FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)

Tuesday, July 11, 2017

12:29 p.m. to 3:27 p.m.

FDA White Oak Campus

White Oak Conference Center

The Great Room

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

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Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(12:29 p.m.)

Call to Order

Introduction of Committee

DR. ROTH: Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, any other devices you have, if you have not already done so. I would also like to identify the FDA press contact, Angela Stark. Angela is back here.

My name is Bruce Roth. I am the chairperson of the Oncology Drug Advisory Committee, and I will be chairing this meeting. I will now the meeting of the Oncology Drug Advisory Committee to order. We will start by going around the table and introducing ourselves. Let's start down here with P.K.

DR. MORROW: P.K. Morrow, a medical oncologist employed by Amgen.

DR. TAYLOR: Wayne Taylor, patient representative.

DR. SUNG: Anthony Sung, assistant professor

of medicine at Duke University.

DR. CHEN: Andy Chen. I'm from Oregon Health Science University.

DR. HARRINGTON: Dave Harrington, statistician, Dana Farber Cancer Institute.

DR. COLE: Bernard Cole, biostatistics, University of Vermont.

DR. ROTH: I'm Bruce Roth. I am a medical oncologist from Washington University in St. Louis.

LCDR SHEPHERD: Jennifer Shepherd. I am the designated federal officer for the ODAC today.

DR. NOWAKOWSKI: Greg Nowakowski, hematologist at Mayo Clinic Rochester.

DR. KO: Chia-Wen Ko, statistical reviewer at FDA.

DR. LEE: Jee Eun Lee, pharmacometrics reviewer at FDA.

DR. JEN: Emily Jen, clinical reviewer, FDA.

DR. PRZEPIORKA: Donna Przepiorka, cross-discipline team leader, FDA.

DR. FARRELL: Ann Farrell, division director, Division of Hematology Products, FDA.

DR. PAZDUR: Richard Pazdur, director of Oncology Center of Excellence.

DR. ROTH: Thank you.

For topics such as those discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and those individuals can express their views without interruption. Thus as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, the FDA will refrain from discussing the details of this meeting with the

media until its conclusion.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks. Thank you.

Now I will pass it to Lieutenant Commander Jennifer Shepherd, our DFO for the meeting, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

LCDR SHEPHERD: Good afternoon. The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is

being provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services, which the government may expect from the employee.

Related to the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children, and for purposes

of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts; grants; CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of biologics license application 761060, Mylotarg, gemtuzumab ozogamicin, for intravenous use submitted by Wyeth Pharmaceuticals, Incorporated, a subsidiary of Pfizer, Incorporated. The proposed indication for this product is in combination therapy with daunorubicin and cytarabine for the treatment of adult patients with previously untreated de novo acute myeloid leukemia.

This is a particular matters meeting during which specific matters related to Wyeth Pharmaceuticals BLA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all

standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. P.K. Morrow is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Morrow's role at this meeting is to represent industry in general and not any particular company. Dr. Morrow is employed by Amgen.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. ROTH: Thank you.

We'll now proceed with the FDA's opening remarks, and Dr. Przepiorka.

FDA Introductory Remarks - Donna Przepiorka

DR. PRZEPIORKA: Thank you, Dr. Roth.

Good afternoon. The topic for discussion, as Lieutenant Commander Shepherd indicated, is BLA 761060 for gemtuzumab ozogamicin or GO. This application was submitted for the proposed indication of combination therapy with daunorubicin and cytarabine for treatment of adult patients with previously untreated de novo CD33-positive acute myeloid leukemia or AML.

For those of you unfamiliar with the treatment of AML, the standard of care for induction of remission is 7 days of cytarabine plus 3 days of an anthracycline or the so-called 7+3 regimen. When daunorubicin is used as the anthracycline, we may also refer to this regimen as DA.

GO was granted accelerated approval in 2000 as a single agent for treatment of older adults

with relapsed AML. SWOG study S0106, a randomized trial of DA plus or minus GO for treatment of newly diagnosed AML, was identified as the trial to confirm clinical benefit. In 2009, the SWOG study was terminated early due to increased induction mortality and lack of improvement in the CR rate, DFS, or overall survival. GO was subsequently withdrawn from the U.S. market.

While GO was in use and in study S0106, the major safety concerns that were identified included liver toxicity and veno-occlusive disease, including fatal events. In an effort to reduce the drug-related toxicities, lower doses of GO have been investigated.

Wyeth, the sponsor, has now submitted a new marketing application based on the results of study ALFA-0701, which used a lower dose of GO in combination with DA for treatment of patients with newly diagnosed AML. During the course of the presentations and discussions today, you will hear about several different GO doses and schedules. This table provides a reference for those regimens.

The original approval for GO monotherapy for relapsed AML was for a dose of 9 milligrams per meter squared. Doses of 6 milligrams per meter squared and a fractionated schedule using 3 milligrams per meter squared have also been studied as monotherapy. SWOG study S0106 used 6 milligrams per meter squared in combination with DA, and the new trial ALFA-0701 included the fractionated schedule using 3 milligrams per meter squared in combination with DA.

The key safety outcomes of early mortality and VOD for the two randomized trials of interest are shown in this table. For the comparison of the GO arm to the no GO arm, the odds ratio for early mortality was 3.58 in the SWOG study using 6 milligrams per meter squared and 1.99 for the ALFA-0701 study using the fractionated schedule. The odds ratio for VOD during the entire safety period of follow-up was 7.62 for the SWOG study and 2.42 for ALFA-0701.

Relative to the control arm, the fractionated schedule of GO with a lower dose

appeared to have a lesser disparity in early mortality and VOD than in the SWOG trial. Both Wyeth and the FDA reviewer will provide additional analyses of safety by dose as well as the actual safety profile of the fractionated schedule of GO in ALFA-0701, leading us to the first issue, which is do the data for the GO fractionated schedule in combination with DA show an acceptable safety profile and address the previous safety concerns about the use of GO in combination with DA?

The second issue regards efficacy. The primary endpoint of ALFA-0701 was event-free survival or EFS. The hazard ratio for the primary endpoint was 0.56, favoring the GO arm with a very significant p-value. This was clearly a positive study with regard to the primary endpoint, however, FDA usually uses survival to assess clinical benefit for patients with AML being treated with curative intent.

The sponsor therefore conducted a meta-analysis to determine whether EFS is a surrogate for OS in AML. The issue of surrogate endpoints

has been discussed many times at ODAC meetings, largely however, for using progression-free survival or PFS. For the purposes of today's discussion, it is important to note that PFS as used for solid tumors, lymphoma, or myeloma is very different from EFS used as an endpoint for acute leukemia.

Both endpoints have components of relapse and all-cause mortality distributed over the entire treatment and follow-up periods, but only EFS has the additional component of induction failure, which is assessed early in the study, only during induction.

The FDA statistician will review the results of a more in-depth analysis of surrogacy, but this figure illustrates the bottom line. In the best-case scenario, if EFS were a surrogate for OS, in the scatter plot showing each patient's event-free survival and overall survival the points would all line up on the diagonal. But here in ALFA-0701, there is a substantial proportion of patients whose overall survival is well out of

proportion to the event-free survival such as those within the green oval and those scattered above the diagonal, presumably due to successful salvage therapy, including allogeneic stem cell transplantation.

In an era now where multiple active agents are available as salvage therapies that extend survival in patients who fail primary treatment, it might not be mathematically possible to demonstrate that EFS is a surrogate of OS at the patient level or at the trial level using the current definition. Nonetheless, since having active leukemia has a major and immediate impact on a patient's life, clearly achieving and maintaining a complete remission as measured by EFS would seem a benefit. Both the sponsor and the FDA reviewer will provide more perspective on EFS as a benefit for your consideration.

So acknowledging that EFS as currently defined does not have a strong correlation with OS, the second issue for your consideration is whether EFS can be deemed a benefit in itself for patients

with newly diagnosed AML treated with curative intent.

Lastly, once you have evaluated the safety data and considered whether EFS is an appropriate measure of benefit, the voting question will be, do the results of ALFA-0701 demonstrate a favorable risk-benefit for GO 3 milligrams per meter squared days 1, 4, and 7 added to DA for patients with newly diagnosed CD33-positive AML treated with curative intent. Thank you.

DR. ROTH: Thank you, Donna.

We will now proceed with the applicant's presentation. Dr. Rothenberg.

Applicant Presentation - Mace Rothenberg

DR. ROTHENBERG: Thank you, Dr. Przepiorka, for framing these topics so clearly. We believe that the data contained in the BLA dossier and to be presented today will establish the favorable benefit-risk relationship for Mylotarg in a syndication and the clinical relevance of event-free survival.

On behalf of Pfizer oncology, I would like

to thank you, Dr. Roth, Dr. Pazdur, Dr. Farrell, ODAC members, FDA staff, ladies and gentlemen, for the opportunity to be here today to discuss Mylotarg. My name is Mace Rothenberg. I am the chief development officer for Pfizer oncology.

Mylotarg is an antibody drug conjugate composed of a CD33-directed monoclonal antibody that is covalently linked to the cytotoxic agent N-acetyl gamma calicheamicin. Once bound to CD33, an antigen that is expressed on AML blasts in 90 percent of patients, the antibody drug conjugate is internalized, the linker hydrolyzed, and calicheamicin is released to bind to DNA and create double-strand breaks that result in cell death.

Mylotarg originally received accelerated approval from the FDA in 2000 for use as a single agent in the treatment of patients with relapsed AML. In 2010, SWOG S0106, a confirmatory trial intended to serve as the basis for conversion from accelerated to full approval, was not able to demonstrate that the addition of Mylotarg to first-line chemotherapy improved efficacy.

In that study, it was also noted there was a higher rate of fatal induction toxicities in the Mylotarg-containing arm. Due to the results of this trial, recognition of an increased risk of veno-occlusive disease associated with Mylotarg in the postmarketing setting, and following consultation with the FDA, Pfizer voluntarily withdrew Mylotarg from the U.S. market in 2010.

What has changed over the past seven years to warrant this new application, and why are we doing this now? Despite its withdrawal from the market in the United States, there remained great interest among AML investigators to evaluate Mylotarg in the first-line setting using different doses and different schedules of Mylotarg.

Some investigators felt that the SWOG trial contained certain design elements that did not enable the full potential of Mylotarg to be realized, but there is a second reason as well.

In the years following its withdrawal from the U.S. market, the demand for compassionate-use Mylotarg not only continued but grew. In light of

the emergence of encouraging data from multiple phase 3 clinical trials and steadily rising demand, the FDA reached out to Pfizer to inquire about our plans to bring Mylotarg back to the U.S. market.

Following a series of eight meetings and interactions with the FDA from 2012 to '16 and publication of Professor Robert Hills' meta-analysis showing that Mylotarg could improve survival in first line AML, key components for a new BLA were identified and agreed upon with the FDA, and tat has led to this unique submission.

Rather than being based largely on company-sponsored trials, this Mylotarg BLA is comprised of data from the pivotal ALFA-0701 trial, an individual patient data meta-analysis which collected information on more than 3300 patients enrolled in five cooperative group studies, including the ALFA and SWOG trials; and supportive Pfizer-sponsored trials. This has resulted in a BLA with data for more than 4,300 patients.

To return to my original question of why we are here, we are here because we believe that there

is now a substantial body of evidence to support the claim that Mylotarg can confer meaningful benefit to a broad range of AML patients. Both the IPD meta-analysis and ALFA study are informative in estimating the beneficial effect of Mylotarg in terms of event-free and overall survival.

We are here because clinical data supplemented by PK and PD modeling have helped identify a lower dose fractionated regimen as an efficacious and potentially safer one than the single high-dose regimen used in the SWOG study. And we're here because we believe that the risks associated with Mylotarg have been well characterized and that through the use of risk mitigation strategies, there is a favorable benefit-risk profile for use of Mylotarg in these seriously ill patients.

Based upon these data, Pfizer is seeking approval for Mylotarg in combination with daunorubicin and cytarabine for the record treatment of patients with previously untreated de novo CD33-positive acute myeloid leukemia. As

agreed with the FDA, this indication will be the focus of today's presentation, but we are also seeking reinstatement of approval for Mylotarg in the relapsed AML setting as well.

In addition to my colleagues, Iain Webb and Debbie Chirnomas, who will be presenting data on the efficacy and safety of Mylotarg; Dr. Richard Stone, director of the Adult Acute Leukemia Institute at Dana Farber, will provide an overview of AML and its therapeutic landscape.

Our presentation will conclude with Dr. Jorge Cortes, chair of the AML section in the department of leukemia at MD Anderson, who will provide his perspective on Mylotarg as someone who sees and treats these patients every day.

We are also joined today by three external consultants, Professor Herve Dombret, chair of the ALFA Cooperative Group; Dr. James Freston, a medical consultant with expertise in veno-occlusive disease; and Dr. Gary Koch for statistics.

I would now like to introduce Dr. Richard Stone to discuss AML and the therapeutic landscape.

Applicant Presentation - Richard Stone

DR. STONE: Thank you, Dr. Rothenberg.

Good afternoon. My name is Richard Stone. I am chief of staff and director of the adult leukemia program at Dana Farber Cancer Institute in Boston. I am a paid consultant to Pfizer, but I have no financial interest in the outcome of this meeting. I am pleased to provide you with an overview of acute myeloid leukemia, AML, and the therapeutic landscape for this difficult disease.

AML represents a clinically and biologically heterogeneous group of malignancies characterized by the accumulation of abnormal myeloblasts which have limited ability to differentiate. Without successful treatment, bone marrow failure, which causes neutropenia and thrombocytopenia with associated infection and bleeding, will lead to death.

During 2017, we expect that over 21,000 Americans will be diagnosed with AML during which time 10,000 people will die of this disease, indicating the severity of this illness. The mean

age of diagnosis is 68 years, so geriatric considerations are very important. Unfortunately, AML treatment has not changed very much in the last four decades and current treatments require prolonged hospitalization due to severe myelosuppression.

As depicted here, there have been minimal improvements in outcomes, especially in older patients in the last 40 years. In younger adults, the better outcomes we have seen have been attributed to improved supportive care, which has made chemotherapy and stem cell transplantation more tolerable.

The initial goal of AML therapy is to achieve remission. Complete remission is defined as a state with there are less of 5 percent blasts in normocellular marrow at a time when there was recovery of platelets and neutrophils to near normal levels. Complete remission with incomplete platelet recovery and/or incomplete neutrophil recovery, termed CRp or CRi, is useful because it may also allow post-remission therapy in the form

of more chemotherapy and/or stem cell transplant, which is required for cure.

As you've heard, cytarabine-based regimens, especially including 3+7 or 7+3, consisting of anthracycline on days 1 through 3, usually daunorubicin, combined with cytarabine on days 1 through 7, are generally employed as a means to take a patient from being sick to achieving a morphologically undetectable leukemia state. However, the inevitable residual tumor burden present at the time of complete remission still needs to be eliminated.

In older adults, we sometimes choose less intensive therapy, particularly if the patient has poor performance status or many comorbidities. Although most patients achieve remission, the complete remission rates vary in age even in patients deemed fit enough to tolerate induction therapy with 3+7.

The current approach to the treatment of fit patients with AML is the use of one or two cycles of 3+7 chemotherapy, which requires hospitalization

for at least 4 to 5 weeks during which time patients are at risk for bleeding and infection. Those patients who don't achieve remission will die within one year, most of them. Salvage chemotherapy to achieve a response sufficient to move to allogeneic transplant is difficult to achieve goal in such patients.

While a minority of patients in initial complete remission are highly chemo responsive and can be cured with intensive post-remission therapy, most require allogeneic stem cell transplant, which is quite toxic and associated with significant treatment-related mortality, sometimes due to veno-occlusive disease. As previously noted, remission rates vary by age with a lower rate in older adults.

Those who achieve remission may unfortunately sometimes die in remission due to treatment-related toxicity, as shown in red on this slide. As depicted in black, many remission patients, especially older individuals, relapse. Unfortunately as well, successful salvage therapy

after relapse, generally chemotherapy by allogeneic transplant, is not as common as we'd like it to be.

Beyond remission, how do we assess therapeutic outcomes? Clinically relevant events in AML include death, failure to achieve remission, or relapse after remission. Lack of achieving remission or relapsing after remission are generally associated with bone marrow failure and increased risk for bleeding or infection.

Let's again review some of the response definitions in the post-remission setting. Event-free survival is defined from the date of randomization or diagnosis to the date of induction failure, relapse, or death, whichever occurs first. Disease-free or relapse-free survival is the time from initial response to relapse or death from any cause, and of course, overall survival is the time from randomization or diagnosis to death from any cause.

As a leukemia doctor, I feel that event-free survival is intrinsically a valuable endpoint in AML. First, a long duration of event-free survival

increases the likelihood of achieving a second remission if the patient relapses and thus the chance for a cure in advanced disease.

Event-free survival, as you've seen, has a moderate positive correlation with overall survival, but not an absolute correlation, as was pointed out, because of being confounded by the occasionally successful salvage therapy. Nonetheless, a longer event-free survival means a longer time for the patient to delay or avoid the burdens and toxicities associated with additional chemotherapy, hospitalizations, and transfusions. Moreover, a longer event-free survival will delay the emotional distress that patients, their families, and caregivers experience on hearing the news that the disease has failed to respond to chemotherapy or has returned after prior therapy.

Patients with AML need better therapies. Since 3+7 was developed 40 years ago, there have been no new therapies, not including of treatment of acute promyelocytic leukemia. Mylotarg was approved in 2000, but as you've heard was withdrawn

in 2010. However, 2017 is the year of hope in AML. Midostaurin has been approved, and two other drugs in addition to Mylotarg may be approved later in the year. However, midostaurin only applies to about 40 percent of the patients with AML whose blasts have a FLT3 mutation; CPX-351, or Vyxeos, to the 25 percent of patients who have secondary AML; and enasidenib to the 12 percent with an IDH-2 mutation; whereas Mylotarg could be used in the vast majority of AML patients because the expression of the target CD33 is common.

In summary, AML is a serious, rapidly progressive, life-threatening hematological malignancy with a frontline standard of care that has changed little over 40 years. More agents are needed to achieve more frequent, deeper, and therefore longer remissions. Longer and more frequent remissions would be reflected in event-free survival, which I maintain is beneficial to patients.

Mylotarg, which is applicable to the majority of patients with AML, combined with

standard induction therapy provides clinical benefit, as Dr. Webb will show, in terms of prolonging event-free survival and improving overall survival. Thank you very much.

Dr. Webb.

Applicant Presentation - Iain Webb

DR. WEBB: Good afternoon. My name is Iain Webb, and I am the clinical team lead for hematologic malignancies at Pfizer. Over the next 10 minutes or so, I propose to provide an overview of the key efficacy data that support our application for approval of Mylotarg for the treatment of patients with previously untreated de novo AML.

This is an overview of the relevant data supporting the application. Included are the pivotal study ALFA-0701 as well as a meta-analysis of individual patient level data from the ALFA study as well as 4 additional randomized trials.

The trials in the meta-analysis were of similar design. They included a range of Mylotarg doses given in combination with intensive

chemotherapy. Importantly, the pivotal ALFA-0701 study incorporated the lower dose fractionated Mylotarg regimen introduced by Dr. Rothenberg.

Before discussing ALFA further, I would like to set the stage by looking at the SWOG S0106 study, which is included on this slide. This is noteworthy because SWOG was the original phase 3 study designed to confirm the clinical benefit of Mylotarg.

Here is how the SWOG study was designed. Patients aged 18 to 60 with previously untreated de novo AML were randomized 1 to 1 to receive daunorubicin at the full dose of 60 milligrams per meter squared with AraC or to receive a single dose of Mylotarg, 6 milligrams per meter squared, in addition to daunorubicin at a reduced dose of 45 milligrams per meter squared, now known to be suboptimal, with the same dose of AraC.

Following consolidation therapy, patients were re-randomized to receive 3 additional doses of Mylotarg or observation. Primary objectives were complete response after induction and disease-free

survival.

Based on the data in this slide, the SWOG study was prematurely closed to enrollment by the data safety monitoring committee at the time of an interim analysis. This decision was taken because there was a lack of improvement in the primary endpoints of complete response and disease-free survival as well as an increase in early deaths in the Mylotarg arm. Following the discontinuation of SWOG, investigation in Mylotarg continued. The ALFA group initiated a phase 3 study in previously untreated patients, also known as MyloFrance 3, and the design of the study is shown in this slide.

Patients with previously untreated de novo AML were randomized 1 to 1 to receive standard full-dose intensive induction therapy with daunorubicin and AraC with or without Mylotarg. In ALFA, the new lower dose fractionated regimen of Mylotarg was used, consisting of 3 fractionated doses of 3 milligrams per meter squared on days 1, 4, and 7 of induction. Patients remaining in remission following induction therapy received 2

courses of daunorubicin and AraC consolidation with or without a single dose of Mylotarg. 271 patients were randomized.

You can see here that for the enrolled patients, the baseline parameters included age, CD33 expression, and cytogenetics, and they were balanced between treatment arms. There was a minimal balance in gender.

Now, let's look at the key efficacy results. In ALFA, there was a highly statistically significant and clinically meaningful improvement in the primary endpoint of event-free survival. What you're looking at are the data at the time of the primary analysis.

As you can see from the wide separation in the Kaplan-Meier curves, with the Mylotarg data in blue and control arm data in orange, median EFS was significantly prolonged. Median EFS increased from 9.5 months in the control arm to 17.3 months in the Mylotarg arm with a hazard ratio of 0.562. The p-value was highly significant at 0.0002.

Improvement was maintained at later time

points with the EFS rate at 24 months being 42 percent in the Mylotarg arm, more than twice the rate in the control arm. Importantly, results of an independent expert blinded review of the EFS data were consistent.

This slide shows updated EFS data with longer follow-up. It continues to show the benefit of Mylotarg. With the date of analysis being 2.5 years after the last patient was enrolled, these data are mature.

The robust effect of Mylotarg on EFS was consistent with the overall results across most subgroups, including those based on age, ECOG performance status, CD33 positivity, and favorable or intermediate cytogenetics. There was also a difference in response rate favoring Mylotarg, but there was not statistically significant. In addition, fewer patients in the Mylotarg arm required a second induction regimen to achieve response, as indicated at the bottom of the slide.

Median relapse-free survival was also improved and almost doubled with Mylotarg,

reflecting deeper and more durable responses. The median RFS was 20 months in the Mylotarg arm versus 11.4 months in the control arm, and the hazard ratio was 0.639. As we saw for EFS, RFS benefit was also maintained over time.

Here you see that overall survival also favored Mylotarg with median OS being 27.5 months in the Mylotarg arm and 21.8 months in the control arm. The hazard ratio is 0.807, but was not statistically significant.

Why was the magnitude of overall survival benefit smaller than the magnitude of event-free survival benefit? Well, first, most patients in both arms received follow-up therapies that could confound overall survival. These therapies included hematopoietic stem cell transplant either in first remission or as salvage therapy. Second, the study was not fully powered for overall survival. With the number of events observed, the power was 76 percent for a hazard ratio of 0.66.

Let's move on to the meta-analysis, which provides additional data concerning the efficacy

and safety of Mylotarg. The five trials are summarized here and included over 3,300 patients. The trials share a similar design and include a range of Mylotarg doses given in combination with intensive chemotherapy. Criteria for inclusion were prospectively determined by Dr. Robert Hills at the University of Cardiff in Wales. Both positive and negative trials were included.

It is important to note that this was not a typical meta-analysis analyzing only published data, but instead consisted of analyses of individual patient level data compiled from the different studies and analyzed in a standardized way. Overall survival was the primary endpoint of the meta-analysis. EFS, RFS, response rate, and safety were secondary endpoints.

Here's the overall patient profile. Importantly, all patients were previously untreated, and 88 percent of patients had de novo AML. 62 percent of patients have favorable or intermediate cytogenetic risk. In the meta-analysis, Mylotarg added to standard intensive

induction chemotherapy provided a significant improvement of the primary efficacy endpoint of overall survival as well as in the secondary endpoints of event-free and relapse-free survival. This is despite differences in dosing regimens and inclusion of studies with variable results, in particular the SWOG study and the AML-15 which did not meet the primary endpoints.

Although the 9 percent decrease in risk of death is not as large as we might have liked, this does represent a step forward for patients with this devastating disease.

To conclude, Mylotarg in lower fractionated doses added to standard chemotherapy provided improvement in event-free and relapse-free survival in both the ALFA and the IPD meta-analysis, as well as an improvement in overall survival in the ALFA study that is supported by the findings of the IPD meta-analysis where it was statistically significant.

I would now like to ask my colleague Dr. Chirnomas to review the safety profile of

Mylotarg. Thank you for your attention.

Applicant Presentation – Debbie Chirnomas

DR. CHIRNOMAS: Good afternoon. My name is Debbie Chirnomas, and in the next few minutes, I am going to share with you what we have learned about the safety of Mylotarg, including the impact of the lower dose fractionated regimen.

In order to do that, I am going to walk you through three main topics. First, we will look at the rationale for the lower fractionated dosing regimen; second, we will review the safety profile from the trials in the newly diagnosed patients; and third, we will go into more detail regarding special safety topics related to the use of Mylotarg, including bleeding, thrombocytopenia, early death, and veno-occlusive disease.

As you have heard earlier, over the course of its development, Mylotarg was tested using a variety of doses and schedules. Early trials evaluated Mylotarg at 9 milligrams per meter squared when used as monotherapy. In this setting, veno-occlusive disease and myelosuppression arose

as safety concerns. The risk of VOD was notably higher in patients who received hematopoietic stem cell transplants. But Mylotarg has efficacy, so there was a lot of interest in how to get this right and strike the balance between efficacy and safety.

Through continued research, a better strategy emerged. First, dose-finding studies identified 3 milligrams per meter squared as the lowest near saturating dose. Second, we learned that CD33 is recycled back to the cell surface in approximately 72 hours. This provided the rationale for the lower fractionated dosing.

As illustrated on the right, cells are exposed to a near saturating dose of Mylotarg. Then once the payload is delivered, CD33 recycles back to the cell surface just in time for the next dose of Mylotarg in 72 hours.

The last and critical piece of data that further supported this strategy is the PK data showing a safety benefit. As you can see on this graph, when the dose is reduced from the 9

milligrams per meter squared dosing shown at the top to the 3 milligrams per meter squared times 3, given 3 times, which is shown on the bottom, the peak concentration, or Cmax, which is directly associated with toxicity, is decreased by 75 percent.

This translated into a direct prediction of reduction in the risk of veno-occlusive disease. Patients with no prior transplant are represented on the left, and patients with prior transplant are represented on the right. The dotted lines represent the Cmax values for the two different dosing regimens. The pink is the low dose, 3 milligrams per meter squared, and the black is the high dose, the 9 milligrams per meter squared.

As you can see, reducing the dose decreases the risk for VOD in patients undergoing hematopoietic stem cell transplant by 50 percent. In patients who do not undergo hematopoietic stem cell transplant, there is also a reduction, but the risk is very low, regardless.

Now, let's turn to the general safety

profile seen in the combination chemotherapy studies presented by Dr. Webb. These are the ALFA study adverse events defined and prospectively collected by the sponsor. Remember that the ALFA study used the lower fractionated dose of Mylotarg I described earlier.

You can see the top three grade 3 or 4 adverse events are nausea, vomiting, and diarrhea; mucosal toxicity; and pain. The frequency of these adverse events was higher in the Mylotarg arm than in the control arm. Other adverse events were either of similar frequency in both arms or higher in the control arm such as skin toxicity.

Additional adverse event data were subsequently collected, although they were part of the original data collection. We just went back and got more details. Rate of infection, as you can see on the top, was similar in both arms. Hemorrhage, primarily grade 3, was increased in the Mylotarg arm. VOD was in 6 patients in the Mylotarg arm and in 2 patients in the control arm, both of whom received Mylotarg as part of the

compassionate use program.

The individual patient data meta-analysis safety profile confirmed the findings from ALFA. The three adverse events I have mentioned earlier -- thrombocytopenia, hemorrhage, and VOD -- are shown in the boxed rows. They are all higher in the Mylotarg arm. Overall, however, VOD has a low incidence in this larger population of 1.1 percent.

Now let's look at these topics in more detail starting with hemorrhage. As a reminder, in the ALFA trial, the incidence of hemorrhage was 90 percent in the Mylotarg arm compared to 78 percent in the chemotherapy only arm.

Low platelets are a common cause of bleeding in AML patients receiving chemotherapy. This is the platelet recovery time in the ALFA study. Patients in the Mylotarg arm on the left experienced a 5 to 6-day delay in platelet recovery compared to the chemotherapy-only arm. This is the most likely reason for the increased rates in hemorrhage we just saw.

Importantly, however, this increase in hemorrhage and thrombocytopenia did not result in an increase in overall early mortality, as shown here. The 30- and the 60-day mortality rates in ALFA show no difference between the two arms.

This is in contrast to the findings from the initial combination trial by SWOG with the higher 6-milligram per meter squared dose of Mylotarg, shown on your right, where there was a significant imbalance between the Mylotarg and the chemotherapy only arms.

I would like to turn now to VOD, veno-occlusive disease, starting with a brief review of the clinical features. VOD is a clinical syndrome comprised of weight gain, free fluid in the abdomen, right upper quadrant pain, and jaundice. VOD can occur as a result of many medications or toxins, but the most well-known and most common is hematopoietic stem cell transplant or bone marrow transplant.

Historically, the incidence of this severe liver congestion syndrome was different to assess,

ranging from 5 to 60 percent in the literature. More recent data, however, suggests a lower percentage, about 10 to 15 percent risk of developing VOD following an allogeneic transplant. Most patients who develop VOD will recover fully, but the subset of patients who develop severe VOD have a very high chance of dying, often from multisystem organ failure.

What is Mylotarg's relationship to the development of VOD? In order to understand this better, a stepwise logistic regression analysis was conducted on the patients receiving monotherapy. In this updated analysis shown here, two main risk factors were identified: moderate, severe hepatic impairment, and hematopoietic stem cell transplant before and after Mylotarg.

Here are the data then across three key trials measuring the incidence of VOD with Mylotarg. The two blue bars represent trials of Mylotarg monotherapy at 9 milligrams per meter squared in relapsed AML patients. The green bar is the ALFA-0701 trial, and you can see that the

overall incidence of VOD has gone down.

Then when we look at the high-risk population shown on your right, the patients who have had a stem cell transplant, we see a higher incidence of VOD overall as we would have expected, but in the ALFA trial in green, once again, we see a decrease of VOD.

When we then look at the rate of fatalities shown in the highlighted row on the bottom of the slide, we can see that in both settings, the lower fractionated dosing regimen had a lower rate of fatality. In particular, you can see that the transplant patients had no fatalities.

These data strongly support the exposure-response modeling I showed you earlier where the lower fractionated dosing was predicted to have a large decrease in the risk of VOD. But clearly, we are left with a real and important risk of VOD, and we are taking action on several fronts to provide meaningful information and guidance in dealing with this risk. These include a boxed warning with clear identification of high-risk patients and

dosing recommendations. In addition, we have an ongoing collaboration with the Center for International Blood and Marrow Transplant Research, who maintain a worldwide transplant registry.

We are working together on a prospective study to capture detailed information regarding the population using Mylotarg to ensure adequate assessment of VOD and Mylotarg in the postmarketing setting. In addition, we have been working on a retrospective matched cohort analysis comparing patients who have received Mylotarg and then a transplant with those who have not had Mylotarg.

Preliminary results show that there was no difference in the VOD rates between those two patient cohorts. These data will be submitted for publication.

In summary, the three takeaways are the following. First, dosing is key. The lower-dose fractionated regimen of 3 milligrams per meter squared times 3 in combination with chemotherapy improved the tolerability of Mylotarg. Second, our clinical experience and exposure-response modeling

have allowed us to define risk factors for myelosuppression and VOD and reduce this risk using the lower-dose regimen. Finally, Mylotarg has demonstrated a well-characterized safety profile in the treatment of AML across thousands of patients over many years.

As we heard from Dr. Stone today, patients with AML are facing a tough battle with few weapons at their disposal and a very high risk of relapse. Mylotarg is an effective and attractive option both for its tolerability and its targeted mechanism of action. We are hopeful that we can offer this important therapeutic to patients with AML again in the near future.

I would now like to introduce Dr. Cortes to speak about the benefit-risk profile of Mylotarg in the clinic.

Applicant Presentation - Jorge Cortes

DR. CORTES: Good afternoon. My name is Jorge Cortes. I am the deputy chair of the Department of Leukemia at MD Anderson and chief of the AML section in that department. I am a paid

consultant for Pfizer, and I have no financial interest in the outcome of this meeting.

The next few minutes, I would like to provide my clinical perspective on the benefit-risk of Mylotarg in AML. To put the value of Mylotarg in context, it is worth summarizing what those of us who treat leukemia and, most important, our patients with AML currently face.

AML is not a common cancer, but it is one that generally has a poor prognosis. While over 50 to 70 percent of patients may achieve a response with standard chemotherapy, most of them will eventually relapse and frequently within 10 to 12 months, and that will lead to a very short survival.

The outcome has improved very little over time, and this is no surprise, considering the treatment we use today is the same we used in the 1970s with no new therapies available for most patients, not for lack of trying but because it is so difficult to achieve even modest improvements in the outcomes of AML.

Patients with AML die of infections from the myelosuppression that is a property of AML itself and a universal occurrence with standard chemotherapy. Patients with active disease aiming to regain remission have high transfusion requirements, frequently many times a week, and recurrent and prolonged hospitalizations for fever and other complications.

Although stem cell transplant can be used, it is successful generally only for patients that have achieved a response to therapy, and once patients relapse, we have very few treatment options short of reusing the same drugs that have already failed or using drugs that have not been approved for the use of AML and that have questionable benefit.

To better illustrate this, I am showing you here the outcome of patients after front-line therapy has failed when treated with the treatment options that we have available now. The majority of these patients will not achieve remission, and the median overall survival is only approximately

six months. Therefore, for my patients with newly diagnosed AML, having a treatment option that provides a better probability of response and delays abysmal prognosis associated with the relapsed disease for as long as possible is of great benefit. For a disease as difficult to manage as AML, patients and those of us caring for them would value greatly having such an option.

Let me review with you the key trials using Mylotarg as part of the frontline therapy, the one from SWOG and the ALFA trial that you just heard about. To reiterate what Dr. Webb showed earlier, key differences includes the use of what we now have demonstrated through randomized studies to be suboptimal dose of daunorubicin in the Mylotarg arm of the SWOG trial and the use of a lower dose, fractionated of Mylotarg in the ALFA study.

The impact of these design differences can be seen in these outcomes. EFA was not reported by SWOG, but there was a higher overall response rate, a larger reduction in the risk of relapse, and a larger reduction in the risk of death with Mylotarg

in the ALFA study. Notably, the use of the fractionated schedule of Mylotarg allowed investigators to use it with a full dose of daunorubicin in the ALFA study, which probably contributed to the overall benefit of the combination.

The value of adding Mylotarg to standard chemotherapy is even more impressive when we look at the event-free survival and the relapse-free survival curves. At two years, nearly half of the patients were alive and free from relapse. This is important because, as I mentioned earlier, once a patient relapses, it is likely that they will die within a year.

I would welcome the opportunity therefore to offer my patients a treatment option with almost 50 percent probability of maintaining their first remission for at least 2 years as opposed to only a 30 percent probability with standard chemotherapy.

In addition, when I look at these survival curves, I see a welcome trend in favor of Mylotarg that is similar in magnitude to what we have seen

in other recent positive trials in AML for specific patient populations, and this trend is further supported by the results of the meta-analysis, even considering the grossly inadequate and negative SWOG study.

Putting all of this together, it is clear to me that Mylotarg addresses an unmet clinical need in patients with newly diagnosed de novo AML. The addition of lower fractionated doses of Mylotarg to standard induction chemotherapy significantly prolonged event-free survival and relapse-free survival compared to 3+7 alone with the benefit extended beyond 2 or 3 years. Given that Mylotarg is directed at CD33 antigen, it could become a potential therapeutic option for the great majority of patients with AML.

Regarding safety, as we heard earlier, Mylotarg is associated with an increased risk of myelosuppression and hepatic toxicity, including VOD. The drug had a box warning when it was on the market for these toxicities. For those of us who treat AML, these are the kind of adverse events

that we are commonly managing in patients treated with standard chemotherapy with AML.

To illustrate this, I am showing you on this slide the frequency of myelosuppression at baseline in the dark blue bar and during treatment in the light blue bar with standard frontline chemotherapy in AML. Severe myelosuppression is associated with the disease itself and thus present at baseline in at least half of the patients, and nearly all will develop severe myelosuppression while receiving standard induction chemotherapy. This then is associated with hospitalization in 93 percent of the patients and admission to the intensive care unit in 28 percent of the patients.

In addition, grade 3 or higher liver toxicity occurs in 22 percent of patients with standard chemotherapy. These are the types of adverse events that we deal with when we manage patients with AML with the treatments that we have today.

In the Mylotarg studies, VOD is associated mostly with the use of stem cell transplant. So a

worthwhile question then is to ask how is the rate of VOD with Mylotarg followed by transplant compared to the risk of VOD following stem cell transplant in general.

Looking at the rate of VOD in the general population receiving stem cell transplant for any reason, the rate was reported to be 14.6 percent between 1995 and 2007 in a large series of studies. The phase 2 pooled analysis studies with Mylotarg took place during this time frame, and the rate of VOD in patients who received Mylotarg followed by transplant was a similar 16 percent.

Over time, our understanding of factors that increase the risk of VOD and how to manage it has improved. So results, the VOD associated with transplant has decreased significantly. In a more recent retrospective analysis using the Center for International Blood and Bone Marrow Transplant research data, that rate of VOD is 4.9 percent from 2008 to 2013 in patients who received transplant for any reason.

In studies separating the rate of VOD in

patients who have received Mylotarg followed by transplant after 2000, the rate of VOD has mirrored this declining rate. Several studies from different groups have reported an incidence of VOD of anywhere between zero percent to 8 percent with transplant following administration of Mylotarg.

Nevertheless, it is clear that there is an increased risk of VOD when transplant patients received transplant after Mylotarg. But remember, we are treating patients with a highly lethal malignancy, some of them who have failed multiple prior lines of therapy and who have a very dire prognosis. These and other similar risks are the ones that we have to face and that we need to deal with every day considering these patients will otherwise die from the disease because they have no other options.

In addition, there are strategies to mitigate the risk of VOD in patients receiving transplant after Mylotarg, and management of VOD has evolved over time. Most institutions that specialize in the treatment of AML and in stem cell

transplant have protocols in place to help prevent, identify early, and manage VOD. For example, certain agents should be avoided during the conditioning regimen such as oral busulfan, sirolimus, or dual alkylating agents. \\

Reduced intensity of conditioning regimens have helped us manage or mitigate the risk of VOD and are commonly used today. During transplant, meticulous fluid management has helped, and we now have defibrotide, an agent that was approved last year for the treatment of VOD following transplant.

Summarized here is my proposed algorithm for the treatment of AML that includes Mylotarg. For previously untreated CD33-positive AML, I would add Mylotarg to standard chemotherapy and considering adding it to consolidation regardless of age or cytogenetic factors. Let's not forget that Mylotarg was previously approved also in the first relapsed setting. I would therefore welcome having it back as an option for my patients in this situation who did not receive it during induction and who cannot tolerate an intensive regimen, which

is a large majority of the patients.

The availability of this additional treatment option would greatly benefit those of us who treat this disease, and more importantly, it would benefit our patients, offering them a better chance of achieving a longer and potentially durable and deeper response.

In summary, based on the data presented today, I believe the benefit-risk evaluation of Mylotarg is favorable. The efficacy endpoints achieved in the studies presented are clinically relevant. The significant and durable prolongation of event-free and relapse-free survival is an improvement that I would enthusiastically welcome for my patients.

Any improvement I see in overall survival with Mylotarg is something I cannot discount. The opportunity to more than double the duration of remission for my patients means that I can potentially offer them a longer period of time away from the hospital, away from transfusions, and more importantly, I can delay the bleak prognosis

associated with the relapsed disease.

The safety considerations are definitely important but well within what my patients currently experience with the treatment options I have available and nothing that is outside of what I am used to dealing with in the management of patients with AML with standard chemotherapy.

Based on the totality of clinical evidence then with Mylotarg and based on my own experience managing AML both in clinical trials and with standard therapy, and using Mylotarg in clinical trials and in general practice when it was available, I firmly believe it should be approved in the previously untreated de novo and in the first relapse setting. Many of us in the AML community want and need this agent back. I thank you for your attention.

DR. ROTH: Thank you, Dr. Cortes.

We were going to have clarifying questions to the sponsor now, but I think we will have the agency presentation first, and then do all clarifying questions both to the sponsor and the

agency at one time.

We will proceed with the FDA's presentation. Dr. Jen will begin.

FDA Presentation - Emily Jen

DR. JEN: Good afternoon. My name is Emily Jen, and I'm one of the clinical reviewers for this BLA. This is the FDA review team for this application.

There are two key issues for consideration in the review of this BLA. The first is the proposed gemtuzumab ozogamicin, or GO, dose and schedule. GO was previously granted accelerated approval in 2000 as a monotherapy at a dose of 9 milligrams per meter squared times 2 doses in patients with relapsed AML.

The confirmatory trial SWOG S0106 used GO at 6 milligrams per meter squared in combination with daunorubicin and cytarabine but was terminated early after an interim analysis showed increased deaths in induction and lack of improvement in complete response rate in the GO arm. GO was subsequently withdrawn from the U.S. market in

2010.

Based on data from studies conducted in the interim, the applicant feels that a fractionated schedule of 3 milligrams per meter squared GO in combination with DA may address the safety concerns seen with the prior dose regimens.

The second issue is that overall survival is the established endpoint for regular approval in AML. We would like to discuss whether event-free survival could be an appropriate endpoint for newly diagnosed patients with this disease.

We will first address the rationale for the GO dose proposed in this application. Dr. Jee Eun Lee will discuss the pharmacology data for GO monotherapy. I will discuss the clinical outcomes of GO monotherapy. Then Dr. Chia-Wen Ko will describe the FDA's analysis of the efficacy of the combination and the surrogacy of EFS for OS, and I will discuss FDA's analysis of the safety of the combination.

The rationale for fractionated dosing regimen: as previously mentioned, the original GO

dose approved was 9 milligrams per meter squared times 2 doses given 14 days apart. The current proposed fractionated schedule of GO is 3 milligrams per meter squared per dose given on days 1, 4, and 7 of induction on day 1 of first and second consolidation.

FDA looked first at the pharmacology and clinical outcomes of GO monotherapy to assess the impact of GO dose fractionation on safety and activity. I will now hand over the talk to Dr. Jee Eun Lee for a discussion of the pharmacology of GO monotherapy.

FDA Presentation – Jee Eun Lee

DR. LEE: Thank you, Dr. Jen.

Good afternoon, everyone. My name is Jee Eun Lee. I am a pharmacometrics reviewer in the Office of Clinical Pharmacology. I will address the exposure-response relationships for safety and efficacy of gemtuzumab ozogamicin, or GO, that support a fractionated dosing regimen.

First, the PK/PD analysis for GO shows that exposures of antibody and the cytotoxic agent

calicheamicin decrease more than proportionally as GO dose decreases from 9 milligram per square meter to 1 milligram per square meter. The left two panels of box plots show that both Cmax and average AUC of total antibody increase as dose of GO increases from 0.25 milligram per square meter to 9 milligram per square meter.

Pharmacodynamic data of binding of GO to the site of action, CD33 antigen, show that GO appears to be saturated with doses of 2 milligram per square meter and above. Because no PK samples were collected from study ALFA-701, we cannot clearly determine the PK/PD of GO following 3 milligram per square meter when given with 7+3 regimen. However, in absence of any interaction of GO given in combination, we expect exposure with the 3-milligram per square meter dose will be lower than with the 9-milligram per square meter dose but sufficient to saturate the target antigen CD33.

Mylotarg is associated with increased risk for VOD. This slide provides the exposure-safety relationship for VOD. As no PK data were collected

from the registration trial, the exposure-response relationships for safety and efficacy were explored using data from study 201, 202, and 203, where only 9 milligram per square meter dose was administered as monotherapy.

In general, interpretation of exposure-response relationship with data from only one dose is limited because the spread of exposure is mainly driven by individual variability, not by dose levels. However, we are trying to utilize the limited data to find evidence to support potential benefit of a fractionated dosing regimen.

The logistic regression analysis results show that the risk for VOD increases as the Cmax after first dose of GO increases. The increase in VOD is more prominent in patients with prior stem cell transplantation. After adjusting for prior stem cell transplantation, the p-value was still 0.034 for the effect of Cmax on the risk of VOD.

The exposure-efficacy relationship for complete remission, however, was relatively flat for any exposure measures, including Cmax after

first dose, AUC after first dose, and average AUC. Covariates associated with baseline disease condition such as baseline platelet counts, baseline bone marrow blasts, and baseline P-gp were significant predictors for complete remission.

After adjusting for these covariates, the p-value for the effect of Cmax on complete remission was 0.605. So there is no clear evidence that a significant loss of efficacy is expected by reducing the dose of GO from 9 milligrams per square meter to 3 milligram per square meter.

From a clinical pharmacology perspective, fractionated dosing of 3 milligram per square meter is likely to reduce the risk of VOD in patients with or without prior stem cell transplantation and yet likely to preserve the effectiveness of the therapy.

Thank you for your attention. I'd like to pass it over to Dr. Jen so that she can continue the presentation.

FDA Presentation - Emily Jen

DR. JEN: Thank you.

To assess the impact of dose and schedule on safety, FDA performed a meta-analysis analyzing VOD rates reported in the literature across studies of GO used as a monotherapy for the treatment of patients with relapsed and refractory AML at 6 or 9 milligrams per meter squared, unfractionated regimens, or the 3 milligrams per meter squared fractionated regimen.

Although the number of patients treated with fractionated GO in the relapsed refractory setting is small, of the patients described here receiving fractionated GO monotherapy, no patients developed VOD. The studies referenced here can be found in FDA briefing document figure 3.

Additionally, the meta-analysis appears to show that the complete response rate is no worse using fractionated GO schedule than with the unfractionated 6 or 9 milligrams per meter squared GO regimens in the relapsed and refractory AML population.

The GO 3-milligram per meter squared dose fractionated schedule would be expected to have

less VOD and no apparent loss of activity compared with the unfractionated GO dose. Therefore, FDA concluded that the GO 3 milligram per meter squared dose fractionated schedule chosen for ALFA-0701 was reasonable to study.

ALFA-0701 has been described in detail in the applicant's briefing document as well as in their presentation. Briefly, ALFA-0701 was a multicenter, open label, 1 to 1, randomized phase 3 trial of GO plus daunorubicin and cytarabine versus DA alone for induction and consolidation therapy. The study included patients between the ages of 50 and 70 years with untreated de novo AML.

CD33 positivity was not required for eligibility for this trial. However, of the 70 percent of patients with available CD33 levels, none had a level of 0.

The primary endpoint of the trial was event-free survival defined as the occurrence of an event, including induction failure, relapse, or death, starting from the date of randomization. Overall survival was the key secondary endpoint.

The study enrolled 271 patients, 135 in the GO arm, and 136 in the control arm.

I will now hand over the talk to Dr. Chia-Wen Ko for a discussion of the efficacy of the GO plus DA combination.

FDA Presentation - Chia-Wen Ko

DR. KO: Thanks, Dr. Jen.

Good afternoon. My name is Chia-Wen Ko. I am the statistical reviewer for Mylotarg. I will present the agency's efficacy evaluation in the first-line AML.

The efficacy evaluation will be based on the pivotal trial results of the primary endpoint, event-free survival, EFS, and a key secondary endpoint, overall survival, OS. Because the agency indicated to the applicant that only OS has been the accepted endpoint for regular approval in AML, the applicant conducted a meta-analysis for OS as well as meta-analysis for EFS and OS correlations. These meta-analyses will be discussed in conjunction with the pivotal trial results.

I will first present the pivotal trial

results. The pivotal trial ALFA-0701's primary endpoint was EFS. It was a composite endpoint consisting of time until death, time to relapse, conditional on having achieved remission, and time to induction failure. I would like to point out that the definition of induction failure, how it is included and how the time to induction failure should be defined have not been consistent.

For ALFA-0701, in the EFS primary analysis, induction failure was defined as not achieving a complete remission or a complete remission with incomplete platelet recovery. Induction failure date was set at the date of post-induction assessment, and EFS was not censored for the occurrence of transplantation.

The result was statistically significant. The experimental arm had 21 percent less events and had 7.8 months longer in median EFS compared to the control arm. The hazard ratio was 0.56, and p-value was less than 0.001.

OS was the key secondary endpoint. It was defined as time from randomization to death.

Primary analysis of OS was based on 168 death events. The hazard ratio of 0.81 was not statistically different from 1. Estimated median survival was 21.8 months in the control arm and was 27.5 months in the GO arm.

Several points are important to the agency when considering the regulatory application in first-line AML. First, OS has been the accepted endpoint for demonstration of clinical benefit. However, an endpoint such as progression-free survival that tries to describe treatment benefit in terms of disease progression on treatment has been accepted as a meaningful endpoint in other settings.

Second, an important salvage therapy such as stem cell transplantation may have impact on OS. And third, because EFS is a composite endpoint, the result may be sensitive to its definition, in particular, how the event and censored observations are defined.

It appears stem cell transplantation could have impact on survival. In ALFA-0701, there was

21.8 percent of patients who had no CR or relapse and had received a transplantation. The median survival was longer in patients who received a transplantation versus the ones who did not receive a transplantation.

The pivotal trial had several sensitivity analyses of EFS by alternative definitions. These alternative definitions were revised from the primary analysis definition. Alternative definitions 1 and 3 used the date of randomization as an alternative induction failure date. Alternative definitions 2 and 3 had EFS censored for occurrence of transplantation. Alternative definitions 4 and 5 used alternative event. One classified any use of salvage therapy as a treatment failure, and the other considered events of relapse and death only.

In general, the sensitivity analysis results were consistent with the results from the primary analysis. Even the last definition, which considered only relapse or death as events, had a significant result.

Next, I will present applicant's OS meta-analysis. The applicant's meta-analysis of OS was based on individual patient data from five randomized GO combinations therapy trials. The analysis suggested a marginal effect with an estimated OS hazard ratio of 0.91. However, there were important differences between the five studies in age and dosing.

Age has been known to be an important prognostic factor for survival. The dose of GO has been revised over the past years for its potential relationship with survival. The agency generally does not accept retrospective meta-analysis of OS as the primary evidence for clinical benefit. This meta-analysis will be considered as an exploratory analysis.

Next, I will discuss the EFS and OS correlation meta-analysis. Considering overall survival was not the primary endpoint in the pivotal trial, applicant conducted EFS and OS correlation analyses. The analyses were based on individual patient data from the same trials used

for OS meta-analysis and based on summary data from 33 published trials of various treatments in AML.

EFS and OS correlation was assessed at the individual level based on Kendall's tau for EFS and OS concordance in individual patients as well as at trial level based on R-square for linear regression of EFS versus OS treatment effects. For analysis in the 5 GO trials where the individual data were available, a modeling technique with copula models was applied.

There are a couple points to consider when we evaluate EFS and OS correlation. First, it is important to consider the correlation at both the individual level and the trial level. Based on hypothetical data, these two figures give an example where EFS can be considered as a surrogate endpoint for OS because a strong correlation between EFS and OS was observed in individual patients as well as in estimated treatment effects. Second, a correlation of 1 would imply a perfect correlation, so a correlation close to 1 would indicate a strong correlation.

The applicant's analysis did not suggest a strong correlation between EFS and OS. The Kendall's tau for individual level correlation was estimated in a range from 0.48 to 0.52 by various models. For the trial level correlation, when the R-squared was estimated using only the 5 GO trials, it was estimated in a range from 0.45 to 0.62. When using results from all the published trials, the estimated R-squared was 0.46.

As the applicant's correlation analyses suggest EFS and OS were not strongly correlated, we looked into the EFS and OS correlation in individual patients. This figure shows the scatter plot of EFS and OS for the pivotal trial by EFS and OS events. The ones on the diagonal line were the patients whose EFS and OS were the same because they either died in CR or were still alive in CR. The blue and purple ones were patients who achieved a CR but later relapsed, and the ones in the box were patients who did not achieve a CR.

In the applicant's correlation meta-analysis, the induction failure date was set at the

date of randomization. As you can see, the EFS and OS correlation was not evaluable in patients with no CR because EFS was the same for this group of patients but OS ranged over several years. A similar pattern was also observed in the other four historical trials.

As I have shown before, a patient who received a transplant could have a longer survival than the ones who did not receive a transplant, but it's difficult to know how much the EFS and OS correlation is impacted by the use of transplantation when there is no standard criteria for whom and when to receive a transplant.

For instance, in study ALFA-0701, either a treatment responder or non-responder could receive a transplant, the status of transplantation relative to EFS could either be before relapse for response consolidation or after relapse as post-relapse salvage therapy.

To see how the EFS and OS correlation may change with the definition for induction failures and with the use of transplantation, we re-ran the

individual data meta-analysis under various EFS definitions. These definitions were similar to the ones used for sensitivity analyses in the pivotal trial.

The first five definitions all considered induction failure as an event. They are different in how the induction failure term is defined, whether or not to consider partial or incomplete remission as a treatment response, and whether or not to censor for transplantation. None of these definitions has suggested a strong correlation between EFS and OS at both individual level and trial level, but they have suggested better correlations than the ones from applicant's analyses.

In particular, the final definition considering events of relapse or deaths only had estimated a good individual and trial level correlation between these two endpoints. However, wide confidence intervals were associated with these estimates because individual data were available from only five studies.

In summary, one, the pivotal trial demonstrates a statistical significant effect of GO on EFS. Results from sensitivity analyses using alternative definitions with or without considering induction failures as an event and occurrence of transplantation were consistent with the primary analysis.

Two, confirmatory benefit of GO on OS has not been clearly demonstrated. The pivotal trial did not find a statistically significant effect on OS, and the OS meta-analysis was limited by number of studies and different dosing across studies.

Three, EFS as defined was not strongly correlated with OS. The applicant's EFS and OS correlation analysis did not suggest a strong correlation between EFS and OS. Agency's evaluation suggested EFS and OS were not strongly correlated, but the correlations improved with different definitions of EFS, and transplantation had complicated the interpretation on these analyses.

Finally, I would like to remind you that the

agency has accepted endpoints in the same family of EFS, for example, the progression-free survival in other disease settings.

Thank you. I will pass it back to Dr. Jen.

FDA Presentation - Emily Jen

DR. JEN: From a clinical standpoint, overall survival clearly represents a benefit. Durable complete response is also beneficial for the patient, and event-free survival reflects durable CR and survival. The surrogacy of EFS for OS may be influenced in part by active salvage therapies, including stem cell transplantation. Therefore, the lack of correlation between EFS and OS is not unexpected, and as has been mentioned, FDA has accepted progression-free survival for drug approvals in other diseases with similar circumstances.

We would like the committee to discuss whether event-free survival itself could represent a clinical benefit for patients with newly diagnosed AML. This concludes our discussion of efficacy. I will now focus on the analysis of

safety of GO plus DA.

FDA's analysis of safety was based on all patients treated in ALFA-0701, data from the applicant-submitted individual patient data meta-analysis, and a review of randomized trials of GO plus chemotherapy in the literature.

There are some potential limitations to this data. ALFA-0701 was not prospectively performed for regulatory purposes, and only predefined grades 3 and 4 adverse events were recorded. Therefore, the applicant performed a retrospective collection of adverse events of special interest, capturing all grades of hemorrhage and VOD, severe infections, and any other adverse event that led to early permanent discontinuation of GO or chemotherapy.

All safety analyses done by FDA have been conducted on this dataset of retrospectively collected AEs. Additionally, for the IPD meta-analysis, safety data is available only for a limited list of prespecified composite grade 3 and 4 events. Therefore, a more detailed analysis is

not possible.

FDA reviewed the available data, focusing on early mortality, treatment-related adverse events, VOD, hepatotoxicity, hemorrhage, and prolonged thrombocytopenia. Although ALFA-0701 randomized patients 1 to 1 between the GO and control arms, some patients randomized to the GO arm did not receive GO in each phase of treatment. This resulted in an as-treated population that changed unpredictably with each cycle. The as-treated patient numbers detailed in this table are the ones used in FDA's analysis of safety, and all adverse events of special interest and patient deaths were independently adjudicated by FDA. Therefore, there may be small differences in the numbers presented by FDA and those presented by the applicant.

In ALFA-0701, early mortality, defined as death within the first 30 days of treatment, occurred in 4 percent of patients in the GO arm compared with 2 percent of patients in the control arm. Of the 5 deaths occurring in the GO arm, 4 were determined to be treatment related. Two

patients died of CNS hemorrhage, 1 of hemorrhagic shock, and 1 patient died of VOD. In the control arm, there were 3 deaths overall, 1 determined to be treatment related, which was due to sepsis in the setting of bone marrow aplasia.

In this figure provided by the applicant, the IPD meta-analysis supports a trend towards a reduction in the odds ratio for early mortality with reduced doses of GO. This trend persisted when results from the published data were considered.

In particular, the disparity in 30-day mortality between treatment arms in ALFA-0701 is lower than in the confirmatory trial SWOG S0106 with odds ratios of 1.99 and 3.58, respectively. This suggests that the 3-milligram per meter squared fractionated GO schedule is safer with regards to early mortality.

This slide shows ALFA-0701 adverse events occurring during induction in order of risk difference of GO compared with the control arm. Adverse events that were higher in the GO arm were

due primarily to bleeding and to a lesser extent, infection. VOD was also greater in the GO arm. These differences in rates occurred during each phase of treatment, and more detailed lists can be found in tables 18 and 22 of the FDA briefing document.

The proportion of patients permanently discontinuing treatment due to adverse events was higher in the GO arm at 31 percent versus 7 percent in the control arm. The adverse events that primarily accounted for this difference were thrombocytopenia and hepatobiliary disorders.

Six patients in the GO arm of ALFA-0701 developed VOD, and 3 cases were fatal. Additionally, 2 patients in the control arm developed VOD after receiving compassionate use GO for relapsed disease. Seven of the 8 patients developed VOD without a prior transplant. 1 of those 7 went on to develop VOD a second time a few days following transplant, and the remaining patient developed VOD 25 days after transplant. In the meta-analysis and literature, there was a trend

towards decreased imbalance of VOD with decreasing doses of GO.

In ALFA-0701, grade 3 and 4 bilirubin increases and AST elevations were more common in the GO arm versus the control, and AST elevations were not significantly higher with GO. There were 8 potential Hy's Law cases, 5 cases in the GO arm, and 3 cases in the control arm. Hy's Law identifies patients who are at high risk for fatal drug-induced liver injury.

In the GO arm, 1 patient died of VOD, and 1 died due to disease progression. In the control arm, 1 patient recovered after discontinuation of chemotherapy. The remaining 5 out of 8 patients had resolution of their abnormal liver tests without discontinuation of treatment. The meta-analysis data show a trend for decreased imbalance in grade 3 and 4 bilirubin and AST elevations with decreasing GO dose.

Hemorrhage occurred at a higher rate in patients treated with GO both overall and in each phase of treatment. Grade 3 or higher hemorrhage

was almost more frequent in patients treated with GO, and fatal hemorrhage was reported in 4 patients in the GO arm compared with none in patients treated with DA alone.

Of note, ALFA-0701 had a higher overall risk difference for grade 3 and higher hemorrhage in any phase than other protocols in the meta-analysis or literature review, with a risk difference of 13.4 percent with GO plus DA over DA alone.

Overall and during each treatment phase, time to platelet recovery was longer in patients in the GO arm versus the control arm. Furthermore, a delay in platelet recovery time of greater than 45 days was reported in a larger percent of patients in the GO arm in each phase of treatment.

Here on the far right, included in the control arm, 2 of the 6 patients in consolidation 1 and 8 of 28 patients in consolidation 2 had been treated with GO in the previous cycle and had GO permanently discontinued due to prolonged thrombocytopenia, indicating that this effect may be cumulative. In contrast, time to neutrophil

recovery was similar between arms, as can be seen in FDA briefing document table 20.

The mechanism of this prolonged thrombocytopenia is unclear, but the meta-analysis shows a trend for reduced imbalance in thrombocytopenia with reduced GO dose.

In summary, ALFA-0701 was not prospectively performed for regulatory purposes, and the safety analysis is limited by the retrospective nature of the adverse event collection. However, 30-day mortality was not significantly different between treatment arms.

Adverse events that were more frequent with GO were due to bleeding or infection, and these differences occurred during all phases of treatment. VOD occurred in 5 percent of patients treated with GO versus zero percent of patients who did not receive GO.

Hemorrhage events occurred more frequently, and platelet recovery appeared delayed in patients treated with GO compared to those with DA alone. The additional data from the published literature

were consistent with the clinical trial safety findings.

An issue for discussion is whether the available safety data allay the concerns about the safety of GO when added to DA for treatment of patients with newly diagnosed AML.

To briefly summarize, fractionated GO in combination with DA showed a clinically meaningful EFS benefit with an improvement in median EFS of 7.8 months with GO plus DA over the control arm.

The hazard ratio for EFS was 0.56 with a p-value less than 0.001. However, a corresponding OS benefit was not seen, and in the meta-analysis, EFS was not found to have a strong correlation with OS. This analysis may have been confounded in part by active salvage therapies, including stem cell transplantation.

From a safety perspective, there remains a risk of VOD with an incidence of 5 percent with GO, and patients treated with GO had prolonged platelet recovery time and more high-grade hemorrhage. But the difference in early mortality with GO plus DA

versus DA alone is small, and the disparity in 30-day mortality between treatment arms in ALFA-0701 is lower than that reported for S0106, suggesting that the lower dose of GO in the fractionated schedule is safer with regards to early mortality.

Overall, the GO 3-milligram per meter squared dose fractionated schedule appears to be safer for use with DA than the previously studied 6-milligram per meter squared dose. We will ask the committee to discuss whether event-free survival may be a reasonable endpoint for new therapies for treatment of patients with newly diagnosed AML.

The voting question is, do the results of ALFA-0701 demonstrate a favorable risk-benefit for gemtuzumab ozogamicin 3 milligrams per meter squared on days 1, 4, and 7, added to DA for patients with newly diagnosed CD33-positive AML? This concludes our presentation.

Clarifying Questions

DR. ROTH: Thank you, Dr. Jen.

We will move on to clarifying questions, both for the applicant and the agency. If you have a question, just give a little hi sign to Jennifer here. She can write your name down, and we will try to take those in order.

I would do as I say, not as I do, and remind yourself to say your name before you ask the question for those transcribing the notes for today. Dr. Sung?

DR. SUNG: I actually have three questions about safety and two questions about efficacy. With regard to the first question about safety, as Dr. Chirnomas and Dr. Lee presented, it's predicted that a lower Cmax with a 3 by 3 dosing would lead to less VOD. However, according to the briefing documents supplied by Pfizer in SWOG S0106, there was a 1.7 percent rate of VOD with the 6 milligram per meter squared versus 4.6 percent in ALFA-0701. So it appears that the VOD is actually higher unless there was a typo or something.

DR. WEBB: Thank you for the question. Yes, as you recall, in the SWOG study, the dosing was

the higher single dose of 6 mgs per meter squared versus the 3 fraction, the 3 mgs per meter squared. The SWOG study was stopped early based on the data safety monitoring committee decision, and so the follow-up is relatively limited in comparison to the ALFA study.

I'm not sure if we know exactly what the total incidence of VOD might have been in SWOG. What we know is what's published and has been reported by SWOG. But we do know quite well the rate in ALFA, given that those patients were followed for a long period of time.

DR. SUNG: Related to that, the documents from Pfizer also presented the VOD rates in the 201, 202, and 203 studies, and it appears to be about 5.4 percent there, which again seems quite similar to 4.6 percent in the ALFA study.

DR. WEBB: Yes. If we could call up slide MA-62 to refresh everyone's memory. So this is a slide that summarizes the incidence of VOD in the different studies, in the 201 to 203 studies, which you mentioned, which were the first three

studies that led to the accelerated approval of Mylotarg in the year 2000 all with a dose of 9 mgs per meter squared, you do see the rate is 5.4 percent. Then there was a real-world experience study that was done as a post-approval commitment, the 847 study, which is in the light blue on the slide. We showed the higher incidence of 9.1. And then there is the ALFA study, as you referenced.

Certainly, one needs to take into account not only the incidence of VOD but certainly the incidence of fatal VOD, which you will note is lower with the fractionated dosing in the ALFA study both in the context of overall incidence as well as following hematopoietic stem cell transplant.

DR. SUNG: Continuing the subject of VOD, I would also refer to the briefing documents from Pfizer, page 43, table 10, where it shows that in the 31 patients on the Mylotarg chemotherapy arm, there was a 9.7 percent VOD incidence in the patients who received transplant. In the

chemotherapy alone arm, it notes 2 patients. But am I correct in understanding those are the two patients who received GO, and therefore the incidence of VOD in transplant patients in the chemotherapy alone arm is actually zero?

DR. WEBB: That is correct, yes. So following the withdrawal of Mylotarg from the market, an expanded access program was initiated. And the two patients in the control arm in ALFA did in fact receive Mylotarg as part of the compassionate use program, I believe both in the salvage setting. My understanding is both of them recovered from their VOD.

DR. SUNG: One question I had in terms of efficacy -- and this is for the broader group of presenters -- I noticed on Dr. Webb's presentation, slide 33, that patients with poor-risk cytogenetics did not appear to derive any benefit from Mylotarg.

We are currently in an era where we are trying to personalize our therapies for our patients depending on their disease characteristics. I cite the Beat AML trial

sponsored by LLS as one prime example where we are even willing to delay induction chemotherapy to try to personalize and give the best treatment for our patients.

In patients with poor-risk cytogenetics, whether we discover it when they're newly diagnosed or patients who we know have poor-risk cytogenetics because they have a previous MDS, should they receive Mylotarg? Is there any efficacy?

DR. WEBB: Yes. So if we could show, first, slide MA-33, and then we can show EF-232 after that. This is the slide from the main deck that you're referring to.

First of all, before we start, certainly, we all acknowledge the limitations associated with subgroup analyses. You can see here that the number of patients in the adverse cytogenetic group in comparison to the favorable or intermediate is relatively small, but as we did note, the odds ratio for event-free survival in that group in the ALFA study was 1.11.

If we can show slide EF-232, this is looking

at the data with the advantage of the greater patient population included in the meta-analysis, and you can see here that both event-free survival and relapse-free survival are improved with the treatment with Mylotarg.

The odds ratio for overall survival in the adverse cytogenetic group is 1, indicating that some patients certainly did not benefit in terms of overall survival. However, it also in aggregate does not show evidence of deteriorating overall survival with treatment with Mylotarg.

Also, you need to take into account that in many patients, as you referenced the concept of personalized medicine, you may not have cytogenetic data available at the time that treatment needs to be initiated.

DR. SUNG: Then my final question in terms of efficacy, if you have a patient you know that you're going to transplant and all you need is a CR to get them to transplant, and there's no difference in CR, what is the benefit in giving that patient Mylotarg, exposing them to the safety

risks and also the 10 percent VOD risk?

DR. WEBB: If we look at response rates in the two arms, there is an improvement in response rate in the Mylotarg arm that is not statistically significant. The true CRs per se are quite similar in the two arms, and CRP is slightly higher in the Mylotarg arm.

I think that whether to take that patient to transplant or whether to treat them with Mylotarg in order to take them to transplant, I think it's probably best addressed by one of our physician colleagues.

Dr. Stone, you would mind addressing that question?

DR. STONE: I think it's an excellent question. However, I'd just like to point out that not all CRs are the same, and the transplant community has been quite correct to point out over the years that CRs when there's still measurable residual disease do poorly. So the CR rate in the ALFA trial was higher. There's data, which we didn't have time to go into, that suggests that at

least when it can be measured, the depth of CR is better in those people that were exposed to Mylotarg upfront.

I think there is pretty good data supporting the use of better, a more deep remission treatment, which you can do with Mylotarg in getting a better result after transplant. There is data that those who were transplanted in the ALFA study, and if you look at those who were transplanted and first remission, the ones who received Mylotarg actually did better, not statistically significant, but they did better, analogous to what we saw in midostaurin or what we've seen in CPX-351.

DR. ROTH: Dr. Nowakowski?

DR. NOWAKOWSKI: Greg Nowakowski. Question to the applicant. If you look at the data on overall survival from ALFA study showed on slide 36, they appear to be correlating closely to overall survival shown in the meta-analysis on slide 41 in terms of the median overall survival.

However, if you look at the primary endpoint of ALFA study of event-free survival, they appear

to be significantly different than event-free survival seen on meta-analysis on slide 41 with GO arm median event-free survival of 20.3 months versus 9.6 months median event-free survival in meta-analysis.

Would you discuss the difference between the event-free survival in meta-analysis and in ALFA study?

DR. WEBB: Yes. So certainly, really focusing on the meta-analysis, it's important to note that the studies were selected based on the prespecified criteria determined by Dr. Hills, that those be studies looking at combinations with intensive chemotherapy in the previously untreated population.

So the meta-analysis criteria-selected studies before their results were known, and that really is the reason why the event-free survival hazard ratio is 0.85 and the meta-analysis was 0.56 in the ALFA study.

It's important to note that the meta-analysis did include negative studies,

including the SWOG study, which is the study that led to the withdrawal of Mylotarg when that did not meet its endpoints. In addition, it included another study with a higher dose regimen of 6 mgs per meter squared, the GOELAMS study, as well as the AML 15 study, which was also negative. So it's really a reflection of variation in effect across positive and negative trials.

DR. NOWAKOWSKI: The definition of EFS was the same in both analyses, right?

DR. WEBB: The EFS result is somewhat different. As you heard earlier, in the sensitivity analysis the FDA did, it really doesn't impact results.

Dr. Benner, if you could perhaps share some of the sensitivity analyses that we did to look at different definitions across the studies.

DR. BENNER: Becky Benner of Pfizer statistics. Actually, I think I might like to follow up first on the differences in the definitions briefly.

Yes, as mentioned, there was a slight

difference in terms of how the date of induction failure was determined, where the primary analysis of ALFA, it was at the time they were determined to be an induction failure, whereas using the individual patient level data meta-analysis, it was taken to be the randomization date.

From the sensitivity analyses we've done of that, that doesn't really make much difference in terms of the hazard ratios. So I don't think that's necessarily a large driving factor into this.

Then another factor that was different between the two definitions is in order to have some consistency between slightly different aspects of the induction period of the five studies, the patients were counted as a responder if it was within 60 days of randomization. So there was also some slight differences in the definition due to this point.

That's just a little bit of the elaboration, although I don't think these subtle differences in the definition are making a large impact in terms

of the results.

DR. NOWAKOWSKI: Thank you. The second question is in regard to CD33 expression. If you look at the forest plot provided by the sponsor in figure 6 in the briefing document, there appears to be no relation between the efficacy and CD33 expression. Even in patients with lower expression of CD33, you see effect on efficacy.

With targeted therapy, we would usually expect some correlation with the expression of the target. So could you elaborate a little bit more on the lack of correlation of the CD33 expression?

To follow up on this, Dr. Cortes just showed us in his algorithm that in CD33-positive AML, he would add GO to induction regimen. So what's the level of positivity here because this study, as I understand it, did not require CD33 positivity at the enrollment. So what's the actual cutoff, 1 percent, 10 percent, or where do we draw the line?

DR. WEBB: Thank you. I'll ask my colleague Dr. Laird to address your questions.

DR. LAIRD: Douglas Laird, Pfizer, translational oncology. That's an excellent question. In the context of the ALFA-0701 study and also the IPD meta-analysis, we explored 30 percent and 70 percent cutoffs to look at the impact of the degree of CD33 positivity on clinical endpoints.

What we saw in the IPD meta-analysis where we have the greatest patient numbers, allowing for the fact that these are retrospective subgroup analysis, we saw a potential for clinical benefit for the addition of Mylotarg to chemotherapy using both the 30 and 70 percent cutoffs for the lower fractions in each case. Those endpoints included EFS, overall response rate, OS, and relapse-free survival.

In terms of a threshold below which there might be no benefit, certainly in the less than 30 percent population, which constituted about a quarter of the population in the IPD meta-analysis, the benefit appeared to be maintained for all the readouts. That said, we have insufficient data to

comment on the potential for benefit in true CD33-negatives, i.e., patients with positivity rounding down to zero, for example, of which there are very few subjects.

Given the mechanism of action of the compound, which is after all a CD33-directed therapeutic, we do feel that the conservative approach is to propose including CD33 positivity in the indication even though CD33 positivity was not an inclusion criteria in the studies in the IPD meta-analysis.

DR. NOWAKOWSKI: The cutoff for CD33 positivity would be defined as?

DR. LAIRD: There is no universally agreed definition of CD33 positivity. So I think certainly from the point of view of -- we've certainly looked at the population broken up into deciles and saw that, overall, for example, we had 11.5 percent of subjects were below 10 percent. But again, those sorts of numbers don't support efficacy analysis.

DR. NOWAKOWSKI: Thank you.

DR. ROTH: Roth, St. Louis. Don't go anywhere because I was going to hop on the back of Greg's question there.

Let me ask it a different way and maybe kind of a contra-argument to Dr. Sung's personalized medicine. I'm having a difficult time figuring out why mandating CD33 positivity would be in the indication. It wasn't required for eligibility for the pivotal trial. We see that 90 percent of patients, both from Dr. Stone, Dr. Cortes' slides, express it, and from Dr. Webb's slides, that the level of expression didn't really predict for benefit of EFS or not.

Not to be a cynic, but the more restrictive the indication, the more an excuse for a payer not to cover a drug. Unless you can tell me that they're not going to benefit from it, and as a majority of the people do, I was just trying to make that leap of why we would be more restrictive in the indication.

DR. WEBB: The reason that the CD33 is included in the proposed indication statement is

that we do not have significant data in CD33-negative patients. Certainly, we have data in patients with very low levels of CD33, but we don't have specific data to address that question in terms of benefit.

DR. ROTH: Thank you. Dr. Harrington?

DR. HARRINGTON: Two questions of clarification, I think both for the sponsors. I believe it was Dr. Cortes pointed out in his presentation that there are strategies for mitigating VOD post-transplant, and I wonder if there are any data that show that those strategies might be effective in the presence of Mylotarg.

DR. WEBB: Thank you for your question. I'll ask my colleague Dr. Chirnomas to respond.

DR. CHIRNOMAS: Hi. Debbie Chirnomas, Pfizer oncology. The direct answer in terms of head-to-head studies really showing specific medical mitigation strategies preventing VOD are not available. However, when you look at really the VOD rates across all transplant, as Dr. Cortes mentioned, in the last 17 years, we've seen a

steady drop in the VOD rates overall. And I think it's going to be very hard to try to isolate the use of Mylotarg.

We do have data, as I mentioned, some preliminary data from the CIBMTR telling us that -- they looked at their patient database from 2008 to 2011, and they looked at the patients who had been exposed to Mylotarg, and they case controlled.

They did age matched and disease status matched case controls for patients who did not have Mylotarg, and the Mylotarg-exposed patients had a 4 percent rate of VOD, and the non-Mylotarg patients had a rate of 3 percent. And that's consistent with the recent ASH presentation from the CIBMTR looking at the rate of VOD in 13,000 patients, which showed a 5 percent rate of VOD overall.

So the answer again directly is no, we're not sure that specifically targeting doing better with Mylotarg will make VOD less. But we know that those mitigation strategies overall for VOD have made VOD less, and so we have reason to hope that

that will continue to be the case.

DR. WEBB: Thank you.

I'm sorry. Just to add to that, one of the goals of the prospective CIBMTR collaboration that was referenced is actually prospectively to collect data concerning such elements such as therapy since the data is really very anecdotal at the moment.

DR. HARRINGTON: Thank you. For a non-clinician, setting aside the notion of surrogacy here, I guess I'd like an explanation that a non-clinician can understand why EFS is a better clinical endpoint or at least as useful as relapse-free survival. What is it telling you that is helpful in the future management of the patients?

DR. WEBB: Thank you. I'll ask my colleague Dr. Stone to address your question.

DR. STONE: As was pointed out, relapse-free survival is calculated in AML from the time a patient has a complete remission. So the relapse-free survival benefit here was evident in the ALFA study, but event-free survival is a composite endpoint, as was pointed out numerous times, which

also involves people who don't go into remission.

Not going into remission is a bad thing if you have AML. If you're not in remission, you've been in the hospital for six weeks. Maybe you've got one or two cycles of induction chemotherapy, and you're still not in remission. So there's very little chance you're going to be able to salvage those patients. Extremely poorly and numerous data have shown that from MBS and elsewhere.

If you want to analogize progression-free survival to event-free survival, you take a bunch of tumor cells, which are throughout the body rather than in one lump, you give chemotherapy, and it shrinks either not at all or just a tiny bit. So that would be a progression-free survival event and a pro-free survival analysis to my mind.

That's why I think event-free survival is a relevant clinical endpoint because it picks up the problem of not going into remission and relapsing after remission. I hope that answered the question.

DR. HARRINGTON: I think it does. I'm

struck by the strikingly larger correlation between relapse-free survival and survival than event-free survival.

DR. STONE: I think that has to do with the sensitivity analyses that were shown quite elegantly by you and that event-free survival is very sensitive to how you measure it. But in general -- and so relapse-free survival, you're in remission, it's easy. Event-free survival is a bit more complicated. I think that's part of the problem with the lack of correlation, but I'm not a statistician.

DR. HARRINGTON: Thank you.

DR. ROTH: Dr. Cole?

DR. SUNG: Sorry. Can I just make one more comment on that as well, just as a clinician? If you pull up slide 33 -- can we show MA-33? Thanks. FDA slide 33. It's the one with the event-free survival curves. I'm sorry. I must be looking at a different set than -- sorry, 18. I apologize. Thank you.

So as a clinician, I don't always show my

patients these curves, but those who ask, I can just point to them and look. I say, "Which of these two curves would you rather be on? Would you rather be on the curve where you have significant event-free survival, you don't need a transplant, you're doing well, or would you rather be on the side where you have to have salvage chemotherapy, you have to go to transplant with the associated risks?"

Transplant has 20 to 30 percent treatment-related mortality. So as a clinician, I believe that event-free survival is a critically important endpoint.

DR. ROTH: Dr. Cole?

DR. COLE: Thank you. My question is along those same lines, in fact. There seems to be something of a survival benefit or a trend toward survival benefit with GO in the ALFA-0701 study, but it doesn't achieve the statistical significance. So we're left with this issue of the absence of a clear survival benefit in a pivotal trial, the decision to use GO might be justified by

considerations of quality of life; namely, whether delayed relapse confers a quality of life benefit in light of the increased toxicity with GO.

My question is whether any evaluation of the quality-of-life impact or this tradeoff was performed.

DR. WEBB: We did not have quality-of-life or PRO data for Mylotarg, which largely reflects the time frame in which the studies were conducted. So unfortunately, we don't have data to specifically address your question. One would have to infer from the adverse event data and the maintenance of remission as an indicator of positive likelihood of quality of life.

DR. ROTH: Dr. Chen?

DR. CHEN: I have one question on efficacy and then a question on safety. One thing I did notice in the 30-day mortality data was there did seem to be an increase in treatment-related mortality of 4 versus 1 at the 30-day treatment-related mortality. I was wondering if there was longer follow-up of that. Was there a difference

at 100 days or longer, even though there wasn't a difference in all-cause 30-day mortality.

The second question I had was in terms of echoing the prior comment by Dr. Sung, the AML 15 study, the AML 16 study, and this pivotal study here, they all did not individually show a benefit in adverse cytogenetics, and they all did show a significant benefit, particularly in the good cytogenetic risk group.

You are asking for a broad approval across all AML when there may be certainly an increase in toxicity. In the patients that have adverse cytogenetics, you could argue that they would actually do worse with this treatment.

DR. WEBB: Thank you for your questions. I'll ask Dr. Chirnomas to address the first question relating to causes of early mortality and Dr. Cortes to address considerations in treatment of patients with adverse cytogenetics.

DR. CHIRNOMAS: Debbie Chirnomas, Pfizer oncology. I showed in the main deck -- but there was a lot of information. If we could look at

MA -- I'm going to get it wrong. But what I would like to show is that at 30 days, the all-cause death was similar, but not the same, as you point out -- MA-57, please -- but at 60 days, the death rate is the same.

Is that what you were asking about?

DR. CHEN: No. My question is treatment-related mortality, not all-cause mortality.

DR. CHIRNOMAS: If we can pull up SA-261, please. Thank you. Here, you can look at the differences between the causes of death, and as you might expect, there is again one liver case, and then there's some infection; again, a little bit more hemorrhage, which I think is consistent with what we've seen; so not a big change, just more consistent with the known profile.

Does that answer your question?

DR. CHEN: Yes, to a certain extent, but I do see from this small data cut, there still is an increased higher rate of non-treatment-related mortality in the Mylotarg arm.

DR. WEBB: Perhaps you could clarify the

question. Is there a question associated with that comment?

DR. CHEN: No, there's not a question.

DR. ROTH: Dr. Taylor? Oh, I'm sorry.

DR. CORTES: Thank you. I can just make a comment -- first before answering the question about the cytogenetics, about this early mortality rates, there is a small imbalance. We just saw that. However, we in general think that any early mortality below 5 percent is quite acceptable in AML.

So all our treatment options are within that range, and you will see different studies showing small variations within that number. But again, anything below 5 percent, we consider within acceptable ranges.

In terms of the cytogenetics, there's no question that there is no survival benefit with the studies that we saw today. There's no survival disadvantage with the addition of gemtuzumab, but there's no survival benefit. We do see, however, particularly when we consider the totality of the

patients in the meta-analysis, that there is a benefit in event-free survival and a benefit in the relapse-free survival.

This particular patient population is very difficult. There's really nothing that has worked in this patient population. Our best hope for a patient with these kind of characteristics is to try to get them to a transplant. Even within transplant, those patients have the worst prognosis compared to patients that have -- but at least we have a chance.

Having a better chance of response and a more durable response will give me a better chance of identifying a donor and getting them to a transplant. So although I would, of course, welcome the benefit in survival, the benefit in event-free survival and the benefit in relapse-free survival is not only welcome, but it's among the best that I've seen in any other approach that has been tried in AML.

DR. CHEN: One last question, if I may. The consolidation used in this study was not the

standard that is used in the United States. The United States uses high-dose AraC for consolidation, the standard 3 grams per meter squared that we're all familiar with as clinicians. This study did not use that, and how do you -- what was the reason for using this alternative regimen, and do you think that would have any effect on our interpretation of these results?

DR. WEBB: Thank you. I'll ask Professor Dombret to address your question concerning this grouped study.

DR. DOMBRET: Thank you very much. Good afternoon. My name is Herve Dombret. I'm from the University Hospital Saint-Louis in Paris. I'm the director of the leukemia program here, and I'm chairing the Acute Leukemia French Association, the ALFA group, for 20 years.

To answer your specific question on the consolidation design, you have to remind that the patient population ranged from 50 years of age until 70 years of age, so it's not the totally younger patient, adult patients.

In this age range, there is no standard post-remission chemotherapy well accepted at the worldwide level. We retain two courses based on intermittent dose cytarabine during this trial mostly because of this age selection.

DR. CHEN: If that was the case, then why is the application not restricted to ages 50 to 70?

DR. WEBB: The age range of the study was selected based on competing studies at the time. Our assessment of the data is that if there is evidence of benefit in the older patient population who are more likely to do poorly, it's reasonable to assume that the ALFA regimen, at least the experience with the induction regimen would be applicable to the younger patient population, which of course was included in the meta-analysis, if you look at those results.

DR. ROTH: Sorry. Now Dr. Taylor.

DR. TAYLOR: Thank you. Yes, I wanted to follow up on what Dr. Cole had asked. I know you said that you didn't have any quality of life actual measures, but is there -- I guess we use

this word "surrogate" a lot here today. Are there surrogate measures like hospital length of stay, number of blood products used, things like that?

Certainly, as a patient who had AML, for me, event-free survival, relapse-free survival, those all mean progression disease or free of progression of disease, and those are very important. But were these folks -- because the toxicity that we talked about, were they happier with that longer event-free time?

DR. WEBB: I'll ask first Dr. Benner to share the data that's available concerning those endpoints, and then I'll ask Dr. Cortes to share his assessment of patients' quality of life.

I think you do need to take into consideration, though, that once the patient is in remission that the need for those transfusion, et cetera, is going to be much less. So there's this intense period during therapy and then the longer period, which is reflected in the EFS and the RFS.

We can share the data with you later. We'll

get that for you. If I can have Dr. Cortes come up and address his clinical impressions.

DR. CORTES: Thank you. I don't have the direct data from the studies, but what I can mention is that in clinical practice, certainly a patient that achieves a remission, even though they continue with consolidation, their general condition seems to be very different.

I will explain, for example, what happens in our setting in my institution. The induction chemotherapy is done in an inpatient setting, and once they recover, the consolidation, it tends to be an outpatient administration. If we do it inpatient, we actually have a unit that's less intensive because these patients go in and come out of the hospital very quickly.

They are much less frequently in the hospital, much less frequently in the clinic. They tend to go more back home. Many of the patients that come see us come from distant places, so whereas a patient who is not in remission, they have to stay locally, they are more admitted to the

hospital with complications. They always are admitted to the higher intensity unit, et cetera.

I don't have direct data. We manage these patients very, very different because they are in a very different situation. My expectation is that -- and I would like to see the data, but my expectation would be that we would see a gross imbalance in terms of blood utilization and hospital admission, et cetera.

DR. SUNG: If I could just comment on that as well, returning back to table 10 from the documents from Pfizer, they show that 31 patients in the Mylotarg arm went on to receive a transplant, or 24 percent versus 53 in the chemo alone arm, or I believe that was 40 percent. So if you can keep a patient from having to go to transplant, I think that's a huge win because again, transplant, it's 3 months at the hospital, 6 months to a year of recovery, 20 to 30 percent treatment-related mortality.

So if you can keep patients from having to get a transplant, even if their overall survival is

the same because if you get cured from your transplant, I'd much rather be cured just from chemo alone or chemo plus GO than to have to go through a transplant to get that cure.

Again, I think the more tricky situation -- and not to harp on this, but it's come up -- is the patients with poor-risk cytogenetics or the patients who you're going to take to transplant anyway. Are you really getting an advantage there by giving them GO, or are you giving them a 10 percent risk of VOD?

DR. ROTH: Were you done, or did you have another -- was somebody else looking for a slide or something?

DR. WEBB: We're good. Thank you.

DR. ROTH: I'm going to ask now, though. Dr. Morrow?

DR. MORROW: Just a little clarification. Dr. Cortes did a really nice job of discussing the strategies to mitigate risk of VOD, and the sponsor also talked about their potential actions to address VOD, including the box warning,

identification of the high-risk patients, and dosing recommendations.

Can you give a little bit more granularity as to how you will potentially incorporate some of the strategies for mitigation of VOD within the prescribing information incorporating Dr. Cortes' discussion?

DR. WEBB: I'll have Dr. Chirnomas share some of the mitigation strategies that are obviously still under discussion and would ultimately be reflected in the final label, but our current proposal, certainly, there are individual institutions which will also have their own practices beyond that.

Dr. Chirnomas?

DR. CHIRNOMAS: Thank you. Debbie Chirnomas, Pfizer oncology. If I can have slide MA-64, please. So this is what we had been referring to earlier. As Dr. Webb said, we're in close conversations and will be in further conversations with the FDA to get this right. But in conversation with our advisors and clinicians

that are using it, we would be talking about lab parameters; of course, identifying the risk factors of severe or moderate hepatic disease. Let's see.

In terms of one of the key things that has come up, is timing from transplant, that's something we don't have a lot of data on except to say that further away is likely a little bit better. But we really are trying to get granularity on that, working with the CIBMTR.

So those are the types of information we'd like to provide. In addition, we have guidelines on if the LFTs are elevated, to wait until they come down, et cetera, and more detail about that.

I just wanted to also show slide SA-232, please. This is going a little bit backwards, but I know that there's a lot of concern about the different risks cytogenetic groups -- no, I'm sorry. That was not -- I wanted to show you the forest plot that we have that shows that the relapse-free survival and the event-free survival of the adverse cytogenetic population really does benefit and that it's the overall survival that is

neutral. But again, as we've discussed, if you have a patient and you're waiting on your cytogenetics and you want to treat them, you really want to give them the best shot of a benefit.

The adverse cytogenetics, EF-232, please, I just want to remind everyone that you're not disadvantaging, putting them at any disadvantage, to treat before you can get those results back for them.

DR. ROTH: Can I ask one final question? Looking at the PK/PD data, do we need doses on days 4 and 7? There's at least some data that you quote looking at single doses of 3 versus 6. So I just wonder as you're launching into discussions about dosing and schedule whether that had come up.

DR. WEBB: Certainly, this is an area we've looked at very carefully.

Dr. Knight, if you could come up and address the question.

DR. KNIGHT: Beverly Knight, clinical pharmacology, Pfizer. So we did do exposure-response modeling to look at the relationship

between exposure and the response, and what we found is that one dose of Mylotarg alone is not very effective.

The FDA presentation detailed the fact that there is dose non-proportional exposure. What that means is when you go from a dose of 9 down to a dose of 3, the exposure is going to decrease more than you think, and that's due to target-mediated clearance, and this also causes the first dose of Mylotarg to be cleared much faster than later doses.

When you give a single dose of 3, you're really only getting about 3 percent of the exposure that you saw with your original 9 mgs per meter squared regimen.

If you could show slide PK-7, please. So here you can see the relationship between the Mylotarg AUC and the probability of CR, and you can see in the top two plots, this is mostly with monotherapy dosing, so it gives you an idea of the efficacy of Mylotarg alone.

If you give only one dose of Mylotarg, the

efficacy that you can achieve at maximum is quite low. However, in the second dose when you're getting those re-expressed targets, you're really able to get to a higher level of efficacy. So you really are trying to strike a balance between having a low Cmax to reduce the safety effects and having enough exposure for efficacy, and we think the fractionated dose regimen really strikes that balance.

DR. ROTH: Thank you. Any other --

DR. WEBB: Maybe just to add something.

DR. ROTH: Go ahead. Sorry.

DR. WEBB: I appreciate that. If you look at the dosing then, we're looking at the original SWOG study, which we know there were major toxicity problems with a single dose of 6, even though the prospective plan was to reduce the dose of daunorubicin in the Mylotarg arm to try and increase safety, it still didn't work out very well. But with the ALFA study, you're able to give those three doses of 3 mgs per meter squared with standard full dose intensive chemotherapy,

including full dose daunorubicin with what we assess is an acceptable safety and efficacy profile.

DR. ROTH: Thank you. Any other clarifying questions?

(No response.)

DR. ROTH: I think we'll take a break. It's currently 2:45. Let's resume the open public hearing portion of the meeting at 3:00.

(Whereupon, at 2:47 p.m., a recess was taken.)

Open Public Hearing

DR. ROTH: If we could come back to our seats and get started with the open public hearing.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it's 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 any industry group, its products, and if known, its direct competitors.

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

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

The FDA and this committee places great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One

of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully, treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. SANTIAGO: Good afternoon. My name is Kristen Santiago, and I am with the Cancer Support Community. The Cancer Support Community does receive funding from Pfizer, however, we did not receive any funding nor compensation to be here today. Throughout my remarks, I will refer to the Cancer Support Community as CSC.

CSC serves patients through a network of 150 affiliate sites and satellite locations as well as a cancer support help line where patients and their families receive evidence-based programming, social, and emotional support. We provide free

programs, which include professionally-led support groups, educational seminars, nutritional workshops, exercise, and mind-body programs.

Our mission is to help people living with cancer regain the sense of control over their lives, feel less isolated, and restore their sense of hope for the future regardless of their stage of disease.

In 2016, nearly 100,000 individuals, including patients and caregivers affected by AML, visited our affiliates. Of those 100,000 individuals, they made more than 900,000 visits. CSC is also home to the only research and training institute whose work is focused on understanding and elevating the patient and caregiver voice about the cancer experience.

My comments today reflect what we have learned from our cancer experience registry through the research and training institute as well as what we see in our locations around the country each day.

CSC serves people with all types of cancer,

and we are seeing that there is a high unmet need for individuals living with AML. AML is a difficult disease for patients to address with very few effective treatments and ones that come with many side effects. Patients are frequently given few treatment options with little hope of achieving any meaningful benefit nor long-term survival.

The physical discomfort and pain combined with the psychological stress of living with a disease with limited treatment options is debilitating. Given the growing patient population, severity of disease, and limited treatment options, which have all been discussed today, additional novel treatment options are needed.

The ultimate treatment decision should be made between the patient and the healthcare team following a thorough review, which includes the examination of risk-benefit profile as it relates to the patient's particular needs.

CSC encourages the sponsor to continue to monitor patients taking Mylotarg in a postmarketing

study to continue to build a body of data on the patient experience. Because we know that the patient experience is broader than just the physical assessments of disease symptoms, treatment side effects, and physical functioning, CSC encourages the sponsor to collect additional patient experience data to better understand what is truly meaningful to patients.

This patient experience data should include such information and patient concerns as they relate to disruption of work and family life due to treatment regimen, concerns related to nutrition, financial impact, et cetera, to provide meaningful feedback from patients in real-time about issues that may not be identified through the current measures.

At CSC, we have learned a great deal from those we support, and we believe in the importance and value of an educated and empowered patient. Since people with cancer also feel stigmatized, alone, and overwhelmed with grief, they feel stronger and more hopeful when they have more

control of the best decisions for them. Access to a full portfolio of treatment options as well as supportive care solutions helps to arm them for making the best decisions for their personal situation.

Today we ask that you carefully consider the challenges of those facing AML and the need for a wider array of treatment options. We urge you to look at a broad range of treatment options that will encourage patients to be informed, empowered, and optimistic about their treatment. Thank you.

DR. ROTH: Thank you. Will speaker number 2 please step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. MITCHELL: Good afternoon. My name is Jack Mitchell, and I am director of health policy for the National Center for Health Research. I thank you for the opportunity today to speak before such a distinguished audience.

The National Center for Health Research is a research center which analyzes policy and

scientific data to provide objective health information to patients, providers, and policymakers. We do not accept funding from pharmaceutical or medical device companies, so I have no conflicts of interest to report to the panel.

I'm not a scientist or clinician, but previously, I worked in a senior position at the FDA Office of the Commissioner, and we have a number of science and public health PhDs on our staff. I'm presenting our staff's and organization's view on behalf of the many patients and consumers for whom we advocate and represent.

While we strongly support the need for better treatments for AML and its many patients, we're concerned about the data used to support the application for GO. First of all, the only pivotal trial was open label, which increases the risk for bias.

The purpose of blinding in a clinical trial is to control for the placebo effect since the knowledge that one is taking the newest

experimental drug tends to encourage patients and clinicians to have a greater belief in a perceived effectiveness.

Second, all lower-grade safety events and some important severe safety events were collected retrospectively, which increases the risks for inaccuracies, and which, as I believe FDA has already noted, has somewhat limited the analysis of the safety profile.

Third, the trial took place with only French patients. This is of note because there are numerous examples of medical products that do not work as well on American patients as they do in patients in other countries.

These issues would raise concerns even if the data supporting approval was strong, which we believe is not the case. Instead, it is not clear to our reviewers that the data support the safety or efficacy of GO.

The application is based on a single pivotal trial along with a review of the literature. The pivotal trial does not provide evidence for overall

survival, and the previous clinical trial included in the literature review found an inconsistent effect of GO on overall survival.

It is important to remember that this drug was approved and later removed from the market in part because postmarketing studies did not demonstrate effectiveness.

The pivotal trial and literature review do demonstrate improvement in event-free survival. The trial also shows an improvement in relapse-free survival. However, the important metric is overall survival, which we believe is not clearly demonstrated.

FDA reviewers showed that event-free survival does not correlate well with overall survival. This especially is a problem in an open-label study where a placebo effect cannot be controlled.

Our research center recently published an article in the AMA journal, revealing that many cancer drugs have been approved based on surrogate endpoints, but later studies have found that these

drugs did not improve overall survival or quality of life. We found that patients and their insurers were spending $100,000 or more and suffering serious adverse events for treatments that often had no measurable benefits for their health or continuing survival.

This change in dosing does appear to reduce adverse events compared to the earlier version of the medication. Nevertheless, there were still serious adverse events, as we've heard today, that can result in death. The drug was associated with increased bleeding events, including fatal hemorrhages and liver disorders, including fatal cases of VOD.

There were no hemorrhage or VOD events that occurred without exposure to the drug. However, we acknowledge the sponsor's continuing efforts to address the VOD risk profile, although as I note, it's a little bit disconcerting that a box warning may be necessary.

It's noteworthy that these results were in a clinical trial where patients are carefully

monitored. Patients in the real world are typically monitored less carefully than patients in clinical trials. As a result, it is possible that more patients can continue on a drug causing serious adverse events because they hope the drug will improve their condition.

Well-intentioned doctors who are unaware of the history of this drug may also decide to increase the dose on patients who are not improving, putting patients at greater risk for adverse events without improving their chance for survival.

In summary, surrogate endpoints such as event-free survival often do not predict overall survival or other measures of improved health and quality of life. Given the research design, one pivotal study, the lack of U.S. patients, and a literature review, we believe that the data to date does not sufficiently support approval.

We believe that the evidence does not indicate that the benefits outweigh the risks, which is what the most important consideration that

you're taking under consideration today. I thank you for providing this opportunity for us to express our views, and good luck with your deliberations.

Questions to the Committee and Discussion

DR. ROTH: Thank you.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We'll now proceed with the question to the committee and subsequent discussion. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

If we could see the question, please. Do the results of ALFA-0701 demonstrate a favorable risk-benefit ratio for gemtuzumab ozogamicin 3 milligrams per meter squared days 1, 4, and 7,

added to daunorubicin and AraC, for patients with newly diagnosed CD33-positive AML? Then we'll ask for people after the vote to please explain their reasons for the vote.

We'll now open up to see if there's any clarification necessary to question the question. Dr. Sung?

DR. SUNG: One question I had is, is this an indication for all patients, or could we vote approval for some indications and not other --

DR. PAZDUR: Let me address that. Many of the issues that you were bringing up as far as subgroups of patients, those are issues that we will handle in labeling negotiations with the sponsor. So we generally do not change the questions because we could get into this morass of everybody wanting their own question to vote on.

These areas that you have brought up, we will discuss with the sponsor. I do want to emphasize these are subset analyses that were not prespecified and, hence, any decisions, dogmatic decisions based on these unspecified subgroups have

to be viewed as exploratory in nature.

But we do not change the question, number one, and number two, many of these issues of age, whatever, are usually handled in labeling negotiations with the sponsor.

DR. ROTH: Thank you, Dr. Pazdur. Any other -- Dr. Harrington?

DR. HARRINGTON: Rick, notwithstanding the warning that we don't change the question, the word "favorable" strikes me as somewhat odd there. Manageable, perhaps. Favorable to what?

What did the agency have in mind when they chose that word?

DR. PAZDUR: Favorable to the control arm generally, that's what we mean. This is a standard question that if you come to many of the ODACs is our standard question that we ask on almost every application that we bring forward.

DR. ROTH: Any other questions?

(No response.)

DR. ROTH: If there's no further discussion of this question, we will now begin the voting

process. Please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Please press the button firmly. After you've made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

LCDR SHEPHERD: For the record, the vote is 6 yes, 1 no, zero abstain, zero no voting.

DR. ROTH: Everyone has voted. The vote is now complete. Now that the vote is complete, we'll go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. We'll start from this side. Dr. Taylor?

DR. TAYLOR: Yes. Wayne Taylor, patient representative. I voted yes because I do believe that the evidence supports that event-free survival in this disease, AML, which is very heterogeneous, has not -- in this disease, AML, event-free

survival along with relapse-free survival is -- they have proven that the benefit outweighs the risk. That's what I think.

DR. ROTH: Dr. Sung?

DR. SUNG: I believe that in the patient population with favorable and intermediate-risk cytogenetics, this drug is favorable, and if the question was limited to that patient population, I would have voted yes in answer to that question.

However, I believe that in the patient population with poor-risk cytogenetics or who otherwise is heading to transplant, I believe, as per this discussion, there is an increased risk of treatment-related toxicities such as VOD, hemorrhage without significant benefit to compensate for those toxicities.

I do believe, again, in the favorable and intermediate-risk groups that although those toxicities exist, they are outweighed by the benefits.

DR. ROTH: Dr. Chen?

DR. CHEN: I actually share many of the same

concerns as Dr. Sung, but I voted yes. I do believe that event-free survival is a reasonable endpoint in AML.

The second issue is in terms of safety. I agree with Dr. Cortes, as stated that there is a -- to me, my read of it was that there was an increase, slight, in treatment-related mortality in the GO arm, but it did seem to be relatively manageable at under 5 percent.

In terms of the risk-benefit in efficacy, I concur with Dr. Sung, but acknowledge that the cytogenetic issue was not directly addressed a priori, although it was specified in the AML 15 study. But I think we'll have to -- I think the benefit, and particularly the favorable-risk cytogenetics and intermediate-risk, is quite substantial, and there did not seem to be a significant increased risk of treatment-related mortality in the poor-risk patients that may not benefit from the disease [sic].

I would vote yes and err on the side of the treating physician to make that determination on

whether or not the individual patient under their care would benefit.

DR. ROTH: Dr. Harrington?

DR. HARRINGTON: I voted yes because I'm convinced that event-free survival is a meaningful clinical endpoint even if it's not predicting or highly correlated with survival. I was struck by the fact that while it's a regimen that certainly has some risk, the risk seems to be now in the ballpark of other treatments for AML. So it doesn't seem to be substantially more dangerous than others that are being used.

DR. ROTH: Dr. Cole?

DR. COLE: Bernard Cole. I voted yes. The benefit of GO in terms of event-free survival is robust, highly significant, and was demonstrated in a high quality randomized study. Certainly, the elevated risk of adverse events, including VOD and early mortality, with GO is a concern, and we lack clear overall survival benefit in the pivotal trial. However, there are advantages to delaying relapse in patients who achieve remission.

As a result, the decision from a practical perspective to use GO might be based on considerations of patients' quality of life; namely, whether delayed relapse confers a quality of life benefit in light of the increased toxicity with GO. And I would urge the sponsor to address this issue with additional study and analyses.

DR. ROTH: This is Bruce Roth. I voted yes. First, I think the applicant has sufficiently decreased the toxicities that got the drug pulled in the first place with this fractionated schedule. It's certainly much more tolerable, not non-toxic, but more tolerable than certainly it was before. And I've been convinced by my leukemia colleagues that EFS has some importance unto itself without a relationship to overall survival.

I think one has to only look at that one graph, where people that did not achieve CR lived either a few months or more than five years, to know that that relationship is never going to be a good correlation. Nevertheless, I thought that individuals who delayed their time to the next

event benefitted from this drug.

Dr. Nowakowski?

DR. NOWAKOWSKI: Greg Nowakowski. I voted yes for the reasons which were already mentioned. I believe the fractionated dosing of GO has improved the safety profile as demonstrated in the presentations. More importantly, I believe that EFS is a valid clinical endpoint in acute leukemia, and failure of achieving CR is detrimental to the patients. Therefore, EFS captures it appropriately, and we have seen the benefit in EFS in the study in this regard.

DR. ROTH: Before we adjourn, are there any last comments from the agency or Dr. Przepiorka or Dr. Pazdur?

DR. PAZDUR: No.

Adjournment

DR. ROTH: Panel members, please take all of your belongings with you as the room is cleaned at the end of the meeting day. All materials left on the table will be disposed of. Please also remember to drop off your name badge at the

registration table on your way out so that they may be recycled.

We'll now adjourn the meeting. Thank you for your support.

(Whereupon, at 3:27 p.m., the meeting was adjourned.)