal is not complete remission but suppression of the leukemia, and perhaps try to determine of that actually increases survival--especially in an older, sickly population?

DR. APPELBAUM: That's an excellent question, Dr. Brawley. And the lessons that had been learned in acute leukemia in younger patients, where it's a much more proliferative disease, have sort of given the indication that you really have to get a complete response if patients are going to survive for any length of time, because the disease is so very proliferative.

Now, on the other hand, if you take the totally other tack of looking at myelodysplasia as

being a sort of symbol for a less aggressive disease--we now have data that a drug which doesn't get complete response rates, so that it phibezacytadine by perhaps a slowing--some people can argue why phibezacytadine works. Some people believe it's a differentiation factor. Other people believe that it actually is working as a cytotoxic. But, without getting complete responses, it appears that it may prolong survival.

Years ago, the way that many patients--very old patients with AML--were treated was with much less aggressive therapy using oral 6MP, or using daily or weekly VP16, trying to keep the cap on things. And I believe that there were some suggestions--not proven in randomized trials ever, but suggestions that there was improvement in survival.

You are, I thin, correct that it is possible that there will be drugs--maybe many drugs--that could cause differentiation, slowing down the proliferation, and be of some benefit to the patient without getting a complete response.

But the lessons from the more aggressive disease is that generally those effects are temporary and not as lasting as physicians would

like.

I'm not sure if that answers the question adequately.

DR. BRAWLEY: Actually, it answers it wonderfully.

The reason I asked the question is I look at our data on Zarnestra, and I wonder what a lower dose of Zarnestra for a longer period of time, without an endpoint for complete response would do in terms of patient benefit.

Do you think I'm going down the wrong path to say that that's something that perhaps we ought to be looking at with a farnesyl transferase inhibitor?

DR. APPELBAUM: I think that it's going to be very patient-dependant. I believe that there are--well, I know there are AMLs in older patients which look just like AMLs in younger patients, which are explosive diseases, rapidly

proliferative, and I think it's less likely that we're going to be able to keep very good control of the disease without establishing a complete response.

There are other patients who are older who [technical difficulty] very similar to myelodysplasia and, in fact, getting rid of--it's much less proliferative and, you know, there are cases, in fact, of erythroleukemia in the elderly where simply giving red cells causes blasts to decrease, and the average survival in some of those patients, even without aggressive chemotherapy, can be six to nine months. So it's very patient-specific.

DR. MARTINO: Dr. Cheson?

DR. CHESON: Hi, Fred. I have two questions for you.

The first one follows on what Otis was sort of asking you. A lot of the data we have on survival of AML are from olden times, when we were young. And there's a drug that was pretty good at controlling the disease: hydroxyurea. And now that

we have better antibiotics, better supportive care, better growth factors, etcetera, one wonders how you might be able to control this disease using a collection of those agents and do very nicely without--you know, less expensive, etcetera.

The second question relates to the fact that there have been a number of randomized trials in the past of chemotherapy versus supportive care in elderly patients with AML. And I was wondering if you could comment on those?

DR. APPELBAUM: Well, the first [technical difficulty] interesting one, and I agree that, with better support care, with better antibiotics, possible with better hematopoietic growth factors, we may be able to eke out some increased survival of months or even longer without getting complete responses, [technical difficulty] responses, or just diminished blast percentage.

The quality of life of those patients--I think most of us who care for a lot of AML patients--as you do--isn't great, but [technical difficulty] trips to hospital, a lot of transfusion

support--[technical difficulty]--

[Communication lost.]

DR. MARTINO: Can anyone help us at this point?

DR. CHESON: We lost you, Fred.

DR. MARTINO: Fred, if you can hear us, we cannot hear you. So, stand by, please.

[Pause.]

[Communication re-established.]

DR. APPELBAUM: As far as the randomized trials of support care, there have not--well, maybe you can inform me about any large, modern randomized trial of supportive care versus chemotherapy for AML in the elderly. The ones that I'm aware of were don--were quite small, and done decades ago, without current supportive care measures.

I'm not aware of any that have been done in the last 20 years.

DR. CHESON: Right, but the results of chemotherapy versus supportive care in those studies--some of which were modestly sized,

including the ones from Europe--suggest that a chemo really probably wasn't of much benefit. But, again, that's before supportive care, growth factors, etcetera.

DR. APPELBAUM: Yes, and those are a couple of decades old. And what they did show is that those--if you take a population of patients, you're exactly right, the patients that got a CR benefitted--or at least appeared to benefit--but the overall population did not. But, again, those are several decades old, they were done in the '70s, without current supportive care measures.

DR. MARTINO: Are there other questions?

Yes?

MR. FLATAU: Dr. Appelbaum, I was wondering if you could comment on survival with supportive care in older patients with de novo AML, versus AML that arises from [Off mike.] [Inaudible.]

DR. APPELBAUM: If I understand the question, you're asking about what is the survival with supportive care alone in AML in the older patient compared to the younger patient. Is that

the question?

MR. FLATAU: No, I'm wondering: de novo AML in older patients on supportive care, versus AML that arises from prior myelodysplasia.

DR. APPELBAUM: Oh.

Historically, the median survival for de novo AML on supportive care is about two months when patients are given supportive care alone. With older individuals given just supportive--now, it depends on what you mean by "supportive care." It's been a long time since people just got supportive care, with using 6MP as a single agent, or VP16 as a single agent. There were some studies published in the '70s which suggested survivals of four to five months, using single-agent chemotherapy in older patients with AML.

Most of those studies did not, at that time, break down the groups between AML that was de novo versus AML that was secondary to a prior myelodysplasia. I'm not aware of any data which shows that with supportive care there is any difference in the survival of de novo AML versus

AML that arises from a prior myelodysplasia. All the data that I'm aware of simply says that AMLs that evolve from a prior myelodysplasia are much less sensitive to chemotherapy, but not that the pace of disease with supportive care alone differs.

Now, there may be data out there that I'm unaware of, certainly. And if anyone there knows such data, I'd be interested to be educated about it.

DR. MARTINO: Dr. Temple.

DR. TEMPLE: It's worth mentioning that the trial here didn't show improved survival compared to a control, either. It showed that some individuals seemed to do well.

A lot of data went by fast--but tell me if my impression here is correct. It seemed to me, as you were going through the decreasing response rates and survival in people with progressively worse baseline status, you still were at a point where the response rates--complete response rates--were in the 20s, and that was really with the very bad people. But for most of the people

with modest dysfunction, it was higher than that. And that's still higher than we've seen here.

And your estimates of five-year survival of 15 percent seem well greater than in the population that was studied with Zarnestra now. That's not fair, it's not the same population--I realize that.

But I wonder if you'd comment on that.

And the thrust of my question is: it seems to me that this drug makes sense only for people in whom you've unequivocally decided you don't want to try chemotherapy--or, conceivably, you do this before you try chemotherapy and see if you're lucky.

Can you comment generally on that?

DR. APPELBAUM: Yes. I apologize if I presented the data too quickly.

DR. TEMPLE: That wasn't a complaint. It just was a lot.

DR. APPELBAUM: [Laughs.]

If you take a single risk factor, like cytogenetics, or like prior myelodysplasia, or like a very high white count, or poor performance

status--each one of those profoundly impact the overall CR rate. And you are correct that, when you look at those univariately, you will get CR rates in patients over age 60, using standard daunomycin-Ara-C, that will be in the 25 to 30 percent range in general. If you start combining multiple poor-risk factors, such as having prior myelodysplasia plus having unfavorable cytogenetics plus having multidrug resistance, then you can select some very bad populations where you would expect CR rates of even less than 10 percent, if you combine multiple poor-risk factors.

But if you look at the general population, the CR rates are 50 percent in general; 25 to 30 percent with single bad prognosis; and then, as I stated, less than perhaps 10 to 11 percent, if you have multiple bad risk factors.

The CR rates are reflected in, then, improved survival. Those that get CRs tend to survive for nine to 12 months, whereas those who do not have very short survivals. And you are correct: in the overall population--and the MRC was

the largest, that's a population of almost 1,400 patients--there was about a 15 percent survival at five years.

But, again, that is a population that includes patients who are in their late 50s, 60s and 70s--all the way up to 90. It isn't just patients over age 70.

DR. MARTINO: Are there other questions?

[No response.]

If not, Fred, I'll take the last question. This is Slivana Martino.

What are you thinking of a patient where you're going to provide supportive care? What actual drugs, in the chemotherapy arena, do you think of in that setting? And why do you think of those?

DR. APPELBAUM: If there's a patient who either, because of patient choice does not want aggressive chemotherapy, or I do not think that chemotherapy is warranted because of very poor performance status, then it depends on what the initial problem is. So that there can be patients

who have AML, who have a very rapidly rising white count, where the goal is to avoid leukostasis, and you have to use a chemotherapeutic agent to try and support them. And in those circumstances we use a number of different drugs: hydroxyurea, as Bruce mentioned, is a classic one. Single-agent VP16 sometimes can work; single-agent topotecan is sometimes used. There, the goal is to just decrease the white count.

Now, there are other patients where the white count isn't running up that quickly, and the real problem may be that they have no granulocytes, and there, trying to eke out a few granulocytes even with a G-CSF, or trying to use something like 5-azacytadine, hoping that you're going to get some differentiation, may be useful.

In other cases, erythroleukemia, for example, you can get quite a bit of satisfactory responses simply by giving red cell transfusions, which diminish the red cell blast count in the bone marrow, and help the problem.

So the problems in those individuals are

different. Some, the threat to life is--or quality of survival--is acytopenia, in other it is the rapidly growing white count.

In none of the cases, though, is the outcome very satisfactory. They're very difficult cases when patients have very poor performance status and are in their 80s or late 70s and have leukemia. There are not a lot of good options for such individuals.

DR. MARTINO: Thank you. And, seeing no further questions, we appreciate your presentation. Thank you.

DR. APPELBAUM: Sure. Thank you.

Open Public Hearing

DR. MARTINO: The next portion of the meeting is the open public hearing. And we do have one person who has signed up to address the group. But before I allow them to speak I need to read something to you.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To

ensure such transparency at the open public hearing sessions of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors; for example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at this meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

MS. CLIFFORD: We have one speaker. His name is Roland McPherson.

If you can take the mike in the back, please.

MR. McPHERSON: Is it on now? Okay--thank

you.

My name is Roland McPherson. I live in a suburb of Cleveland, Ohio. I have not been given any financial remuneration--didn't even buy stock in Johnson & Johnson as I probably should have done. But that's all right.

[Laughter.]

I was diagnosed with myelodysplasia in January of 2001. I had some symptoms maybe six weeks before. I found myself out of breath on the tennis court, which wasn't me. And so I was treated for myelodysplasia, primarily with Procrit for some time. And then I needed a few transfusions. And then, in 2002, the year after I got this, I had a therapy of arsenic trioxide and thalidomide. And that worked fine for about two months, and then it stopped working.

I'm not quite sure about the years on this thing, but don't worry about that. But then I was

not completely pleased with the cancer center I was going to, so I looked around at different ones. And finally I found a Dr. Mary Laughlin at the University Hospital in Cleveland that I seemed to hit it off with. First of all, I liked her. The first time I met her she said, "Well, first of all, it's the Hippocratic oath: do no harm. And I agree with that."

And by that time, the bone marrow tests showed that I really was in the low range of AML. And so she talked about all these induction therapies, and the problem was, at my age--as you've heard and probably already knew anyway--the side effects can be very bad. And so she said, "Well, let's just try maintenance for a while."

And so I simply had transfusions as needed--which wasn't very frequently, but I needed some. And then, of course, I had to take decirol because of the iron buildup. And, at the same time, I began looking at the NCI clinical trials on-line to find things, and I would bring them in to Dr. Laughlin, and she'd say, "Well, this still

isn't right."

So--let's see, in early 2004--I've forgotten the exact month--I hit this Zarnestra trial. It looked good to me. And I brought it in, and she said--I don't remember what she said, but I would have said, "Bingo." Because she said, "This looks like the thing to do." And she called Dr. Karp at Johns Hopkins, and said, "Well, this is one to try."

So I did come here in April of 2004 and had a meeting. And then maybe at the end of April of 2004 we started the first Zarnestra. And we went through three sessions of three weeks each, with a couple weeks off between. And at the end of that period--in fact, before it was all done--Dr. Karp informed me that my blast count was down to zero.

And so this continued to be good until another six or eight months. Now, I had some side effects, but they weren't severe. I would get a little tired, and sometimes I had trouble sleeping and a few other things, but nothing severe and it

didn't last very long.

And, let's see--oh, I might point out that I was very fortunate when I found this study that there were five places in this country doing it, and my brother lives in Montgomery County Maryland, so I had a place to stay. And I also learned later that Dr. Karp in Johns Hopkins was the lead in this study, anyway, so that was fortunate.

So, about December of last year, when I came here for a day of testing, Dr. Karp informed me that my blasts were up now--I think the number was like 30 percent. So in January we started another series, and at the end of that series, my blasts were down to--I may not have the exact number, but I think they were 6 percent. But my blood counts were still kind of low, hadn't really come up. And then I had another series in March. And at that time, the blasts were still down. And I'm not sure--I have some notes, but I didn't want to bring them up here.

But I think some time in the last few months, my blast count got down to zero, but my

blood counts have not come up--especially the neutrophil is the big thing to worry about.

So here I am. I guess I didn't mention that I'm 77 years old, so I certainly fit in with this group of elderly patients. And well, that's sort of a short summary.

I don't know if anybody has any questions. I'm happy to answer anything to the best of my ability. But that's sort of where I am..

DR. MARTINO: Thank you, Mr. McPherson. And we're all very happy to have you here. Thank you.

MR. McPHERSON: Thank you for the opportunity.

DR. MARTINO: Okay, at this point, shall we do lunch next, and reserve the questions? Because it's 11:30.

DR. PAZDUR: I can give you the option of working through lunch.

DR. MARTINO: Well, realize that we have questions. We're going to have discussion. And I'm not sure that--how many of you are interested

in lunch?

[Laughter.]

Because we're not likely to finish in an hour or two. So that's my concern here, is that you may not be interested in lunch right now, but you will be an hour from now, and then people are going to get antsy. And I'd rather not have people in a semi-distressed circumstance--okay?--as they're deliberating on this drug.

DR. PAZDUR: We can take lunch.

DR. MARTINO: So I think I'd rather do lunch, and maybe we can come back a bit earlier? Is that reasonable? Okay?

Now, before I give up the mike, where does one have lunch in this fine, fine institution and building?

DR. PAZDUR: You'd have to ask Johanna about that.

DR. MARTINO: The place across the street. I'm not sure why she doesn't want to say it publicly.

DR. PAZDUR: She doesn't know the name of

it.

DR. MARTINO: But, at any rate--so, does that mean that--should I give everyone the entire time, is what I'm asking here, Johanna.

Okay. So shall we plan on coming back at maybe 12:30-ish? Is that okay?

All right, let's aim for return at 12:30, and starting shortly thereafter.

[Off the record.]

DR. MARTINO: Ladies and gentlemen, I'd like you all to take your seats and we will resume our proceedings.

Ladies and gentleman--and Dr. Temple included.

[Laughter.]

Ha-ha.

Questions from the Committee

DR. MARTINO: The next portion of our meeting are questions to either the pharmaceutical company or to the FDA.

And I think Dr. Perry already is champing at the bit.

DR. PERRY: Yes, I have two questions for the sponsor, if I may.

If you look at Slide 53 in your

presentation, the complete remission rate by site, I'm struck by the fact that Cornell, which put on 16 percent of the patients, and Georgia, which put on two percent of the patients, had absolutely no complete responders.

So I want to know whether there's something wrong in some portions of New York--because if you go to Rochester, you do better? Or whether there's something else involved? Eighteen percent of the patients had no responses at those two sites. That seems to me to be more than a statistical aberrancy.

DR. DeLAP: We did look for any reason that there might be a different result at different sites. We did not find a reason to account for that, in terms of demographics, risk factors.

We can discuss further the statistics of it, if you'd like. We feel that the overall result of the study--the overall response rate--15 percent

for the study, the planned analysis as described in the study, I think that's our best estimate, and that includes zero from some sites and like 25 from other sites. But the net is 15.

DR. PERRY: Were they putting--you don't know whether they were putting in sicker patients in some other ways?

Basically, the question I'm asking: has somebody looked at that?

DR. DeLAP: Yes, and we can show you some data.

DR. THIBAULT: Alain Thibault, clinical.

We have--while we're waiting for our slide to come up--yes, bring the slide up. No, that is not it.

While we're waiting for the slide to come up--we have looked at all sites. There is 15 percent CR rate total. The rate of response varies from zero to 25.

At Cornell, this is a site that accrued 22 patients. As far as we can tell, in terms of median age, in terms of number of risk factors, in

terms of incidence of prior MDS, these patients were all similar.

We've looked at baseline factors, as well, such as blast count, and we have found nothing there, either.

And so what we are left to postulate: we noticed the difference, but we're left to postulate is that we are looking what you would call a statistical aberration, or an effect of subgroup analysis.

DR. PERRY: Okay.

DR. THIBAULT: What I should mention--not to belabor it too much--is at this site there were patients who achieved partial remissions and hematological improvements that were maintained for several months. And therefore that means these patients had a reduction in tumor burden, but not quite the recovery of peripheral counts you would expect.

DR. PERRY: Okay. I have a second question--and maybe you're the person to ask.

Several times during the presentation the

point has been made that these patients have to take a pill; you know, that this is a great drug, they only have to take a pill. By my count, they take 12 pills a day; six 100 mg tables in the morning and six in the evening.

So my question is: how did you ensure that you actually got compliance in the people who had to take a lot of pills?

DR. DeLAP: Yes--I'll ask Dr. Zukiwski, actually, to address that.

DR. ZUKIWSKI: As outlined in the FDA presentation, detailed compliance diaries were not kept at all sites. However, we're confident that the patients did take their medication as prescribed.

There was dispensing logs in the pharmacy. The drug was dispensed in blister packs of seven. It was dispensed for the entire 21-day period.

The patients, we believe, were highly motivated coming into the study. They were assessed weekly by the research personnel or the physicians, and we would have anticipated that if

the patients were having a problem taking their drugs it would have been picked up at that time and would have been reported.

In addition, one of the other studies that Dr. DeLap has outlined--INT-17--has a very similar safety profile to what was observed in CTEP-20. And in the INT-17 study we kept detailed patient diaries, and the safety profile is the same. So we're relatively confident that the patients did take the drug.

But I will ask Dr. Karp to give her experience, as the PI, regarding the compliance issue.

DR. KARP: Thank you very much. I'm Judy Karp. I'm the principle investigator of this study.

AS Dr. Zukiwski said, this was a very motivated group of patients. And my patients would never lie to me.

[Laughter.]

DR. PERRY: Right.

DR. KARP: [Laughs.] If you were one of my

patients, you wouldn't lie to me.

[Laughter.]

I wouldn't want that, anyway.

I think we have some clinical evidence. I mean, people's counts went down--not spontaneously.

The other piece of evidence we have is that we looked at the ability of Zarnestra to inhibit farnesyl transferase activity at two sources. One was in the bone marrow, and the other was in buccal mucosa. And the buccal mucosal studies, 92 percent of the patients tested, we were able to demonstrate enzyme inhibition. So I think that that's evidence that the patients actually took the drugs.

DR. PERRY: Well, I'm sure they took some of the drugs. My question was whether they took all of the drug. That, I think, is a question that's a little more difficult to answer.

Thank you.

DR. MARTINO: Dr. Mortimer?

DR. MORTIMER: I have two questions for the sponsor. One goes back to the question about

growth factors, because I think the literature of growth factors in leukemia in the elderly is somewhat confounded. There are positive trials.

And I wonder what the use of growth factors was-- whether it was dictated on the trial--unless I missed it in the information we were give.

DR. DeLAP: There was very little use of growth factor in the study. And I'll ask Dr. Thibault for the exact number.

DR. THIBAULT: Yes, we've actually collected information on specific growth factors. Twelve patients took growth factors, overall, in this study. And it induced an improvement in the ANC count in five of them. So the vast majority--120, roughly, patients--did not use any growth factors.

DR. MORTIMER: The second question I have actually relates to the patient population. And I think you're to be congratulated for investing in a trial like this, in the geriatric population.

But the patients were not ideally to be

candidates for chemotherapy, and yet 10 subsequently got chemotherapy--six of whom actually responded. And I think that kind of confounds the results a bit, that there were six CRs --and none of whom had responded to tipifarnib before getting salvage therapy.

DR. DeLAP: I'll ask Dr. Thibault to comment on the use of subsequent chemotherapy.

DR. THIBAULT: Yes, we've collected very detailed information on the subsequent use of chemotherapy.

May I have the slide up, please.

[Slide.]

Of the 136 patients who were treated, the majority went on to receive palliative care. This is the subsequent treatment that the 136 patients received. Seven were re-treated with tipifarnib, and one of them achieved a complete remission.

Seventeen patients received single-agent chemotherapy, and none of them achieved any remission to that type of treatment. Twelve received combination chemotherapy--Ara-C with

anthra-cycline at the usual dose.

The patients who received anthra-cycline in combination chemotherapy included two who had responded to tipifarnib first. Out of the 12, only two were 75 or older, and they tended to have a lower blast count at the time of re-treatment in the range of about 30 percent, based on blast count when they entered tipifarnib was about 45 percent.

So this is re-treatment of a very small minority of patients. And we think it reflects on the fact that the vast majority of the patients were felt by the investigators not to be adequate candidates for intensive chemo.

DR. MARTINO: Dr. Levine.

DR. LEVINE: I have several questions.

The first relates to myelodysplasia. You gave us information on pathologic re-review, or central review of the CR. But who diagnosed the myelodysplasia, and who confirmed the myelodysplasia? So that was my first question.

DR. DeLAP: The antecedent myelodysplasia at the time of entry into the study, that was not

something that was part of the pathologic review, that was part of the patient's history. So, again, that's not part of the central review.

DR. LEVINE: Do we have any idea of the length, the duration of myelodysplasia prior to study? The number of transfusions that were given prior to study--you know, during myelodysplasia? And then afterward? Is there any information there?

DR. DeLAP: We do not have a presentation on that. Perhaps Dr. Karp can give us some insight into the range of prior dysplasia that was present in these patients?

DR. KARP: Well, the minimum duration, per definition: one month of documented antecedent hematologic disorder. We had patients whose myelodysplasia--as per a patient who spoke to us today--had a duration of myelodysplasia prior to transformation of up to three years.

I can't tell you what the median is. But it was a broad range.

DR. LEVINE: Another question--I'm just

trying to get at the poor prognosis. It was the same as Dr. Mortimer: were these really poor-prognosis cases?

So one of your definitions of poor prognosis was organ dysfunction. So could you define "organ dysfunction?" And it had to be organ dysfunction within the confines of what was allowed onto protocol--right?

So then my next question, beyond that is: if you exclude organ dysfunction, if you just look at factors of age and cytogenetics, and myelodysplasia, what percentage of the patients had one of those three, forgetting the organ dysfunction?

DR. DeLAP: I'll ask Dr. Thibault to start with this.

DR. THIBAULT: The proportion of patients who had therefore three risk factors, if we don't count for the proportion [sic], was high. We would have 82 percent of them having MDS. We will have 49 percent of them having prior myelodysplasia. We will have 41 percent of them having both.

And then 55 percent of the patients were 75 and above.

DR. LEVINE: So, in other words, 41 percent

had both myelodysplasia and the cytogenetic abnormalities.

DR. THIBAULT: Yes. The majority--as you recall, the inclusion criteria were for 65.

DR. LEVINE: Okay. Another question: going back a little bit to the compliance, one of the major non-hematologic toxicities was nausea and vomiting. Do you think that might have influenced the number of pills that these people took? Or how do you deal with that? You're going to need to know whether they really are taking this pill or not. Or 600 BID, or what they're doing.

DR. DeLAP: Yes. Nausea and vomiting was a relatively minor problem for most patients, but we'll ask Dr. DePorre to go through the data.

DR. DePORRE: DePorre--clinical.

Indeed, patients had nausea and vomiting. However, in the vast majority of these patients, that was Grade 1 and 2. It resolved without any

intervention, and it was of short duration.

DR. LEVINE: So, in other words--that was another question: so they are not on antiemetics for all this time.

DR. DePORRE: Correct.

DR. LEVINE: And with continued use, the nausea goes away? Is that what happens?

DR. DePORRE: Yes. Correct.

DR. LEVINE: Okay.

One more: the confirmed complete remission--so that was one month after the initial CR. Those confirmations were on drug? On continued drug?

DR. DePORRE: Yes, patients who were taking drug and had a confirmed complete remission at one month would obviously continue drug.

DR. LEVINE: Okay.

DR. MARTINO: I'd like to ask the next question.

I am aware that there is a Phase III trial ongoing that deals with this agent in this patient population. At some point, someone needs to

explain that trial and help me to understand where it is, where it isn't, and what the objectives are.

DR. DeLAP: Are you referring to the AML-301 trial? Yes.

Dr. Zukiwski?

DR. ZUKIWSKI: Yes. Could we have a slide up, please?

[Slide.]

Well, let me just take you through some of the background on the AML-301 trial.

This is a randomized trial of tipifarnib versus best supportive care. It is being conducted outside of the United States. The trial is active and ongoing.

There is a total of 90 sites that will be activated; approximately 67 sites have been opened to date, and the accrual is continuing to ramp up.

The overview is here. The eligibility: patients greater than or equal to 70 years of age. This is a consensus that was reached with the ex-U.S. investigators. There was a lot of discussion on what the actual patient population

could be. And this was where the consensus agreement was reached.

These are patients with initial AML. The patients--we'll be collecting karyotype categories-- favorable, unfavorable, intermediate. We'll be collecting data on prior myelodysplastic syndrome. There will be a stratification built in. There is no interim analysis. There is an IDMC to give us guidance on whether or not to continue with the trial.

We anticipate that this trial will have data, so we will be able to submit to the Food and Drug Administration sometime in 2007.

DR. PERRY: Excuse me. I have a hard time believing that's the only eligibility criteria--just leukemia and greater than 70? No end-organ function tests? Nothing else?

DR. ZUKIWSKI: I can go through the detail, but this is just the overview. If you'd like--

DR. PERRY: Well, it doesn't give us a very good idea of how severely ill these patients are. They just have leukemia.

DR. ZUKIWSKI: Can we go on to the next slide, please? Next slide.

[Slide.]

Okay, I think it's on Slide 9.

[Slide.]

Basically, the ECOG is 0 to 2, newly-diagnosed, not willing to receive induction chemotherapy. So this is a conversation that will take place between the treating physician and the patients--that determination will be made on whether or not the perceived risk is worth the possible benefit in those patient populations.

And, obviously, the thoroughly-described study, where we will be--the informed consent does describe the "best supportive care" elements. And so it does list other options for patients.

DR. TEMPLE: About that, can you say something about what the consent form is going to say in that study?

DR. ZUKIWSKI: Dr. Temple, I'd have to get the exact informed consent. I'll get back to you on that one. I don't have it off the top of my

head.

But it's important to note that this study is being done to determine the magnitude of the survival advantage which we believe will take place. So, 306 patients--we'll have that data sometime in 2007.

DR. MARTINO: How many patients are in the trial at this point, Doctor?

DR. ZUKIWSKI: Currently, as the accrual is ramping up, there is approximately 88 or 90 patients. I got an update in the last day or so.

DR. MARTINO: Okay.

DR. ZUKIWSKI: So I'm not certain of the exact figure.

DR. MARTINO: And how much of this is happening in this country versus elsewhere?

DR. ZUKIWSKI: This is entirely ex-U.S.

DR. MARTINO: It's entirely--

DR. ZUKIWSKI: It's not being conducted within the United States.

DR. MARTINO: Thank you.

Dr. Cheson?

DR. CHESON: Yes, first a comment: I would like to thank you for changing the definition of elderly from 60 to 65.

[Laughter.]

Then I have two questions left, since everyone's been asking all the other ones I wrote down.

One of the major points that would be attractive for this drug is the fact that it often doesn't require hospitalization. Your figure is that 40 percent of patients did not require hospitalization.

How many of that 40 percent were responders? In other words, is it just the patients who got too sick and they decide it's not worth putting them in the hospital? Or are these patients who were actually benefitting from the therapy, getting their complete--and perhaps partial--responses, and still able to stay out of the hospital?

DR. DeLAP: Part of the benefit, actually, of the complete response is improvement in

disease-related morbidity and the ability to stay out of the hospital. So we do see that patients who have a response do better, in terms of--

DR. CHESON: Do you have numbers?

DR. DeLAP: yes. Dr. Thibault will show you.

DR. THIBAULT: Yes, may have the slide up, please?

[Slide.]

This is a slide that focuses on patients who achieve a CR. On the left-hand side are variables of interest: hospitalization, transfusion of platelets and red blood cells; use of growth factors.

And on the middle column you have the hospitalization rate and rate of other interventions--in those CR patients prior to reaching their CR. The time to CR is 43 days.

Then in the extreme right column you have the use of health care resources, once the patient was in CR.

So what you can see is that once the

patient achieved a CR, only six patients required further admission, some of them for treatment of ancillary disorders. But the majority of patients--15 of the 20--were hospitalized.

The duration of these hospitalizations is 12 days in the CR patient.

DR. CHESON: Okay--so three-quarters of the patients who did respond, did require hospitalization initially. And then are those the same ones--those further six--

DR. THIBAULT: Yes.

DR. CHESON: I mean, those six are the--

DR. THIBAULT: Are these six a subset of--

DR. CHESON: Or does it make it all 20 required hospitalization at one time?

DR. THIBAULT: I will have to verify this. My recollection is these six belong to the 15.

DR. CHESON: Okay.

My next question: when we devise a response criteria, we recognize, as most people do--not an original idea--that complete remission is the most important response category. And we

recognize, and put in the paper that partial response was primarily useful to identify the activity of a new agent, not necessarily saying anything about the efficacy of the new agent.

You have a bunch of patients who have partial responses, and so-called "hematologic improvement" which was in the MDS response criteria is not really a response criteria in AML.

Do you have evidence of clinical benefit in patients who got partial responses? Stable disease, hematologic improvement--what is the evidence that these patients really did experience benefit, other than the complete responders?

It would be nice if, you know--even if you didn't get a complete response, if you could demonstrate decreased transfusion requirements, decreased infections, decreased hospitalizations compared to previously--etcetera, etcetera, etcetera, etcetera.

DR. DeLAP: We do have some analysis that suggests some benefit in the partial response, the hematologic improvement subset. It's not as well

established, obviously, as complete response.

I'll ask Dr. Zukiwski to--

DR. CHESON: And when we did come up with a hematologic improvement, we also had "major" and "minor"--which we'll probably get rid of at some point.

So, how important was the hematologic improvement? In other words, if the hemoglobin went from 6 grams to 7 grams, it's probably not a big deal. If it went from 6 grams to 10 grams, then maybe it's something worth talking about.

DR. ZUKIWSKI: Okay.

Unfortunately, Dr. Cheson, we did not cut the PR or the hematological improvement as we did with the CRs to show you hospitalizations and other utilization of resources, etcetera. What we did do is we did do an exploratory analysis, looking at survival, for our internal purposes, and we found it to be very encouraging, looking at the CR patients, the PR patients and those non-responders.

So, for our internal planning purposes for the 301 study, it gives us a lot of encouragement

that there will be benefit even derived from the patients who have achieved a PR.

DR. CHESON: It would be--hopefully--to the advantage of the drug if you did have those numbers. Because if you could demonstrate improvement in these parameters in patients who didn't get a CR, it makes the drug a lot more interesting.

DR. ZUKIWSKI: Right. And this slide just flashed up.

[Slide.]

This slide has to be taken for exactly what it is: this is an exploratory analysis, what would be called "classic responder, non-responder." No firm conclusions can be drawn. The only purpose we had done this is to look for internal data. And there is a trend that gives us some indication that PR patients may have an improved survival--but no conclusions can be drawn from this data at all.

DR. MARTINO: Dr. George?

DR. GEORGE: I have a number questions in sort of different areas. One is a follow-up on the

details on the confirmatory trial--the AML-301, I think it's called.

What kind of difference in survival are you thinking--what are you looking for there? What is the study powered to pick up?

DR. DeLAP: The study is powered to pick up a 50 percent increase, in terms of the hazard ratio, from approximately three months to approximately four-and-a-half months.

DR. GEORGE: We can come back to some of that in discussion, but some of that has to do with what kind of difference you might have expected based on the potential benefits--satisfiable based on the response rates. But that's--we'll come back to that in discussion, I think.

Is there any quality of life study included in that confirmatory trial? The randomized trial?

DR. DeLAP: We're not doing the formal quality of life-type questionnaires that are sometimes used in that trial.

DR. GEORGE: Okay. Another area had a

little question about--maybe for the sponsor or the FDA. It has to do with the discrepancy between the CR assessment--rate assessment.

If I'm understanding it right, out of those 20 cases, there were three that the FDA didn't count because they weren't confirmed by the usual definition. Now, those are for different reasons: one died early. And maybe you could address that.

DR. RYAN: one patient died early, before confirmation. Another patient progressed, died on confirmation. The third one does not have sufficient bone marrow data to support a confirmed CR.

DR. GEORGE: But that third one was a long-term survivor.

DR. RYAN: Yes. Then there were two patients who had complete hematological response, who do not have bone marrow slide to support CR.

DR. GEORGE: Okay. I'm just--

DR. DeLAP: Yes, there were a couple of cases where the slides were lost in transit,

basically, and could not be reviewed by the independent reviewer. And for that reason they were not included in the 15 cases that could be confirmed and verified.

But it's important to note that the slides for those patients that were lost in transit had been reviewed at the original institution. So we do have readings.

DR. GEORGE: Okay. The last point is a more generic question, I guess, and I know you won't be able to answer this directly.

But one of the things that most impressive from all these presentations for me is that this indication--this particular medical condition is a very serious one--but that it's highly heterogeneous. And that's one of the issues, of course, that's going to come up in discussion of any single-arm trial.

But, what Fred Appelbaum presented, if you looked at the cases with different risk factors, from the worst to the best was really dramatic. I mean, the ones with three risk factors had an

estimated response rate of 11 percent. Remarkably, that's the same thing that the FDA came up with on their study. And the best cases had an 81 percent response rate.

Now, these are patients that, of course, might have been different in other ways. They did receive chemotherapy, for example. And that relates to my question.

Is there any way--do you have any feel, or any way to know this--what percent of the patients on the CTEP-20 study actually might have received chemotherapy, as opposed to the eligibility criteria was sort of "not able to willing" basically, to receive chemotherapy, which--I can understand what you're getting at there, but there is a difference.

If you're trying to relate, you know, what you observed to what might be obtained with chemotherapy, it's kind of hard for me to figure out how many of those patients actually might have received chemotherapy, and might have been on the study, as opposed to those that just really were

medically unfit for chemotherapy.

DR. DeLAP: Yes, I'll ask Dr. Stone to comment on that. The other side of the equation of risk-benefit, of course, is that in addition to a low response rate we're looking, with combination chemotherapy, with a high treatment-related and other mortality in the first 30 days, which is 25 percent or more.

So that's--again, in terms of the risk-benefit, I think it's rather clear why patients would not get the combination chemotherapy.

But I'll ask Dr. Stone to comment further.

DR. STONE: Well, Dr. George, I assume I understand what you're saying: it would be nice to know exactly how these people would have done had they had chemotherapy run into their veins, or had they had supportive care, perhaps.

All we can do is try to extract that type of data from the cooperative group trials--which may not be analogous because those patients were getting chemotherapy. But even if you do that, you

can see from the data that Fred showed, that I showed, that if you just look at prior myelodysplasia, which characterized a great deal of these patients on CTEP-20, the remission rate would be about 20 percent. And the mortality rate is going to be at least as high as the average mortality rate that was in those trials, which was about 25 percent.

Probably the decrease in the remission rate in people with those poor prognostic factors is, in part, due to resistance manifested by a lack of going into remission and, secondly, of higher mortality rate. Hard to tease out, but I think, in looking at this as a leukemia doctor, I would say that the CR rate had chemotherapy been run into their veins, would probably be in the magnitude we discussed in the slides: in the 10 percent range.

Probably most of these people were really like the triple-losers that Dr. Appelbaum mentioned. If they had had MDR, they might have been positive, and that would be about 11 percent.

So--I mean, that's the best I can give you

on that. The mortality would be very high, reflecting the, probably, 90 percent who didn't go into remission, probably half would have died.

DR. MARTINO: Dr. Brawley?

DR. BRAWLEY: Thank you.

Can you bring back up the slide of hospitalizations that Dr. Thibault was talking about? I need to try to understand that a little better.

DR. DeLAP: This is the slide about hospitalizations for the patients that had remissions?

DR. BRAWLEY: Right. Right.

The question is--

[Slide.]

--yes, there we go.

The period of time prior to CR, versus the period of time during remission--you know, if one were to take the margin and say that "during remission" was seven days, and "prior to CR" was six months--this slide doesn't make any sense.

So what I'm wondering is: do you have a

similar slide that compares hospitalizations after treatment for individuals who did not have a remission, versus individuals who did have a remission?

DR. DeLAP: One thing I'd like to comment, in line with your question.

DR. BRAWLEY: Sure.

DR. DeLAP: And then we'll show that slide.

The "prior to CR," these patients entered CR after one to two cycles of treatment. So that interval is limited. And then the "during remission," obviously the median duration of remission was several months, so that interval is actually quite long. So that's another thing you have to think about when you look at these percentages.

DR. BRAWLEY: That helps me to understand this slide and actually think of it as valid data. Thank you.

Do you have the other data, as well?

DR. DeLAP: I'll ask Dr. Thibault.

DR. THIBAULT: I'll show you very similar

data. Next slide up, please.

[Slide.]

This is the same slide with an extra column added. On the extreme right you are seeing the hospitalization rate for the patients who never achieved a CR, and you see that the hospitalization rate if you don't achieve a CR is similar to the hospitalization rate of the CR patients prior to their entering a CR. Then after they enter the CR, then they seem to derive benefit in terms of reduce hospitalization.

DR. BRAWLEY: Show this slide first next time.

[Laughter.]

DR. THIBAULT: We're hoping we won't have to come back again.

[Laughter.]

DR. MARTINO: Dr. Brawley, anything else you'd like to contribute at this time?

[No response.]

Are there other questions?

Dr. Bukowski.

DR. BUKOWSKI: Can you help me understand the rationale that was used to select the dose that has been used in this particular study: the 600 mg

BID?

You mentioned that in the Phase I trial, there was some hint of activity, and the slide mentioned that you achieved the IC 50 in vivo with that dose. Can you just clarify? I mean, were there responses at lower doses in the Phase I trial? And have you had any experience with other dosing levels?

DR. THIBAULT: Well, we have our most extensive experience at 600 dose.

If you want me to take you through: in the Phase I trial, the doses were 100, 300, 600, 900--1,200 was not tolerable. There was one remission at 300--sorry, one remission at 100, one remission at 600. This is a very limited data set: approximately six patients per dose level.

Most of our experience is, of course, at 600. The reason we chose this dose was because at 600 we are certain that the farnesyl transferase

enzyme is fully inhibited. We are also covering the range of IC 50s--of the different cell lines that have been tested. There's about a 10-fold difference in IC 50 when you look at the different blinds. And so we're covering that at 600 for a longer duration of the treatment period than we would if we were at 300.

And then, finally, when we looked at the toxicity of this, we knew that we would go into Phase II with a dose that would require about a third of the patients to be dose-reduced--which is kind of the definition of the MTD. And so the data supports that approach.

We do not know whether treating these patients, right off the bat, at 300 would yield the same results. But we do know that we treat them at 600, and then we adjust the dose, we get the results that we're showing today.

DR. BUKOWSKI: So the 600 is the MTD from the Phase I trial?

DR. THIBAULT: Yes, in the definition we've used, "MTD" is the dose level below the one that

causes more than a third of the patients to be in TLT. So this is the recommended Phase II dose.

DR. MARTINO: Dr. Porter?

DR. PORTER: Just a clarification on your Slide 67. You have "AEs leading to deaths," and then "Drug-related." I realize this is the investigator's opinion, but since you only have one drug, and it's an AE from that drug, you really have 10 drug-related deaths--to read that table correctly.

Is that a correct interpretation?

DR. DeLAP: Can we have that slide up, please?

[Slide.]

DR. DePORRE: Let me first clarify one point: it is that the "1" and the "9" should not be added. The "1" was part of the "9." So it--

DR. PORTER: Isn't total. Okay.

DR. DePORRE: --is total, nine patients who had a death that was attributed to an AE.

And I agree with you that it's very difficult--not to say almost impossible--to discern

whether the death was due to the AE, or due to the underlying disease.

DR. PORTER: Well, this is the way you classified it, though: you said, "AEs leading to death."

DR. DePORRE: Correct. But that is--the drug relatedness is difficult to discern between disease and drug. And the one patient was attributed--the AE was attributed very clearly by the investigator to the drug. For the other eight, there are other confounding factors, that is, in the context of the progression of disease.

But an absolute certainty to discern between the two is not possible.

DR. PORTER: Okay

DR. MARTINO: Are there other questions?

DR. DeLAP: I would come back again to the overall mortality, which was 12 percent in the first 30 days with this drug. And, as we've heard from Dr. Stone, that's well below the expectation.

So, for this patient population, with the natural progression of their leukemia, we feel that

tipifarnib is not contributing substantially to an early mortality issue. We think that deaths we're seeing in the first 30 days reflect the natural history of the disease, by and large.

DR. MARTINO: Dr. Temple?

DR. TEMPLE: A study, INT-17, was mentioned. That was in people who had been previously treated. If I recall, the response rate was virtually nil in that--something like 3 out of 250, or something like that? Did I read that aright?

DR. DeLAP: The response rate is low.

DR. TEMPLE: So, I just want to be clear: you have no intent that people who've been previously treated be treated with this drug--correct?

DR. DeLAP: We do not have risk-benefit data to support treatment of previously treated patients.

DR. TEMPLE: Okay--but I mean, that might even be something we would ask to go into labeling, if the drug were otherwise okay. Because the rate

was so low.

DR. DeLAP: Our intent would be that the patients for whom we have the established risk-benefit, where we can show the durable remissions and the good outcomes, that those are the ones who should get the drug--yes.

DR. TEMPLE: Okay, just one other question.

I mean, obviously, as everybody's been hinting, the response rate here is quite low. So, presumably, people who are candidates for regulation chemotherapy, you'd want them to get it.

Is this also a drug that someone who's at the margin might give a whack at, and then use chemotherapy afterward, if nothing came of it here? Is that part of your thinking, too? You know, take the easy one and if it doesn't work, go on to real chemotherapy?

DR. DeLAP: Yes, it's difficult to address exactly that issue. I think that--again, the recommendation in labeling would be to stick as closely as we can to the risk-benefit that we've established, and treat those patients.

But I'll ask Dr. Sekeres, who can talk to us about how the decision is made as to chemotherapy or no.

DR. SEKERES: Hi, I'm in clinic. It's a great question you ask.

And this is a disease that I think of as the worst solid tumor you can imagine; people coming in with State IV disease, and then add on top of that, poor prognostic factors.

So we don't have a lot of room to work with when we talk with patients. A typical conversation I'll have is: "I can offer you options A, B or C. A is supportive care--"--I like to call it "aggressive supportive care" so patients don't think I'm giving up on them. B is some sort of mid-range therapy. And C is remission-induction therapy.

My approach, for better or worse, whether this works is will aggressive chemotherapy, to look somebody in the eye and say, "The chance I can get you into remission is, for all comers over 60, somewhere between 40 and 55 percent; for a

70-year-old, or 80-year-old, that will go down to 30 percent. And with worse risk factors, as low as 15 percent, and a treatment-related mortality of 20 to 25 percent.

And you've heard that message over and over again.

Option B is mid-range therapy. Now, what I have to offer in mid-range therapy are clinical trials or Hydrea. And I can't look somebody in the eye and say, "I can offer you a complete remission" with either of these approaches.

And I leave the decision up to the patient. Now, I may weight it a little bit, but I give them real percentages, if at all possible. And then whatever decision they make, I support it.

If a person were to choose option B--if that option happened to include a farnesyl transferase inhibitor such as tipifarnib, I would support them through it. If they were then to progress, I'd probably re-address the issue with them.

DR. MARTINO: Are there any other

questions?

Yes?

MR. FLATAU: I'd just like to ask the question: if you're looking a patient in the eye and you're going to treat him with tipifarnib, you're going to say: "You have a 15 percent chance of getting into remission." And what about the 85 percent of the people? What are you going to tell them?

DR. DeLAP: After Dr. Sekeres, I'd also like Dr. Karp to come up and say, because she has, obviously, the direct experience in the protocol.

DR. SEKERES: It's not easy to look somebody in the eye and give them those percentages. It really isn't.

Fifteen percent isn't zero percent. So I would say to that person: "There's a 15 percent chance you could go into a complete remission."

I'd try to be clear that complete remission is not the equivalent of cure. If I have data to support the fact that that person may live eight or 10 months longer than with no other therapy, then I'll

make that statement also, and I'll say to that person: "If you don't happen to go into a remission, and your leukemia remains, we'll discuss what your options are after that."

That may involve remission-induction therapy, if that's what a person wants. It may involve aggressive supportive care. Or it may involve something like Hydrea if they want something in the middle.

MR. FLATAU: But, I guess the point is: you can't tell them that this is better--if they're in that 85 percent, that this is better than best supportive care, because you don't have any data.

DR. SEKERES: I don't know where they'll fall when I first have that discussion. So I just give them the percentages as I just gave them to you. And then if their disease comes back, I wouldn't be disingenuous about what I'd say in the future: "You have relapsed leukemia. This is something we need to worry about. We can offer things that can manage your disease, but we can't reliably offer you something that will improve your

survival."

DR. DeLAP: I think the question about the patients who don't have a complete remission, and what to say to them--I think there is some other observations perhaps Dr. Karp can give us about things that were seen in the trial. Although, again, the complete remissions are the ones that have the established link to patient benefits.

DR. KARP: Well, first of all, not to be too brutal, but this is a fatal disease. So, if one is fortunate enough to be in that 15 percent who will achieve a complete remission, the benefit of that is very palpable.

Now, for the other 85 percent, there are patients who do get partial remissions, there are patients who get hematologic improvement--which is not as concrete a definition. And then there are patients--in fact, I believe 30 percent of our patients--had something that was akin to "stable disease." And you can say, well, what is "stable disease?"

These patients did not progress. And, in

fact, these patients didn't quite quality for bona fide palpable improvement, yet they were alive; they felt relatively well; they were out of the hospital; they were living at home. And there are a number of patients who went on for months like that.

I have a gentleman 76 years old--I seem to specialize in older men--

[Laughter.]

--[whispers] especially if they're wealthy.

[Laughter.]

But he's a 76-year-old gentleman who had myelodysplasia for about a year, and then transformed into AML, with virtual replacement of his bone marrow by blasts, and no functional platelet production, no functional red-cell production.

This patient has been on Zarnestra for one year. He has been taking Zarnestra for 21 out of every 28 to 42 days for one year. He does not have a "partial remission" by standard criteria, and yet

he has not required a platelet transfusion for eight months. He has not required a red-cell transfusion for eight months.

So, when Dr. Sekeres was talking I said to myself, "Well, what would I tell my patient? I think I'd have him call Dr. Sekeres, because he said it so eloquently."

And so it is a very painful thing to say to someone that "I don't have anything for you." And that may--you know, when we think about benefit, it may not be such a terrible thing for there to be a benefit for the caregivers, as well. Because there are so many patients--so many elderly patients--for whom intensive chemotherapy is clearly not the answer. And it is painful to either say to them, "Well, we can do this. We can do anything. But we stand a very good chance of killing you in the process--or certainly doing you no help." Or, on the other hand, "We don't have anything that we can do. We can turn a couple of dials."

Having another option, I think, is

extremely important for everyone concerned in this partnership: the patient, the physician, the nurse, all the family members.

DR. MARTINO: Anyone else have any questions?

[No response.]

Seeing no further questions--Dr. Pazdur, I think you wanted to address the committee before we go into the discussion phase?

DR. PAZDUR: Let me just clarify some of the comments that I made earlier.

Originally, when we asked the question, we were asking a regular approval. And I prefaced my comments that the agency had looked at complete remissions with sufficient duration--I should emphasize--as equaling clinical benefit.

But I think it's important when we discuss this, we cannot just look at the endpoint "complete remissions" without looking at the magnitude of change on this endpoint. Because, obviously, a complete remission rate of 80 percent, with a durable duration, is much different than something

with an 11 percent duration.

So I think we have to address that question is: is this an established--with the endpoint of complete remission, with the magnitude that is associated with this, is this an established surrogate for clinical benefit; in other words, will it equal an improvement in survival of these patients, if the entire patient population was followed out? Or would people want to discuss whether we should look at this as a surrogate reasonably likely to predict clinical benefit; i.e., looking at an accelerated approval situation? Okay?

And let me go into a little further description about accelerated approval, since there are some people that have not been on the committee before.

For accelerated approval, we're looking at life-threatening diseases--which this obviously is. The surrogate has to be reasonably likely to predict clinical benefit. You have the surrogate: it's a complete remission rate of x

percent--whether one wants to believe it's 11 percent, or 15 percent; whether one wants to put into this equation the partial responses, or the disease stabilization. That's something that you have to consider.

Generally, in acute leukemia we've looked at complete responses--or complete remissions--alone, and not these other evidence of activity.

But, in your mind, is that reasonably likely to predict clinical benefit? Okay?

The other caveat to accelerated approval--and this is a very important question that deserves more discussion here--is that the therapy has to be an improvement over available therapy.

Now, that improvement can be an improvement in terms of toxicity, and it could be an improvement in terms of efficacy--and I'll get to that later. But I think one of the major issues here is the concept of available therapy. And that has to have an impact on what population are you

talking about.

When we originally discussed this application and bringing in a single-arm study, we were told that this patient population would not be treated by hematologists or by medical oncologists, because these people generally are not treated; they're too old, there's a consensus, relatively among oncologists that these individuals that are greater than 75, or greater than 65 with MDS, would not constitute a patient population that would receive standard induction therapy. And, hence, we believed that going ahead with a single-arm trial seemed reasonable in that situation.

It's interesting, however, that there are individuals that were on this study that went on to, obviously, standard induction therapy. So I think one has to define, you know, what is the population.

Clearly, the indication that has been presented here by the company--the treatment in elderly populations--is not something that we would consider. At the least we would--or at the

most--we would consider really defining the population as studied; i.e., patients that are greater than 75, or patients that are greater than 65 with MDS--and perhaps even put in a caveat "that cannot tolerate chemotherapy."

But, here again, I think that requires, again, some discussion by the committee. Because what is this population? Should they receive standard induction therapy? Are we defining the population correctly here, by the inclusion criteria that the sponsor put into this single-arm study?

When we originally discussed this application with the sponsor, we did discuss accelerated approval, and that's why this ongoing study with a supportive care arm is ongoing. One may question why is this study going on predominantly in Europe? One of the issues was that if this drug received accelerated approval, this would have a significant impact on the accrual of patients onto this trial. Obviously, if the drug is not approved under accelerated approval, we

could re-look and re-examine the sites of study.

I think when we do the questions and actually come to the voting, and as you ponder this application, there are three decisions that we will be asking you to make.

One, should this be regular approval? In other words, does this 15 or 11 percent complete response rate equal clinical benefit? Is this an established surrogate for clinical benefit? Or, should this be considered for accelerated approval? And if it's for accelerated approval, you have to feel that this endpoint of complete response rate and other--of supporting evidence--is reasonably likely to predict clinical benefit. In other words, what you're seeing here, do you, in your clinical judgment, think that this confirmatory trial that they're doing is going to turn out positive? Okay?

And then you have to also ask yourself: is this therapy, in the patient population they're defining, an improvement over available therapy. And, again, I said that improvement can be an

improvement in toxicity evaluation, or in efficacy. And obviously, in this situation, most people, I think, would look at the safety issues and the safety benefit. But then one has to weigh that, potentially, against: are you giving up some efficacy, potentially, in this patient population--and make a risk-benefit decision.

So you have two decisions.

And there's a third decision here. And that third decision would be to say: "I don't like full approval. I don't like accelerated approval. And perhaps we should wait for the completion of the ongoing randomized study looking at this drug against best supportive care."

All three of these decisions are on the table. And I'll turn it over to Silvana.

DR. MARTINO: Thank you.

Discussion of the Questions

DR. MARTINO: I would like to take the questions in a certain order, and it's the order that Rick has suggested.

So what I first would like a discussion on

is the first question, which I will read to you: Does the risk-benefit analysis support regular approval of Zarnestra for the first-line treatment of AML patients aged 65 or older, with prior MDS, or age 75 and older.

So it is the regular approval concept that I want your thoughts on first.

Dr. Cheson, I'm going to start with you. What are your thoughts on this?

DR. CHESON: I didn't volunteer, but I'll do it.

[Laughter.]

DR. MARTINO: Yes, that's right.

DR. CHESON: I'm fairly uncomfortable with giving full approval for this drug for this indication, for all the reasons that have already been dealt with.

It's a heterogeneous population of patients, some of which--we do treat patients 65 years or older with aggressive therapy, and some of them do rather well. I've just it to somebody. And given that there is such concern about that,

and the fact that there is a randomized trial going on, I--in all good conscience--couldn't support that.

The data are--there are some answers to my questions which I still haven't heard. The data aren't available. The patients are heterogeneous. There are other therapies out there. And supportive care has gotten better. And I'd like to see the results of that Phase III trial. I don't feel comfortable with this.

DR. MARTINO: Dr. Perry.

DR. PERRY: First, I'd like to thank the sponsor--

DR. MARTINO: That's for you, Dr. Cheson.

DR. CHESON: Oh, there were a bunch of questions regarding the benefitted patients who got less than a CR--things that you said you didn't have the data on yet.

DR. DeLAP: We have worked to get a little more of that data, and we could still show it if you're interested.

DR. CHESON: I'd like to see it, but I'm

not sure it will change my feeling about it.

DR. THIBAULT: Well, of the 10 patients who did not achieve a CR, there were three patients who achieved a partial remission. All these patients had a 50 percent reduction in blast count, down to 5 to 19 percent. Their recovery of peripheral counts was an ANC to 3.4 thousand, and a platelet count of 240,000.

For the patients who achieved hematologic improvement--there were seven of them--again, in the bone marrow there was a 50 percent decrease in the blast count to a range of 5 to 19 percent. The recovery of counts was not complete: ANC was at 2,000, but the platelet count recovery was at 75,000.

In terms of reduction of transfusion, we see it during the duration of that benefit, which averages three months.

DR. MARTINO: Dr. Perry.

DR. PERRY: First I'd like to thank the sponsors for a very concise and very well organized presentation. You guys can take this show on the

road any time, I think.

Secondly, I'd like to echo Bruce's comments. I would feel uncomfortable with approval--with regular approval. I would like to discuss further the issue of accelerated approval.

I was not on the committee when Iressa came before this committee, and I think it was my--probably, although it as not attributed to him-- my new best friend Dr. Brawley, who pointed out that Iressa's approval was perhaps a mistake.

I would feel more confident if we gave this drug accelerated approval, and then waited the results of the 301 study.

DR. MARTINO: Now, I still want this group to deal with this issue of regular approval before we move on to anything else.

Dr. Levine?

DR. LEVINE: So my frustrations relate to: number one, I really, really think that it would have been helpful to have very strong clinical benefit data; not just talking, but what are the transfusions before and after, in all of these.

That would be extremely helpful to know.

The second thing--I can't help it, but it frustrates me, because MDS is what you're hanging your hat on. And it would make me very much more comfortable to know that I know that that is MDS, and it's not somebody who, for a month before the diagnosis of AML, you know, was a little anemic. You know, maybe that's not really MDS. I would feel much better.

And so when I'm looking at this, I'm just looking at--I can look at age, over 75, and I can look at the poor chromosomes. You know, those are very strong. But it depletes the larger study.

So I would not be comfortable at this point in regular approval.

Dr. Bukowski.

DR. BUKOWSKI: Yes, I'd like to echo those comments.

I get the impression--I used to take care of acute leukemia when I was younger, under the age of 50.

[Laughter.]

I'm impressed, Bruce, that you still do this. That's good.

But, anyway, this seems to be a very

heterogeneous disease. Not one entity. We're asked to make a judgment on Phase II data in a very different group of patients. There may be subsets of individuals here.

Therefore, I think, in reality, I'd like to see more data before voting for regular approval at this point in time. I just am bothered by the heterogeneity of the population that may reflect some of the results. So this concerns me somewhat.

DR. MARTINO: Dr. O'Brien, you've been very quiet. But I do want to hear your voice.

DR. O'BRIEN: I think that the clear problem, in my mind, with the data is again how well defined the population is.

Certainly, within AML, this is a high-risk group, in terms of achieving a remission and induction mortality, because they're older and because they have poor cytogenetics, and prior myelodysplastic syndrome. But, from a patient

point of view, they're not really that bad.

So what am I trying to say by that? I looked in our data base before I came here. We have about a thousand patients treated over the age of 65. And I actually pulled out these same eligibility criteria: over 75, or 65 to 74 with MDS and performance data zero to one. And I looked at the abnormal cytogenetics, were about 45 percent--so very similar to this trial, of 49 percent.

And then I only looked at regimens that included Ara-C and anthra-cycline. And the CR rate was about 38 percent, and the induction mortality was 18 percent.

Now, the first thing anybody can say is: well, those patients were well enough to get to M.D. Anderson, and that selects them. And that's absolutely true. But these patients were also well enough to get to Stanford or Hopkins or Cornell. In fact, you heard that Mr. McPherson came from Ohio to Hopkins to get treated.

So I think in that point of view they were

similar. This is not a seek-out trial.

I think the biggest factor which affects whether the patient and the physician decide whether they're going to get chemotherapy or not in this older age group is the performance status. But these are all performance status zero-to-one patients that are walking in the door. It's way different if a patient comes in the door in a wheelchair. But that's not the population that we have defined here.

And it also excluded patients with high white counts over the age [sic] of 30,000, which I didn't do when I looked at my analysis. And they have clearly a higher induction mortality and a lower CR rate.

So, I think if I was a patient I would rather get a CR on Zarnestra than chemo--it is easier. They spend less time in the hospital--there's no question.

My concern is that there may have been patients in the study who really would have gotten a CR with chemotherapy. And I think that was

alluded to before, when 10 of the patients went on to get chemo, and six got a remission.

So I think the drug clearly has activity, but I think the heterogeneity of the population in this trial, and the fact that I am hard pressed to believe that really all of these patients would not have been offered chemotherapy if this trial wasn't available.

Now, the randomized trial may make that a different story, because there the people know they're not going to get anything. So both the patient and the doctor are clearly going to agree, in that randomized trial, that they're not going to take anything.

I don't think that that's necessarily the case here: that these patients wouldn't have gotten chemo and might not have benefitted from it.

DR. MARTINO: Dr. Brawley.

DR. BRAWLEY: you know, this really is a lot like Iressa all over again; even the 11 percent response rate.

What we have here is a drug that clearly

has activity. Some people do very well on it when they respond. I think the slide that Dr. Thibault showed after I asked him is very compelling for some type of approval.

But the reality of the situation is: if we approve this drug generally, we're going to be telling a company--we're going to put a company in a terrible conflict of interest situation. We're going to tell them that your market is all people over a certain age with AML, or all people over a certain age with MDS and then AML--but go out and find the 10 or 11 percent of people in that population that you really should be selling the drug to.

So their job, after approval, will be to decrease--yes, actually Dr. Cheson, in great wisdom, said this when we, as a group, voted for Iressa. So I'm very torn.

There is clearly activity. This drug clearly helps some people. We clearly need to figure out a little bit better who among the patients would be best served by getting this drug,

and who among patients would be best served by going to something else, and not wasting their time and money on this drug.

I would love to see--that all being said, I would like to see some type of approval of this drug. I don't know if full approval is the right approval. And I accept the fact that accelerated still creates this problem that I just talked about.

DR. PAZDUR: For clarification: since people are mentioning Iressa here and there, Iressa did have accelerated approval--so everybody understands that. Because there's some people on the committee that may have not been present.

DR. MARTINO: Are there other comments?

MR. FLATAU: Yes.

DR. MARTINO: You're my blind side, and I do apologize.

MR. FLATAU: Yes, I guess I'm not really comfortable with full approval. I mean, this is a disease in these patients that, with or without Zarnestra, is uniformly fatal. And, at best, we

can hope to extend their life with a reasonable quality of life. And 85 percent of the patients, we have really no idea whether their life is extended or shortened or its the same, and how their quality of life is.

And without that, I don't know how people can be said--you know: here, you have a choice of this drug, or not.

I mean, there is standard therapy now. Standard therapy is, I guess, supportive care. And maybe they'll do better on supportive care than on this drug. And we don't really know.

DR. MARTINO: Dr. George.

DR. GEORGE: Just a general comment: there's a longstanding issue of single-arm Phase II trials' being problematic, particularly in an area where the heterogeneity issue is really important. There are some Phase II trials that can be done in more homogeneous populations, where you have a little better feel for the patient population. But in this setting, not only is the disease very heterogeneous, but the way the patients got on this

study is still, I think, contributes to the heterogeneity that makes--all of that makes for sort of unquantifiable kinds of uncertainties that, to me, raise to the level of not--just to address this issue--not meeting the full-approval criteria.

DR. MARTINO: I have a bigger problem with this whole issue. I think you're all being remarkably kind.

I do think this drug does something to some people. I'm just sitting here being made very uncomfortable by the suggestion that something that works 10 to 15 percent of the time--and in this regard, I'd like to give the company the benefit: let's make it 15--okay?

But as the gentleman on my left keeps reminding all of you--and I'll remind you that he represents the real world, he's our patient representative--someone's expecting me to walk into a patient's room and to say, "85 to 90 percent of the time this thing ain't gonna work. Do you really want it?" Okay--that's what you're asking of me as a physician. Okay?

Are we really that excited about a 15 percent CR rate? I have a much more global problem here.

DR. PAZDUR: Could I address something here? And that is: what accelerated approval is.

Accelerated approval is not "approval light." Okay? [Laughs.] I want to make that point.

This is an approval of a drug, with marketing of that drug--okay? Companies can charge for that. Companies can advertise. There are some advertising restrictions. There are some restrictions on that advertising, as far as being cleared by the FDA. There are provisions in that accelerated approval, Subpart H, that can allow the FDA to withdraw the drug--and we may be getting into that issue in the future.

The other areas are post-marketing studies; that we have more teeth to really make sure that they are done, and to look at, and to address.

But it is a marketing approval of the drug here. And I think we have to understand this.

This is not "approval light;" some issue of--and you have to consider, it is an approval of a drug here. And as such--let me finish, Bruce--you have basically two criteria that you have to meet here: one, that the surrogate is reasonably likely to predict clinical benefit. And you really have to ask in your mind while you're contemplating the decision here: given this data here, is this reasonably likely to predict clinical benefit--okay?

Number two: the issue of basically being better than available therapy, and what is the available therapy in this population? And how do you compare it? Is it a homogeneous population that Dr. George has been alluding to, that would give you confidence? And how can we define that population?

DR. MARTINO: Dr. Cheson?

DR. CHESON: While I strongly support the spirit of the accelerated approval--you know what I'm going to say--when you have drugs--well, you know, we can make up a name and call it "the Iressa

principle," since we seem to be throwing that around--when one has a drug with three negative Phase III trials, and it hasn't been taken from the market, it gives us a great deal of discomfort when we have another drug, with one Phase III trial out there, and if we give this accelerated approval--I know we're not there yet, I'm sorry, Madam Chairman, but I can't resist this--and that trial is negative, then what's going to happen?

So, again, exactly the same scenario--and, as you know, I was one of the three unpopular people back then who voted against Iressa. It just makes me uncomfortable that there is sort of an edentulous position about the accelerated approval process. I would have felt a lot more comfortable--we tend to be a little historical here. We have been reacting to a number of things over again. It has hurt some drugs and it has helped others.

But it makes me much less comfortable to do that in the context of what happens with that compound. Because I have no faith that if this is

a dead-negative trial, that the drug is not going to be continued to be sold.

And I'm sorry for that position, but I'm talking it, and I'm going to stand by it.

MR. FLATAU: How many drugs have gotten accelerated approval and have subsequently been withdrawn?

DR. CHESON: None. None. That was the point. Zero. Thank for--if I didn't make that clear. That's the one who really should have been out of there--clearly.

DR. MARTINO: But I just want to remind the group--and I do appreciate that there is history here. Our decisions need to be based on the merits of this drug. Okay?

So, again, I want to take you back to regular approval.

Are there any additional comments before I take a vote on the question of regular approval?

[No response.]

If there are none, then I will start the voting. And in that process, first please identify

yourself, and then give us a "yes" or "no" vote.

The industry representative does not get a vote.

DR. O'BRIEN: Susan O'Brien No.

DR. CHESON: Bruce Cheson. No.

DR. GEORGE: Steve George. No.

DR. BRAWLEY: Brawley. No.

DR. MORTIMER: Mortimer. No.

MS. HAYLOCK: Haylock. No.

MR. FLATAU: Arthur Flatau. No.

DR. LEVINE: Levine. No.

DR. MARTINO: Martino. No.

DR. PERRY: Michael Perry. No.

DR. BUKOWSKI: Bukowski. No.

DR. MARTINO: Eleven "nos."

Now I will turn your thoughts to do we want to give this agent accelerated approval?

Who wants to speak to that, please?

Dr. Perry.

DR. PERRY: I'd like to make a motion that we consider accelerated approval, please.

DR. MARTINO: Tell me that again? I just

want to make sure I heard you correctly.

DR. PERRY: I said I'd like to make a motion that we consider accelerated approval.

DR. MARTINO: So moved.

DR. PERRY: I'm trying to follow Robert's Orders here. I'm sorry.

DR. MARTINO: All right.

DR. BRAWLEY: Yes, I'll second that.

DR. MARTINO: Thank you. I accept the first and the second.

Now, I'd like some discussion.

[Laughter.]

DR. PERRY: All right. I'll start out then.

I think this drug have activity in a group of patients that don't have very viable options. It's true, there are some patients who did get chemotherapy afterwards, but I can't escape the thought that maybe they improved on this drug to the point that they could be considered for chemotherapy when they wouldn't have--they and their doctors wouldn't have considered it before.

And I think this is a niche drug. This is not going to be a drug for thousands and thousands of people. It's going to be for a small patient

population that, in my mind, has no other option, other than supportive care.

And I think with 301 in the background, already underway, we'll know at some point in the near future whether or not it really does have a significant survival advantage. And at that time, if it doesn't, it can be taken off the market.

But, in the meantime, I think there's a potential to help people.

DR. MARTINO: Dr. Brawley.

DR. PAZDUR: Could I please emphasize: please concentrate. We have to make sure people understand the two principles here: that this is a surrogate reasonably likely to predict clinical benefit, and you believe that this is an improvement over available therapy--that in your voting and your considerations, those two conditions are met.

DR. PERRY: Did my statements confuse in

that regard?

VOICE: Yes.

DR. BRAWLEY: Can we have the hospitalization data back up here again? My favorite slide.

VOICE: The second one.

DR. BRAWLEY: The second one. The second one.

[Slide.]

I think that this slide actually is evidence--since the people who responded stayed out of the hospital a lot more, I think that this slide is evidence that there is some clinical--yes, I think that this slide is some evidence of a clinical benefit: the fact that people who had a CR had less hospitalizations that--

VOICE: [Off mike.] [Inaudible.]

DR. BRAWLEY: Well, that's prior. During remission, it's 30 percent versus 67 percent for those who did not have a CR.

VOICE: [Off mike.] [Inaudible.]

DR. BRAWLEY: Say again?

[Multiple speakers off mike.] [Inaudible.]

DR. BRAWLEY: You can have multiple hospitalizations, is the issue.

[Multiple speakers off mike.] [Inaudible.]

DR. MARTINO: Otis, get to your point, please.

DR. BRAWLEY: Okay--I'm sorry. I'm trying to interpret the slide again.

I do believe that there is a clinical benefit to this drug. I, however, think that there is a sub-population--we talked about the heterogeneity of AML. I suspect that there is a sub-population of individuals with AML who are sensitive to farnesyl transferase inhibition. And I really do think that the science, and the population, would be best served if we could ultimately figure out who that population is before they're given this drug.

You know, this is a great deal like tamoxifen, breast cancer, before we had identified the estrogen receptor--finding the individuals who have the molecular or genetic marker that indicates

that they will respond to farnesyl transferase inhibition.

My great problem is: should we allow patients who have AML, who are in a bad situation the crap-shoot--and a 10 to 15 response rate is a crap shoot--for response before we get to the point that we can figure out who truly benefits from the drug?

That being said--and I may very well be making the same mistake I made with Iressa--that being said, I would favor accelerated approval.

DR. CHESON: can you put that slide back up again--Otis' slide? I have another question about it. Maybe you said this before and I didn't get it.

DR. THIBAULT: Yes, may I have the slide up, please?

[Slide.]

DR. CHESON: Does he right-hand column, which is those patients who didn't get the CR--

DR. THIBAULT: Yes?

DR. CHESON: At what point in time--was

that before, during, after they got the drug?

DR. THIBAULT: yes, I can go over that for you in detail.

The patients who are non-CR patients were hospitalized at any time on study.

The patients who achieved a CR, many of whom--most of them were hospitalized for the initial duration of the CR, and then the time after they achieved a CR, then they remained hospitalization-free.

DR. CHESON: But I still don't understand the right-hand column. Again, back to the 67 percent thing. I'm not sure--

DR. THIBAULT: So, the non-CR--

DR. CHESON: --there's not a better way to analyze it.

DR. THIBAULT: No, the non-CR patients, 66 of them, for 67 percent of the total--

DR. CHESON: That's not 67 percent of the total.

VOICE: [Off mike.] [Inaudible.]

DR. THIBAULT: 66 patients out of 116--yes,

that's right--of the patients were hospitalized. And this is at any time during the study treatment. And these patients spent a greater proportion of their time in the hospital, definitely, than the patients who achieved the CR.

DR. CHESON: But if that's at any time during their treatment, you could say the same thing for the patients who got a CR: 75 percent of them were hospitalized at some time during their treatment.

So that right-hand column doesn't help me any. I'd like to know whether that was before, during or after they got the Zarnestra therapy.

DR. THIBAULT: Our data includes--may I have the next slide up? There's a fifth column.

[Slide.]

No, there's four bullets.

Fourteen of the 20 patients were never hospitalized while in CR. Six were--so--

DR. CHESON: Which means six of 20 were--okay.

DR. THIBAULT: Six were hospitalized at

least once. The time spent in hospital is 21 days, and the range is six to 21 days.

VOICE: [Off mike.] [Inaudible.]

DR. THIBAULT: 12 days--it's the double-language.

DR. CHESON: Dyslexia.

DR. THIBAULT: Then the percent of the remission time spent in hospital is 8 percent.

The reason for hospitalizations: five patients had drug-induced myelosuppression, because Zarnestra is myelosuppresive; and one patient was hospitalized for unrelated co-morbidity, for which he required surgery--GI surgery.

DR. CHESON: Next slide. It's the one that's going to show me what I want to see.

[Laughter.]

DR. THIBAULT: So we do not have this data for the patients who did not achieve a CR. What we do know is that they spent approximately twice as long in the hospital.

DR. CHESON: Well, I don't see those data. I see--you're telling me twice as long. I don't

see numbers.

DR. THIBAULT: I will try to get that for you.

DR. MARTINO: Can I--I'm sorry, people. I need to remind this group what our responsibility is here. It is not to decide whether this drug does something, anything--"hopefully, please: something, anything." It is whether it is good enough for us to give it accelerated approval.

Accelerated approval means to me that something is not barely visible in its activity. There has to be something that's bordering on the exciting, people. God, I wish someone would impress me today.

DR. CHESON: That was precisely what I was trying to get at, Madam Chairman.

DR. STONE: Could I have the floor, or is that not possible?

DR. MARTINO: You may have the floor at the moment.

DR. STONE: Thank you very much. I just want to make one small comment about the remission

rate, and what it means to talk to a patient--in light of what Dr. Sekeres said and, in another respect, what you said.

Although a 15 remission rate is low numerically, in a patient who, faced with the option of--even if you take Dr. O'Brien's very well-characterized MDSM data, has an 18 to 20 percent chance of dying in the hospital, I would submit these patients have a much higher chance of dying in the hospital were they to get chemotherapy.

That has clinical meaning to a patient. If you're sitting with them in the room, as Dr. Sekeres said, it would represent an option which I believe many would take, and I think it would be reasonable for them to do so, having treated many people and seeing them die in mucositis and of sepsis due to chemotherapy, which does not offer a long survival benefit.

I'm not saying it's for everybody, but there are clearly patients out there who would take a 15 percent chance. It is a crap shoot, and we

should learn the science of it. But there are patients out there today who would take such a chance to go into remission, with the knowledge that they had a lower chance to leave the hospital. I talk to them--they go into the hospital, some of them will not come home. This offers them a higher chance to go home and see their family.

DR. MARTINO: I'm not arguing the point that there's some activity here. I'm not arguing that point. But I suspect Laetril has a response rate, too. Okay?

DR. STONE: I doubt it's--

DR. MARTINO: It's an issue of relative merit. And that's the issue before us.

DR. STONE: That's for you to decide.

DR. PAZDUR: Let's go back to the regulations--okay?

It's a surrogate endpoint reasonably likely to predict clinical benefit. This response rate that you are seeing, and the data that you have seen here, do you think that is reasonably likely to predict clinical benefit?

To put it in laymen's terms: this trial that you see here, you in a year or two years are going to see a supportive care trial. Is that

trial--if you were looking at it now, with the data that you have in hand--that data, does that say that that trial is going to be reasonably likely to be positive? That's the issue here.

DR. MARTINO: Dr. Bukowski, I think you're up next.

DR. BUKOWSKI: I don't know that we can answer that question. Exactly--

DR. PAZDUR: That's a clinical judgment.

DR. BUKOWSKI: I understand. That's a clinical judgment question.

I think the data are interesting. Whether you call them exciting or not, I think we could debate that point. But they certainly are interesting. You have a subset of individuals for whom there is no therapy--presumably. They're not eligible for chemotherapy. They won't take it. They will--at least a small percentage of them--have improvement with this agent.

Now, I think the science of this issue is complex, likely because it's pathways, it's not going to be simple to work out. There are many, many divergent paths that lead from farnesyl transferase. So it's going to take some time to work that out.

But, certainly, I'm convinced that there is some benefit to a subset of individuals with this particular drug. They do have hematological remission, they do improve.

I don't know for certain whether the entire population will improve. If partial remission, or partial responses at all have any bearing on this--which they may or may not, then certainly it's a possibility. I think giving the drug the benefit of the doubt, in my mind, is something that is worthy of consideration.

DR. MARTINO: You can give it the benefit of the doubt by allowing another study to take place. It's a matter of how you choose to give benefit of doubt.

DR. BUKOWSKI: Absolutely. But then we're

ignoring some of the aspects that were discussed with regard to patients and their needs for these drugs. Okay--should we look at that? Because that's not part of the accelerated approval. We have to think more in the scientific vein. But that enters into our deliberations, obviously.

DR. MARTINO: Dr. George.

DR. GEORGE: I'd like to address some issues with respect to accelerated approval--in particular, what it means when you say that something is "reasonably likely to predict clinical benefit."

So a number of questions have to be addressed. First of all, what is the population you're talking about? I believe, in this case, it would be those that are not "willing or able"--to use the language that was used earlier--to receive chemotherapy. And one of the problems that I struggle with a little bit is: "not willing" is a little different than "not able." So those are two different things. And I don't know--you can define "not willing"--you just ask. "Not able" is a

little more amorphous and creates the heterogeneity.

But putting that aside somewhat, let's just assume we can agree on what that population is, what would it mean to say you have some evidence that is "reasonably likely to predict clinical benefit?"

Now, I assume, Dr. Martino, that you would think it was exciting if it did predict--if you did end up proving clinical benefit, that's what you might be excited about. Not this evidence. So this is just asking the question of whether it's "reasonably likely" to predict that.

Now, what's going on is a study of 300 or so patients that is designed to pick up a pretty large survival difference. I didn't--it would be difficult to go through all the different things--scenarios, different modeling you could do to try to see whether the evidence from this Phase II trial might indeed predict that kind of outcome. I'm a little skeptical of that myself, so I'm a little worried about that: that even though I think

I might say, in the abstract, this is reasonably likely to predict clinical benefit, I would probably say it's not reasonably likely to predict clinical benefit of that magnitude. And that worries me some, just because of the practicalities of the size of the patient population, and the ability to do these studies.

But I'm afraid that's a reality that we might have to live with. That is, we could very well be in the situation, if we did approve this for accelerated approval, of finding out later that it didn't work in that trial that was supposedly the confirmatory trial.

And that relates to another issue: what is the endpoint. I mean, when you say "predict clinical benefit," we've said before, at the last December, I guess, in a leukemia study that curable complete response is, in fact, a clinical benefit in itself.

Here we're talking a little differently. We're not quite believing that. I mean, you have to be careful, I guess, because you have clinical

benefit, and I think people often confuse this: clinical benefit in some patients. But if you give a therapy, it's pretty clear that some patients benefitted from this. But that's true of a lot of things. And is that enough to give approval? And I think the answer has generally been: no, not by itself.

And so, clearly, some patients benefit. A large number may not benefit and, in fact, may be harmed from certain therapies.

So what is the benefit here? It would have to be overall survival then--I think, in this population. And the comparison group is best supportive care. So it's exactly the trial you have going on. I'm worried that it's a little small.

There may be another clinical benefit that they're not addressing at all in that trial--because I asked the question earlier--and that's quality of life; that it's entirely possible that it does not prolong survival in any meaningful way, but distinctly improves quality of life. A

possibility, but you have to look for it and carefully design those studies.

So, I'm just throwing all this out as information, but I think it's relevant to the issue of whether this really is--we have a surrogate "reasonably likely to predict clinical benefit."

MR. FLATAU: You know, actually, I'm fairly excited about a 15 percent response rate in these patients with this--you know, with the non-toxicity. But I think it's incorrect to say that there's no care. I mean, I'll these patients, whether they get Zarnestra, or whether they get high-dose chemotherapy, or whether get supportive care are going to die from the disease or from its treatment. I mean, it's uniformly fatal. And it's not at all clear to me that survival--the overall survival of patients--is higher in this over standard therapy, which would be best supportive care.

You know, if this was maybe curative, that would be different. But it's not. And I don't see any data that compares those. I have no data to

say whether it's better or not.

And I think that the trial that this--the AML 301 trial has to be done and we have to see the results of that.

DR. MARTINO: Yes?

DR. PORTER: Well, I'd like to just say that I think that there is a strong signal here, and that it is a surrogate. I think that there is a measure here that is valid.

I think that the idea that patients wouldn't be interested in a one change in eight, or one chance in 10 of improving is erroneous. Most patients will accept that if they're desperate. And, as a matter of fact, it's not just in oncology. It's true across the board in other diseases, too: when you have only a slim chance that you can actually benefit, will you take that chance? And the answer is yes.

And I think that accelerated approval--personally, although I can't vote--is the right direction for this drug, because I think that it sends a message to the pharmaceutical world that

we will accept data that even only 15 percent of the patients will improve, but we want you to continue to fight. But we do want to see that second trial.

And we do need the FDA to have more power to pull these drugs back if they don't work. And there's nothing I can do about that.

But I think given the variables we have, accelerated approval is the right direction.

DR. MARTINO: Dr. O'Brien.

DR. O'BRIEN: I think that it keeps coming back to the patient population. If I really believed--which I don't--that everybody in this trial would not respond to chemo, and/or wouldn't have gotten chemo--so it truly would be a comparator of zero, because they're not going to get a response, or they're not going to get treated--I would be perfectly happy with 15 percent.

I don't believe that you can get that out of this trial. Because, as I just told you, I think there are patients who would have been

treated with chemo. We saw that there were patients that went on to get treated with chemo and, in fact, six of the 10 achieved a complete remission.

My concern would be: now you have a pill--which is always attractive to patients--they don't get chemo up front. So you might want to argue: well, they get a pill if they--why not take the easy route, ad was asked before.

Well, what you have to keep in mind is that patients with AML who aren't in remission get sick and have a declining performance status the longer they walk around without getting a remission. So potentially delaying chemo in someone with an excellent performance status, who might go into complete remission, would be a very powerful negative, in fact.

So, I can't get around the fact that--the heterogeneity in the patient population, and the fact that, by definition, they all had a good performance status, I can't put that 15 percent into a perspective that it's 15 percent of what

would otherwise be zero.

DR. PAZDUR: Could I address that issue? Because it brings up a very important regulatory issue that affects both regular approval and accelerated approval.

There's two conditions for approval of an NDA: obviously, the demonstration of safety and efficacy is one; and then the other one is that the clinical trial information has to provide sufficient labeling information. In other words, we have to be able to identify a population that the drug works in.

And, here again, that has some caveats with accelerated approval. And, here again, the second aspect is that this has to be better than available therapy--okay?

So you have to define a population. Now, in the sponsor's indication, it just says "in the elderly--"--I forgot exactly what it was, but a relatively wide indication in elderly patients.

That clearly is inappropriate. If we would--I said we would define the patient

population that was studied in the study: greater than 75, or greater than 65 with MDS. In that population, does that capture what you're getting, or is that still inadequate? Can we provide appropriate labeling that would prevent somebody from being given this drug if, truly, they were a candidate for standard therapy. And I think that is an important question that one needs to answer.

Or, is the committee simply willing to say: well, we'll put in the indication that the physician should make that determination that this is appropriate for patients who cannot tolerate induction therapy.

But I think you're hitting on a very important issue here, and that is: labeling of an appropriate population--that's required by the law: and, secondly, if you do look at accelerated approval, is that population well enough established here that you can say that this therapy is better than available therapy--either in terms of efficacy or safety?

DR. MARTINO: Dr. Cheson?

DR. CHESON: Well, to me, 15 percent in this patient group is important. But you raise--in fact, you've really convinced me about what to do

here.

The fact is, we don't know what this patient population is. And I think there are three of us at this table--maybe four--do you treat leukemia?--there are three of us who still treat leukemia--one, two, three--and the three of us are very uncomfortable with the identification of this patient population.

Susan has data which suggests--and there were recent papers elsewhere which suggested up to 40 percent--there was a paper in Cancer last year--up to 40 percent of patients over the age of 70 or so will respond to seven-and-three kind of therapy.

Alexandra's uncomfortable on the prior MDS. I'm also uncomfortable about the accelerated approval process--but be that as it may. I think that we don't have a good grasp on the patient population that we--I couldn't draft a labeling

indication for this based on what we've shown.

I'm still uncomfortable with Otis' favorite slide. That right column doesn't convince me of anything.

If I thought that it was very clear that there was a big difference in all these features, then I'd be a little more comfortable with an accelerated approval. But the fact is: I don't really know what patients are going to respond, what patients aren't going to respond. It makes it very difficult for me to say: "Okay, we will approve this accelerated approval for this group of patients."

I just treated a 72-year-old with AML with standard seven-and-three, and he's out of the hospital, and he's in remission. You know, if he would have said, "Gee, I don't want chemotherapy, I want that pill," then he'd have been a candidate for this study. But instead he may do better with what he got--in the long run, even though his short-term events were a little more complicated.

I'm just confused as to who I would say is

going to respond to this. And, again, it gets back to other drugs and patients who we didn't know how to predict a response, and we ended up in trouble.

DR. MARTINO: Dr. Levine.

DR. LEVINE: Well, to be honest, this decision is a very difficult one for me. Because, on the other hand, I agree with Bruce: I think 15 percent CR in a very difficult population is something to approve, basically. That number doesn't blow me away.

If I look at the unfavorable karyotypes, on page 52--so that one seems to me pretty objective. And if, in fact, we were going to do this on an accelerated basis and say "greater than the age of 65 with unfavorable cytogenetics," I think there are some data to indicate 14 percent in their counting.

I would never approve this without the other trial there. There has to be that other trial looking at survival benefit. But I have another question to the company, if I might, and that is: the lack of quality of life instrument--I

can't believe you did that. And the lack of adherence data--because it would have helped you. I mean, I'm believing that these patients didn't take the medicines. And I've written articles about this. I've had grants about this. Patients don't take the medicines.

And all I'm trying to say to you is: I'll bet you that the responses were not on this dose. And maybe if it was on the optimal dose there would have been better responses.

So my only point is: on this 301 trial, is there a very careful adherence instrument? And is there a very careful clinical benefit? Because if there isn't, then we're wasting time again.

DR. THIBAULT: On the 301 study, which is an international study, we are trying to focus on the quality of life measures that are the most reliable in the population for a short period of time. So we will have detailed transfusion data. We will have very detailed hospitalization data. We will have very detailed safety data--because we've used the knowledge from CTEP-20 to design

301.

The CTEP-20 trial was what it was, but the 301 study will be the study that will bring this additional information.

DR. DeLAP: Yes, if I could add just one thing: if there are concerns about the statistical power, this is a trial that has been looked at extensively, and the patient number and the design were discussed with FDA. But if it helps to revisit the sample size, obviously we can still do that and redesign the statistical plan.

DR. LEVINE: Are there adherence data that are going to be--

DR. THIBAULT: Yes. May I address, on behalf of CTEP, the compliance monitoring in this study?

All patients on this study had drug dispensed under supervision from the research pharmacy at each site. The patients had instructions on how to use the medication. The medication was packaged in a way to facilitate the accounting of the pills.

The patients also had to bring pills back at each visit. We do not have the exact records of what happened at the visits, because this was--but

from what we saw when we reviewed the data, these discussions occurred--these pills were counted.

And so this happened--remember that each patient was reviewed every week by either the investigator or the health care giver. And we do know which dose they started on. We do know when they were dose-reduced. We do know when there was a delay in treatment.

What we do not know is the details of whether it's 20 pills or 18 pills that were returned at the end of a cycle. But remember, also, that each cycle counted 21 days of treatment, and there was 63 days in total to get this done. So, in the end, they had to finish the pills.

So the patients took 21-day equivalent of tipifarnib in each cycle, unless there was dose-limiting toxicity or an untoward even.

DR. LEVINE: Well, just for the--I mean, if you have data on pill counts, that would really

have been nice to have seen it.

DR. THIBAULT: We do not have the data on pill counts, but we do know it was thoroughly performed by the NCI investigators.

DR. LEVINE: But it doesn't help if we don't have the information.

I have another question: "best supportive care." Is "best supportive care" in Europe the same as "beset supportive care" in the U.S.? Will they have growth factor support? Will they--you know, what exactly will be that arm?

DR. THIBAULT: The arm of the 301 study is "best supportive care." That includes, of course, transfusion, antibiotics, growth factor support--if needed. I remind you that very few needed it for CTEP 20. And then some patients can also use hydroxyurea. Hydroxyurea is included in that control arm.

DR. LEVINE: And the supportive care plus the drug in the Zarnestra arm.

DR. THIBAULT: Oh, the Zarnestra arm will be the same supportive care, except for

hydroxyurea, obviously.

DR. LEVINE: Right. Okay, and then I'd just like to make one other little point which is: if, in fact--I mean, I guess I was impressed by the fact that six out of the 10 patients who did go on to chemotherapy in fact had a CR, indicating two things--indicating that they probably would have had the CR without the Zarnestra, but also indicating that the Zarnestra pre-treatment didn't stop those Crs. So there's just something to think about for the future.

DR. MARTINO: Dr. Perry.

DR. PERRY: I'd like to go back to the second page of the background document that we got from the FDA, and reflect on the fact that the complete remission rate we're talking about here is 11 or 15 percent--to be optimistic. With chemotherapy, it's 30 to 50 percent which, in my experience, is pretty exaggerated for this population group. My little trick is to take the patient's age from 100, and that gives you the chances of response rate.

There will be exceptions. Dr. Cheson's athlete--marathon runner, or whatever he was--to qualify for chemotherapy. If you look down at

treatment-related deaths, 7 percent, greater than 25 percent. We've talked all about response rates. We haven't talked about treatment-related deaths, Madam Chairman. And one-month mortality: 12 percent versus 30 to 48 percent--to me is a clear difference in efficacy.

Bruce will have the opportunity to give his patient chemotherapy if he and he or she decide. If this drug is approved, he'll also have the opportunity to give this drug to patients who are not candidates for chemotherapy--or, for whatever reason, don't want to do it. You know, if you tell somebody they're going to get chemotherapy, they're going to be in the hospital for six weeks. For a lot of people, that's something they can't tolerate. And I think, whether it's right or whether it's wrong, that's not our decision, and we can't second-guess them.

So I don't have a difficult with people

who are unwilling to take this chemotherapy. I'm not going to try to micro-manage their lives. I have a hard enough time with my own.

So I think this is a very good alternative--although albeit limited in its efficiency, it's not all that toxic.

DR. MARTINO: I think how you present things to patients has a great influence on what they choose to do or not to do. You know, we're all sort of pretending like somehow patients make all the decisions. They certainly make many of the decisions. But you and I know it's a definite interaction.

Dr. Mortimer.

DR. MORTIMER: I guess my problem remains the issue of the primary endpoint being complete response. And if we use, again, the numbers by the sponsor, 20 of 136, and if we compare it to the chemo, 6 of 136 minus how many died in the first month, I'm not sure there's a difference. And that's why I have difficulty thinking of it as accelerated approval.

DR. MARTINO: Yes, Doctor?

DR. DAGHER: Just for clarification, since you mentioned this table. And I know everybody

recognizes, since we've had all these discussions and speakers who addressed what the elderly population means, just to notice for the record that: we really had a tough time finding a completely comparable population. So the chemotherapy column in that table--as we say in the text above that--really reflects those 60 and older who had chemotherapy. So it doesn't address whether or not they had poor performance status. It's irrespective of whether they had MDS, etcetera.

So, just for the record.

DR. PERRY: If they had poor performance status, they wouldn't have been offered chemotherapy. So this is the best--this is the best you can expect. And we're comparing the best to a group that's not as good.

DR. MARTINO: Are there any other comments or discussions related to potential accelerated

approval for this agent?

Yes, Doctor?

DR. GEORGE: A question for Dr. Pazdur, maybe, and the logic of this, in terms of regulatory affairs: if, say, the accelerated approval were not to be granted, and then this trial would go--in either case, this trial is going to go on--I assume. I hope it goes on to completion.

If they didn't have accelerated approval, they couldn't do the marketing or anything of the agent during this period while we're waiting for this other trial to mature.

DR. PAZDUR: The drug would not be on the market.

DR. GEORGE: Not be on the market. And so if that trial, then, were positive enough, then presumably they could come in for full approval--

DR. PAZDUR: Yes.

DR. GEORGE: --based on overall survival.

Now, if it's negative, it creates an interesting situation. You'd have--it will be

negative at the end. Whereas, if we do have accelerated approval now, and the trial is negative--I guess what I'm asking: is there any change in the agency's position on withdrawal of agents after--for indications after--

DR. PAZDUR: Well, Bruce had mentioned that in, obviously, we are in active discussion with several pharmaceutical companies regarding their accelerated approval. There are areas of confidentiality, obviously, that I cannot broach at this time. But we are intensely looking at this.

There are issues. We are totally aware of the situation. And let me just say that this is an evolving issue here that you will see some resolution on. And I'm not saying either way what this will go as. But I think it's important that the agency is interested in looking at these commitments. This is a process and evolution. I would not make any decision based on kind of a tea-leaf reading of what we may and may not do for any specific drug.

DR. GEORGE: Well, the reason I brought it

up was it just--

DR. PAZDUR: The regulations, as they are--

DR. GEORGE: I understand.

DR. PAZDUR: --and assume that we will abide by those regulations.

DR. GEORGE: But the conundrum sort of is the effects of the decision now would potentially have a completely different impact--I mean, the results of this Phase III trial will have a completely different impact later.

I mean, if they don't have approval now and the Phase III trial turns out to be not positive enough, then they won't have approval period.

DR. PAZDUR: Correct.

DR. GEORGE: Whereas, the other way, they would have approval, and they may not have it withdrawn, even if that were negative. [Laughs.] So that's an interesting logical--

DR. PAZDUR: But I think you should look at it like if that provision is on the books and it can be exercised. Past performance does not

predict future performance.

DR. MARTINO: Can I ask a question of the company? Let us assume for the moment that you don't get approval of this drug today in the accelerated arena, that strikes me that that would then leave you open to expand your Phase III trial into the U.S., which right now you've chosen not to do in this country.

Would that be your intent? Would that be your thought?

DR. DeLAP: Again, we're already committed to, I think--what is the total number of center?--90 centers globally, and I think we'll be able to achieve the sample size that we currently plan or, again, if we need to revisit the sample size, even a somewhat expanded sample size quite efficiently with the centers we have.

And again, we're quite confident that the results of that trial, given the reliability of complete remission as a surrogate in the experience in AML up to now, we're quite confident in the results of that trial.

DR. MARTINO: Thank you.

Dr. Bukowski?

DR. BUKOWSKI: Bob, what's your estimate of

the trial duration for accrual? You must have that information.

DR. ZUKIWSKI: We anticipate that the accrual should be finished in the first quarter of 2006, right around that time--right around the end of the year, first quarter 2006.

DR. DeLAP: Operationally speaking, it would take some time if we decided to expand it further, with IRBs and everything else. So it's probably sensible for us just to continue with that.

We're certainly intent on following through on this trial, regardless. But, again, we think that given that it will be about two years before we're able to present data from that trial, we think that given the durable complete remissions and the evidence of benefit and safety profile, that it is something that we'd like to make available for patients at this time.

DR. MARTINO: Are there any other comments? If not, I'll take a vote.

And, again, the question is: accelerated approval for this agent. And again, we'll start with Dr. O'Brien.

Please state your name, and your answer.

DR. O'BRIEN: O'Brien. No.

DR. CHESON: Cheson. No.

DR. GEORGE: George. No.

DR. BRAWLEY: Brawley. Yes.

DR. MORTIMER: Mortimer. No.

MS. HAYLOCK: Haylock. No.

MR. FLATAU: Flatau. No.

DR. LEVINE: Levine. Yes.

DR. MARTINO: Martino. No.

DR. PERRY: Perry. Yes.

DR. BUKOWSKI: Bukowski. Yes.

DR. MARTINO: And we have a total: seven no, four yes answers.

Rick, do you have any other questions you want to deal with?

DR. PAZDUR: No.

DR. MARTINO: That being the case, this meeting is adjourned. Thank you.

[Whereupon, at 2:24 p.m., the meeting was adjourned.]

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