FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Tuesday, May 14, 2019

Afternoon Session

12:59 p.m. to 4:41 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

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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

(12:59 p.m.)

Call to Order

Introduction of Committee

DR. RINI: Good afternoon, everyone. Welcome back. I'd first like to remind everyone to please silence your cell phones or any other devices if you've not already done so. The FDA press contact is Amanda Turney, who I know is not in the room, but she's available if needed.

My name is Brian Rini. I'm the chairperson for this meeting. I'll now call the afternoon session of today's meeting of the Oncologic Drugs Advisory Committee to order, and we'll start by going around the table and introduce ourselves. We'll start with FDA to my left and go around the table.

DR. PAZDUR: Richard Pazdur, FDA.

DR. FARRELL: Ann Farrell, FDA.

DR. DEISSEROTH: Al Deisseroth, FDA.

DR. PRZEPIORKA: Donna Przepiorka, FDA.

DR. KRAUSS: Aviva Krauss, FDA

DR. BY: Kunthel By, FDA.

DR. HUNSBERGER: Sally Hunsberger, NIH.

DR. HALABI: Susan Halabi, Duke University.

DR. ULDRICK: Thomas Uldrick, Fred Hutchinson Cancer Research Center.

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LCDR SHEPHERD: Jennifer Shepherd, designated federal officer, FDA.

DR. RINI: Brian Rini, Cleveland Clinic.

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DR. HOFFMAN: Philip Hoffman, University of Chicago.

MS. PREUSSE: Courtney Preusse, consumer rep.

DR. TAYLOR: Wayne Taylor, patient representative.

DR. SUNG: Anthony Sung, Duke.

DR. LINCOFF: Michael Lincoff, Cleveland Clinic.

DR. MORROW: P.K. Morrow, Amgen.

DR. RINI: Thank you.

For topics such as those being 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 that 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 myself. 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 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 many members of the media are anxious to speak with FDA about these proceedings. However, FDA will refrain from discussing details of this meeting with the media until its conclusion. Also, the committee is reminded to refrain from discussing the meeting topic during any breaks. Thank you.

I'll pass it to Lieutenant Commander Jennifer Shepherd, 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 meeting 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 discussion 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 USC 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.

During the afternoon session, the committee will discuss new drug application 212166, for quizartinib tablets, submitted by Daiichi Sankyo, Incorporated. The proposed indication or use for this product is for the treatment of adults with relapsed or refractory acute myeloid leukemia, which is FLT3-ITD positive as detected by an FDA-approved test.

This is a particular matters meeting during which specific matters related to Daiichi Sankyo's NDA 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. RINI: Thank you. We will now proceed with FDA's introductory comments from Dr. Donna Przepiorka.

FDA Introductory Comments - Donna Przepiorka

DR. PRZEPIORKA: Thank you, Dr. Rini, and

good afternoon. The topic for discussion today is quizartinib, a small molecule drug that inhibits multiple tyrosine kinases, including FMS-like tyrosine kinase 3, also known as FLT3. The proposed indication for quizartinib is as treatment of adults with relapsed or refractory acute myeloid leukemia, or AML, positive for a FLT3 internal tandem duplication as detected by an FDA-approved test. Please note that the companion diagnostic itself is not at issue and will not be discussed this afternoon.

The applicant will describe the prognosis and treatment of patients with FLT3 mutation positive AML in detail. This slide summarizes FDA's review of the current treatment landscape for this disease. There are 10 cytotoxic drugs approved for treatment of AML, and when used alone or in combination, these drugs provide for a complete remission in no more than 24 percent of patients with FLT3 positive AML in first relapse. Low-dose cytarabine and hypomethylating agents are used off label, albeit with very low complete

remission rates.

Lastly, although there are 8 kinase inhibitors with activity against FLT3 on the market, only gilteritinib has an approved indication for treatment of relapsed or refractory FLT3 positive AML. FDA's review of gilteritinib showed that 12 percent of patients achieved CR; 21 percent achieved CR with full or partial hematologic recovery; and the median survival was 9 months. Clearly, new safe and effective treatments are needed for patients with relapsed or refractory FLT3 mutation-positive AML.

The applicant will describe study AC220-007 or study 007, a randomized-controlled trial comparing quizartinib to standard-of-care chemotherapy for patients with relapsed or refractory AML with a FLT3 ITD. Please note that at the time of enrollment in this study, patients were prespecified to receive intensive chemotherapy or low-dose cytarabine on the control arm, and this prespecification was used as a stratification factor at randomization.

The FDA analysis shown here demonstrated a statistically significant improvement in overall survival in study 007 with a median OS of 6.2 months for the patients treated with quizartinib versus 4.7 months on the control arm, a difference of 6 weeks. However, FDA also noted that the treatment effect in this study was borderline with an upper 95 percent confidence interval of the hazard ratio being 0.99.

There are concerns raised about the credibility of the results of the analysis due to imbalances between arms and the proportion of patients randomized but not treated and in the proportion of patients for who were censored early. Additionally, it was noted that the treatment effect was driven strongly by the results in the low-dose cytarabine arm specifically, and in this arm, there was an imbalance of the use of allogeneic hematopoietic stem cell transplantation with far more patients on the quizartinib arm being transplanted not in complete remission, 23 percent versus none on the control arm.

Although FDA frequently accepts a single trial to support an approval for a new treatment of cancer, these concerns raise questions about the robustness of the efficacy results, as will be described by the FDA statistician, Dr. By. This concern will lead to our first request to ODAC to discuss whether the results of the OS analysis of study 007 are persuasive evidence of effectiveness of quizartinib.

Secondly, the FDA clinical reviewer, Dr. Krauss, will review briefly the physiology of cardiac repolarization and how blockade of the two outward potassium currents IKr and IKs increase the risk of fatal ventricular arrhythmias. This is important for the discussion of this application in particular for two reasons.

First, quizartinib is a potent inhibitor of IKs, and in clinical trials, this inhibitory activity was associated with a higher incidence of observed prolonged QT in comparison to chemotherapy. At the recommended dose of quizartinib, QTc was prolonged to levels far

greater than accepted for prior approved drugs, and fatal cardiac events were identified in patients treated with quizartinib.

Second, currently approved drugs that prolong QT, including many antibiotics used for treatment of patients with leukemia, are generally inhibitors of the complementary channel IKr, and it is not clear that concomitant use of an IKr blocker with quizartinib, the IKs blocker, would generally be safe since theoretically blockade of both outward potassium currents simultaneously might impair cardiac repolarization to the point of extreme risk of ventricular arrhythmias.

Hence, their second request to ODAC will be discuss the need for and adequacy of measures proposed to reduce the risk of life-threatening and fatal cardiac events resulting from IKs blockade if quizartinib is marketed.

In addition to the cardiac toxicity profile, the applicant will review the other adverse reactions of quizartinib, including nausea, vomiting, diarrhea, elevated liver enzymes, and

cytopenias. Dr. Krauss will review FDA's additional findings of life-threatening and potentially fatal differentiation syndrome and acute febrile neutrophilic dermatosis. This adverse reaction profile will need to be weighed against the efficacy outcome of a 6-week improvement in overall survival; a two-week statistically non-significant difference in event-free survival; a CR rate of 4 percent; and a CR/CRh rate of 11 percent.

We also noted that a 56-day period of transfusion independence was observed in 26 percent of the patients treated with quizartinib, which leads to the final question to ODAC about whether the results of study 007 demonstrate that treatment with quizartinib provides for a benefit that offsets the safety risks for patients with relapsed or refractory FLT3 ITD-positive AML. This concludes FDA's introductory comments. Thank you.

Dr. Rini?

DR. RINI: Thank you.

Both FDA and the public believe in a

transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee have any financial relationships that they may have with firm at issue such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interest in those based upon the outcome of this meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking, and we'll now proceed with the applicant's presentation.

Applicant Presentation - Eric Richards

MR. RICHARDS: Good afternoon, Chairman,

FDA, and members of the ODAC committee. My name is Eric Richards. I am the head of global regulatory affairs oncology at Daiichi Sankyo. On behalf of Daiichi Sankyo, I am pleased to return to discuss the quizartinib application.

The proposed indication for quizartinib is for the treatment of adults with relapsed or refractory acute myeloid leukemia, which is FLT3 ITD positive as detected by an FDA-approved test. The companion diagnostic test is also under review. The proposed dosage is 30 milligrams once daily for the first 2 weeks and then 60 milligrams once daily thereafter. This dosing regimen was designed to mitigate the risk of QTc prolongation, which will be discussed later in the presentation.

Today, we will discuss the continued need for effective treatment options in FLT3 ITD AML, with FLT3 ITD being one of the most important negative prognostic factors in AML. Clinical efficacy has been demonstrated across the development program and is consistent with unique pharmacology of quizartinib.

We will discuss the results of the QuANTUM-R trial, which showed an early and clinically relevant survival benefit versus salvage chemotherapy. Quizartinib has a well-characterized acceptable safety profile for the intended population. The key safety signal of QTc prolongation has been appropriately characterized and is manageable. We will share with you evidence to support that quizartinib, as a novel oral monotherapy, provides an improvement to an existing standard of care.

So why are we here today? We know that the FDA has asked you to consider two important questions. Are the efficacy data credible? Is the QTc risk manageable? Over the next 45 minutes, we will show you data and analyses, which demonstrate that the answer to both of these questions is yes.

In terms of efficacy, we will describe the updated OS analysis that reduces the amount of missing data substantially and the associated sensitivity analyses which show nearly identical outcomes to the primary OS results.

In addition, we will describe the corrected EFS analysis that shows a consistent magnitude of effect as overall survival, and we will describe how the higher transplant rate in patients taking quizartinib is a direct result of the treatment effect.

The totality of the evidence demonstrates that the efficacy data are credible. In terms of safety, we will also share with you how the risk of QTc prolongation has been thoroughly studied in the pivotal phase 3 trial, and what we've learned is that the risk can be managed with proper dosing and monitoring. Overall, we will describe today how quizartinib provides a novel effective treatment option with a favorable benefit-risk profile.

Next, Dr. Mark Levis will provide an overview of AML, the unmet medical need, and the evolving treatment landscape in FLT3 ITD-positive AML. Then Dr. Jorge Cortes, the principal investigator for QuANTUM-R study, will present data on the efficacy of quizartinib. My colleague, Dr. Youngsook Choi, will describe the safety of

quizartinib, and finally, Dr. Cortes will return to provide his perspective on the benefit-risk of quizartinib in relapsed/refractory FLT3 ITD AML patients. Along with other presenters, Dr. Koch and Dr. Kowey are available to help address your questions.

Now, I would like to invite Dr. Mark Levis to the podium.

Dr. Levis?

Applicant Presentation - Mark Levis

DR. LEVIS: Thank you, Mr. Richards.

My name is Mark Levis. I direct the leukemia program at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. I do have a laboratory, but I spend more of my time actually taking care of leukemia patients, including bone marrow transplant. I'm a paid consultant to the sponsor, but I have no financial interest in the outcome of this meeting.

I spent my career, my academic career, studying the biology and treatment of FLT3 mutated AML, and despite recent advances, patients with

this disease, and in particular, those with a FLT3 ITD mutation, who are relapsed or refractory, have high unmet therapeutic needs. It's estimated that there are about 20,000 new cases of AML diagnosed annually, and about 10,000 Americans die due to AML every year.

AML can affect people of all ages, but it's primarily a disease of older adults. The median age of diagnosis is 68. And although our ability to treat AML has improved in recent years, outcomes remain poor. A FLT3 ITD mutation is a very well-established negative prognostic factor in AML, both at diagnosis and at relapse.

In relapsed AML, the duration of first remission is highly predictive of outcomes. Shown here is a recent compilation of data from ECOG studies demonstrating that AML patients who relapse with a duration of first CR less than a year have a median survival of less than 5 months compared to 11 months in patients who have a CR of greater than a year.

These data on the right are from patients

on the Cephalon 204 study in which relapsed FLT3 ITD AML patients were treated with intensive salvage chemotherapy. These patients, who had a duration of first remission less than 6 months, similar to the patients enrolled in QuANTUM-R, had a median overall survival of 3.5 months. Also, the CR/CRp rate was only 12.5 percent, which demonstrates the difficulty in achieving a second remission for these patients.

FLT3 is a transmembrane protein with a juxtamembrane domain that's responsible for stabilizing the receptor in the inactive conformation. A FLT3 ITD mutation occurs when the coding sequence within this juxtamembrane domain is duplicated and inserted in tandem, so we have the internal tandem duplication or ITD. This mutation leads to constitutive autophosphorylation and activation of the receptor. A signaling from this receptor, this activated receptor, blocks differentiation and apoptosis allowing proliferation of immature cells.

The ITD mutation is found in approximately

25 percent of newly diagnosed AML and controls a dismal prognosis. And just like with many solid tumors, FLT3 ITD leukemia evolves from diagnosis to relapse. The leukemia cells in patients who have relapsed/refractory disease are often much more dependent upon FLT3 signaling.

The need remains for agents that improve survival for relapse refractory AML. FLT3 inhibitors clearly have an important role to play for these patients. Midostaurin is approved for newly-diagnosed FLT3 mutant AML when given in combination with chemotherapy, and gilteritinib recently received regulatory approval for relapsed/ refractory FLT3-mutated AML patients.

Other options recommended within this NCCN guidelines shown here includes salvage chemotherapy or hypomethylating agents combined with sorafenib. However, given that most of these patients eventually succumb to the disease, clinical trial participation is appropriately recommended as a first choice.

I have studied, both in the lab and in the

clinic, most FLT3 inhibitors that have been developed, including lestaurtinib, midostaurin, sorafenib, and gilteritinib. Quizartinib is the most highly potent and selective FLT3 inhibitor I have ever worked with. It was rationally designed to potently and selectively target FLT3. It's a type 2 tyrosine kinase inhibitor, which means it binds to the inactive conformation of the receptor.

Quizartinib demonstrates a high degree of in vivo potency against the target FLT3 ITD as shown in this western blot, in which the activated phosphorylated receptor is completely and continuously inhibited from day 1 of treatment. The pharmacodynamic effect translates into a series of antitumor effects.

There's rapid clearance of circulating blasts through induction of apoptosis. Within the bone marrow, blasts undergo cell cycle arrest followed by terminal differentiation over a few weeks, as shown in these photomicrographs, of the bone marrow of a patient on quizartinib.

The result is complete clearance of

leukemic blasts, in most cases within 4 weeks of starting therapy. However, there is partial selective inhibition of c-Kit, and at this dose, that's probably influencing count recovery such that the responses consist predominantly of complete remission with incomplete count recovery, commonly referred to as CRi.

As a consequence, we use a modified version of the IWG criteria when developing trials with FLT3 inhibitors such that a patient who's achieved morphologic clearance of leukemic blasts, but who has incomplete count recovery, is classified as responding to treatment, thereby informing the decision to continue treatment. The modified definition for CLI allows for incomplete neutrophil recovery, with or without platelet recovery, and does not require transfusion independence.

As a leukemia doctor treating these patients, I viewed this in a way as similar to tumor shrinkage like the RECIST criteria. Relapsed or refractory FLT3 ITD AML is usually a fatal disease. Inhibition of the FLT3 ITD mutant protein

is an effective treatment strategy across multiple clinical scenarios.

Gilteritinib, another FLT3 inhibitor, has recently received FDA approval for patients with relapsed/refractory FLT3-mutated AML, and having studied both drugs in the lab and in the clinic, I can say confidently that quizartinib compares quite favorably with gilteritinib.

The two drugs are very different in how they inhibit the receptor, and I think they will complement each other clinically. I think this is analogous to CML, which we have multiple different BCR-ABL inhibitors, and we are very glad that we have different options to offer our patients.

Because it's a type 2 kinase inhibitor, quizartinib is highly potent and specific, delivering a more profound suppression of FLT3 ITD signaling than any other inhibitor I've seen, and possibly a more rapid time to response. It causes partial suppression of c-Kit, which is reflected in delayed normal marrow recovery at the proposed clinical doses, and therefore CRi, complete

response with incomplete count recovery, is the most accurate measure of its pharmacologic activity.

Thank you. Now I'd like to invite Dr. Jorge Cortes to the podium to discuss the efficacy results seen in the clinical development program for quizartinib.

Dr. Cortes?

Applicant Presentation - Jorge Cortes

DR. CORTES: Thank you, Dr. Levis.

My name is Jorge Cortes. I am the deputy chair and professor of medicine in the department of leukemia at MD Anderson Cancer Center. I was the primary investigator of the pivotal study and have been involved in the quizartinib program since its inception. I am a paid consultant to the sponsor, but I have no financial interest in the outcome of this meeting.

Quizartinib has gone through a comprehensive development program, demonstrating consistent efficacy and safety across patient populations, including older patients, patients

with significant comorbidities, and those with more severe diseases.

The first phase 2 study was designed to assess efficacy and safety in two cohorts of patients with poor prognosis, older patients in first salvage and adults of all ages in second salvage or relapse after stem cell transplant. Doses ranged from 90 to 200 milligrams daily. The phase 2b study enrolled read patients with relapsed/refractory FLT3 ITD, randomized to a starting those for 30 milligrams or 60 milligrams daily.

Today, I will briefly summarize the results of the phase 2 studies and then focus on the pivotal phase 3 study. In phase 2, we observed substantial clinical activity in both cohorts with composite complete remission rates referred to as CRc or 56 percent and 46 percent.

We observed a higher rate of QTc prolongation that we anticipated, so we initiated a second phase 2 study to elevate where the lower doses would reduce the incidence of QTc

prolongation while maintaining efficacy. CRc rates were 47 percent in both arms, similar to the earlier study with higher quizartinib doses. However, approximately 3 times as many patients in the 30-milligram arm had to dose escalate for lack or loss of efficacy.

Additionally, a longer duration of response at a higher rate of PR were observed in patients treated on the 60-milligram arm. These data supported the quizartinib dosing regimen using the phase 3 QuANTUM-R study, which I will now discuss.

This study involved only FLT3 ITD-positive adults with refractory or relapsed AML. I want to highlight two inclusion criteria that make these trials unique in the selection of patients with the worst prognosis. First, patients in relapse should have relapsed within 6 months of achieving their first remission or within 6 months of transplant. Second, patients had to have received at least one cycle of a standard anthracycline- or mixtoxantrone-containing induction regimen. Patients who had received only low intensity

chemotherapy were not eligible.

Patients were randomized 2 to 1 to quizartinib or investigator's choice selected at the time of randomization, to include low-intensity chemotherapy with low-dose cytarabine or high-intensity treatment with either MEC or FLAG-IDA. Patients were stratified according to response to prior therapy and to the salvage chemotherapy intensity.

Quizartinib and low-dose RRC [ph] patients continued treatment until no longer clinically indicated. Patients on high-intensity salvage chemotherapy received 1 or 2 cycles per standard practice. In either arm, patients could receive stem cell transplant based on institutional policies, and quizartinib patients could resume treatment after transplant at the investigator's discretion.

The primary endpoint of QuANTUM-R was overall survival, and we will also discuss the secondary and key exploratory endpoints, event free survival, CRc rates, duration of CRc, and

transplant rate.

Dosing was initiated at 30 milligrams per day and up to 2 weeks. If the QTc was below 450 milliseconds, the dose was escalated to 60 milligrams daily. Dose adjustments were indicated for those events, including QTc prolongation. Because quizartinib is primarily metabolized by CYP3A, doses were reduced from 30 to 20 or 60 to 30 milligrams when administered with strong CYP3A inhibitors to provide consistent drug levels.

563 patients were screened and 367 patients were randomized in a 2 to 1 ratio. Of the 245 patients randomized to quizartinib, 4 did not receive treatment, and they were followed for overall survival. For the 122 patients randomized to salvage chemotherapy, 28 did not receive treatment.

That proportion of randomized not treated patients in the control arm, in my opinion, is not unexpected. It is reasonable to assume that they were treated off protocol with standard chemotherapy or investigational agents, including

FLT3 inhibitors that had rapid disease progression.

Additionally, there was one patient in the quizartinib arm and 17 patients in the chemotherapy arm who were censored within 8 weeks of randomization. I will discuss how we have addressed these two imbalances later in my presentation.

The baseline patient characteristics are typical for the population, and the treatment arms were well balanced. The median age was 55 to 58, which is consistent with the typical FLT3 ITD AML population, with more than a quarter of the patients 65 years or older in both groups.

The treatment groups were also well balanced by disease characteristics. Approximately a third of patients were refractory prior to therapy and 22 percent of patients were relapsed after prior transplants. The median duration of previous Cr was short at approximately 3.5 months, indicating a very poor prognosis.

As you can see, the study met its primary endpoint with a statistically significant overall

survival benefit of quizartinib in blue compared to salvage chemotherapy in orange. Separation occurs early and is maintained over the first 12 months of follow-up. The hazard ratio was 0.76 with a stratified one-sided p-value of 0.0177. This translates into a 24 percent reduction in the risk of death during the study period.

As now shown here, we conducted 3 prespecified sensitivity analyses: a per protocol analysis, one censoring for transplant, and one censoring for subsequent FLT3 inhibitors. All three supported the conclusion from the primary analysis.

When we looked at the overall survival in the prespecified subgroups, all the point estimates, with the exception of patients with unknown cytogenetics, ride [indiscernible} to the left of unity, favoring quizartinib. However, this study was not powered to detect differences between the subgroups.

We conducted interaction tests for all subgroups, and none of them were significant. The

FDA raised question whether the low-intensity strata could be driving the overall survival results. We believe that's wrong [indiscernible], and I agree. The low-intensity strata represents less than a quarter of the total study population, and there is a similar training in favor of quizartinib for the patients in the high-intensity strata.

As I mentioned earlier, there were two imbalances noted in the study impacting mostly the assessments of the chemotherapy arm; patients who were randomized but did not receive study treatment and patients who were censored early. We took two steps to address this. First, we conducted a targeted overall survival update to reduce the amount of missing data, and second, we perform sensitivity analyses under neutral assumptions to determine the potential impact of the remaining missing data.

Please note that the following sensitivity analysis utilized the same methodology as we described in our briefing document. However, we

are using the updated overall survival data because it is the most current and better aligns with the FDA briefing document.

At the FDA request, we conducted a targeted survival. Seventeen patients in the chemotherapy arm and one in the quizartinib arm were censored within 8 weeks of randomization. This update reduced the number of patients censored within 8 weeks to 9 in the chemotherapy arm, 7 of whom were randomized, not treated. The remaining 10 patients withdrew consent, and privacy laws and regulations prevented us from obtaining this information.

The updated overall survival analysis substantially reduces potential uncertainty in the results and is consistent with the primary analysis.

Regarding the randomized and not treated patients, we have conducted two complementary sensitivity analyses. The first one assumes that the randomized not treated patients are similar to the randomized treated patients, and the other

assumes they are different. We will focus on the 28 randomized not treated patients in the chemotherapy arm.

On the first analysis, we imputed survival data for the 28 randomized not treated patients in the chemotherapy arm from the 95 treated patients in the same arm. The 28 randomized not treated patients had similar based on demographics and disease characteristics to the treated patients. We assume that their outcomes would resemble that of the treated patients. This analysis showed results consistent with the original ITT analysis.

For the second analysis, we assumed the randomized not treated patients could have had a different survival outcome from the randomized treated patients. Therefore, we sampled the survival for the 7 randomized not treated patients censored early from the remaining 21 randomized not treated patients with longer follow-up. Again, the results were consistent with the primary results.

So whether we assume the randomized the not treated patients are similar or somehow different

than the treated patients, the results remain consistent with the primary analysis.

Finally, let's discuss the 10 patients whose survival status could not be updated. We performed sensitivity analysis to assess the potential impact on the overall results. We imputed survival data for these 10 patients from the remaining patients in their corresponding arm with the assumption that their survival times and statuses would resemble the remaining patients in their corresponding arm, which sampling produced similar results to the original ITT analysis.

Taken together, all the sensitivity analyses demonstrate that the overall survival result is credible and consistent.

We have carefully examined analyses conducted by the FDA, and our interpretation of these analyses. For the patients censored within 8 weeks, She's as follows for the patient's sensor within 8 weeks, 7 of the 9 which are randomized not treating, the agency assumed that they could not have died before 8 weeks. Therefore, they

resampled these patients only from the patients treated on study with survival of at least 8 weeks. However, we know that 22 percent of the patients treated with salvage chemotherapy died within 8 weeks.

Second, for the 21 randomized not treated patients in the control arm with known survival dates beyond 8 weeks, the agency assumes that these patients would have survived as long or longer than they did had they received study treatment. However, based on the data from the patients actually treated on the control arm, it is equally possible that these randomized not treated patients could have had a shorter survival had they received the salvage chemotherapy on the study.

All of these assumptions likely lead to an optimistic imputation of survival for the salvage chemotherapy arm, an overly pessimistic assessment of the of the study treatment effect.

For the secondary endpoint, the planned event-free survival analysis did not reach statistical significance. However, we noted a

sponsor error in the timing of censoring of 18 patients were alive but did not have a post-baseline response assessment.

In the original analysis, the censoring treated these patients as if they did not have an event-free survival event of failure to achieve CRc, even though in fact we do not know their response to therapy. This artificially inflated the outcome of the salvage chemotherapy arm because 17 of these 18 patients were on the chemotherapy arm.

Among chemotherapy patients with response assessment, we know that 60 percent had an event of failure to achieve a CRc. So we corrected the analysis by more appropriately timing the censoring of these 18 patients. The hazard ratio is then 0.78 and the one-sided p-value is 0.0147. These results are again consistent with the overall survival analysis.

An important efficacy endpoint for this study was assessment of the remission rates. Consistent with the previous studies, nearly half

of the quizartinib patients achieved a CRc, most of which, as expected, were CRi. Most of those treating patients with leukemia considered these as a benefit because it represents better control of the disease with an outpatient therapy and allows some patients to proceed to a stem cell transplant. On the salvage chemotherapy arm, 27 achieved a CRc, mostly CRi' with only 1 Cr.

In quizartinib treated patients, the time to remission was fast at 4.9 weeks and the median duration of CRc was 12.1 weeks. As expected with a difference in response rate, there was a difference in the transplant rate between the two arms, 32 percent in the quizartinib arm and 12 percent on the salvage chemotherapy. This difference in transplant reflects the treatment effect of quizartinib, resulting in more patients being considered eligible for transplant based on the reduction disease burden in the bone marrow and the good performance status.

As described in your briefing document, transfusion independence was assessed as a post hoc

exploratory endpoint since it emerged during the review of these applications as a valid and regulatory measure of clinical benefit. For patients treated with quizartinib, 34 percent of those who achieved a CRc became transfusion independent.

In summary, the overall survival benefit has been established in a randomized active control phase 3 study. Quizartinib provided a statistically significant improvement in the overall survival compared to salvage chemotherapy with a hazard ratio for overall survival of 0.76. The results are credible and consistent.

Our comprehensive sensitivity analyses and the updated overall survival addresses the impact of missing data. The corrected event-free survival analysis and the results of the other efficacy endpoints confirm the consistency benefit with quizartinib. These results are also consistent with the clinical activity observed in the phase 2 studies. Taken together, these data support a clear and clinically meaningful benefit of

quizartinib in this patient population.

Thank you. Now I would like to invite Dr. Youngsook Choi to the podium to discuss the safety profile of quizartinib.

Dr. Choi?

Applicant Presentation - Youngsook Choi

DR. CHOI: Thank you, Dr. Cortes.

My name is Youngsook Choi, executive director of clinical safety and pharmacovigilance. My safety presentation is primarily based on the pivotal phase 3 study, QuANTUM-R, as it provides the relevant safety experience with the monotherapy dosing regimen under review today.

As you heard earlier, baseline characteristics were well balanced with the median age in the quizartinib arm of 55 years, and 27 patients were at least 65 years of age. This development program consists of 673 patients who received continuous daily doses of quizartinib of up to 300 milligrams. The median age of the safety pool of relapsed or refractory AML patients was 59 years, and 35 percent were at least 65 years of

age.

As you see, the treatment duration for the two groups were different in the QuANTUM-R study. 241 patients received quizartinib for a median of four 28-day cycles with some patients receiving therapy for over 1000 days. In contrast, 94 chemotherapy patients received a median of 1 cycle and a maximum of 2 cycles. Treatment-emergent safety analysis includes events while on study treatment plus 30 days.

Nearly every patient experienced at least one treatment-emergent adverse event. As anticipated, given the longer treatment duration with quizartinib, there were more grade 3 or serious events and events associated with treatment discontinuation.

Shown here is an overview of safety in cycle 1, which is the most meaningful comparison period with comparable treatment duration. There were more severe serious or fatal events in patients receiving salvage chemotherapy.

Commonly occurring events in cycle 1 are

shown on this slide. On the left are events with quizartinib and on the right are corresponding events with chemotherapy. Most frequent events with quizartinib included nausea, anemia, QT prolongation, thrombocytopenia, and pyrexia. There were more events with chemotherapy with the exception of QT prolongation. QT prolongation is a notable safety finding with quizartinib, and I will discuss this in further detail later in my presentation.

Quality-of-life data was not collected in this study. To better understand patients' clinical experience, we measured the percentage of days spent by each patient with selected critical events, which are shown here. This analysis showed that the fraction of days spent in this cycle, in cycles 1 and 2, was 6.8 percent with quizartinib therapy, lower than 13.9 percent with chemotherapy.

Now, I will review the safety experience with quizartinib for the full study period. Types of commonly occurring events were consistent with what we observed in cycle 1. Shown in red are

events that are grade 3 or higher for the frequently reported events.

As you can see, most of the severe events were associated with cytopenias such as anemia, febrile neutropenia, and thrombocytopenia. QT prolongation was reported in 26 percent for the full study period. Grade 3 was observed in 3.3 percent, and there were no grade 4 events. Although not shown here, the pattern of serious events was similar to the severe events shown on this slide.

Overall, 18.3 percent of patients discontinued quizartinib. Among these, infections were most common at 6.2 percent followed by hematologic abnormalities at 2.9 percent, and intracranial hemorrhage at 1.7 percent.

Differentiation syndrome was discussed in the FDA briefing document. There were no events reported by the investigator. However, in a retrospective analysis, we identified 12 quizartinib treated patients as having possible differentiation syndrome. Among 8 patients with

acute febrile neutrophilic dermatosis reported, one was assessed as having possible differentiation syndrome by the sponsor.

Now I will discuss QT-based dosing risk mitigation; QTc exposure response modeling,; outlier analysis; and arrhythmia events. A number of measures were implemented in QuANTUM-R based on the learnings from the phase 2 program. We excluded patients at high risk of torsade and implemented a protocol-defined QT- based dosing regimen as described by Dr. Cortes.

In addition, depending on the magnitude of QT prolongation, those modifications or discontinuation were also implemented. Concomitant use of QT prolonging medications were permitted when deemed medically necessary. ECGs were obtained in triplicates with time-matched PK samples as shown here.

As implemented, QT-based dose modifications were largely successful in reducing QT prolongation. Medium relative dose intensity was high. ECGs were obtained in 96 percent of all

visits. Concomitant use of QT prolonging medications was reported in 73 percent. Most common were antifungal therapy.

For patients with grade 2 or 3 QT prolongation, which required dose modification, quizartinib dosing was modified in 87 percent. In the remainder, QTcF normalized on follow-up or therapy was withdrawn due to AML disease progression.

Quizartinib results in QT prolongation by IKs inhibition in a dose-dependent manner. The magnitude of QT prolongation was assessed using exposure response modeling. At the mean Cmax achieved at steady state with 60 milligrams, the mean to QTcF predicted was 22.1 milliseconds.

We found no meaningful impact of the covariates tested, including age, sex, or use of concomitant QT prolonging medications. Furthermore, there were no greater increases in QTc prolongation with faster heart rates or with concomitant use of QT prolonging medications.

Now let's review the frequency and degree

of QTc prolongation based on the standardized central ECG reading. QTcF greater than 500 milliseconds, a threshold that is clinically significant, occurred in 8 patients. None had ventricular arrhythmias. In 7 of these 8 patients, QTcF normalized with dose interruption or reduction. The other patient had presented quizartinib withdrawn due to AML disease progression.

With the benefit of central reading, we can conclude that the QTcF greater than 500 milliseconds was uncommon and was effectively managed. This demonstrates that the proposed dosing regimen and dose modifications were appropriately implemented and effective in reducing clinically significant QT prolongation.

In our evaluation of all potential QT related cardiac events, we used a standardized MedDRA query. Once events were identified, they were reviewed individually with two external experts in electrophysiology and cardiology. In QuANTUM-R, there were no events of torsade,

ventricular fibrillation, cardiac arrest, or sudden death.

Thirteen patients had syncope or loss of consciousness. One patient with loss of consciousness had prolonged QTcF of 503 milliseconds. Documented hypotension and severe anemia was thought to result in this patient's fall and loss of consciousness. In the remaining 12 patients, there was no QT prolongation or arrhythmias. There was one non-serious event of ventricular tachycardia, and this patient continued in the study for more than 1000 days without a recurrence.

FDA noted in their briefing book 4 on-treatment deaths potentially due to arrhythmias. These 4 patients were hospitalized at the time of death. Two of these were monitored in an ICU setting, and there were no arrhythmia events reported. All cases were reviewed with external experts, and there were no clinically marked QT prolongation or documented ventricular arrhythmias.

Turning now to the overall relapsed or

refractory AML safety poll, we also conducted a standardized MedDRA query. There was one event of torsade and one other suspected arrhythmia event possibly associated with quizartinib therapy. The patient with torsade was critically ill and was receiving 90 milligrams of quizartinib. This patient recovered, and QTcF normalized with treatment discontinuation.

Of the 3 events of cardiac arrest, an arrhythmia event could not be excluded in one patient with Staph aureus sepsis who was receiving supratherapeutic doses of quizartinib. The sponsor continues to monitor for cardiac signals in ongoing studies, including QuANTUM first, where quizartinib is given in combination with chemotherapy.

To conclude, our first experience in this critically ill patient population treated with quizartinib was well characterized and was manageable with monitoring and dose modification. Most common events such as gastrointestinal symptoms were generally not severe. Serious cytopenias and infections occurred but infrequently

led to treatment discontinuation. Regarding the differentiation syndrome, we will work with agency to determine appropriate ways to address this.

Dose-dependent QT prolongation and ventricular arrhythmia events were observed across the development program. Applying the QT-based dosing regimen, the incidence of clinically significant QT prolongation was reduced. QTc prolongations were managed and QT related arrhythmias were not observed in QuANTUM-R.

Our data did not show additional increases in QT prolongation with faster heart rates or when used with other QT prolonging medications. Thus, the addition of beta blockers or contraindicating the use of QT prolonging medications does not appear warranted.

Risk mitigation strategies will include labeling with QT guided dosing similar to what was used in QuANTUM-R, avoidance of other QT prolonging medications, unless medically necessary, and monitoring for and correction of electrolyte abnormalities. We will provide a medication guide

for patients and education material for prescribers.

Thank you. Now I'd like to invite Dr. Cortes back to the podium to provide his clinical perspective.

Applicant Presentation - Jorge Cortes

DR. CORTES: Thank you, Dr. Choi.

I will conclude the presentation with a clinical perspective on why quizartinib is an important treatment option for patients with relapsed or refractory FLT3 ITD AML. As you have heard today, patients with relapsed/refractory FLT3 ITD AML have a very poor prognosis.

Quizartinib confers an improvement in overall survival, the gold standard endpoint. Although the absolute change in median survival is modest, it is very welcomed to patients and physicians. It is important to acknowledge the underlying patient experience with chemotherapy compared to quizartinib. With standard chemotherapy, patients are usually hospitalized, typically for weeks, often with mucositis,

alopecia, infections, and permanently hooked to an IV pole. With quizartinib, patients can be mostly at home taking an oral medication daily and coming to clinic as needed.

This is the third large randomized trial to show that inhibition with FLT3 pathway can prolong survival in FLT3 mutated AML. In the relapsed setting, even with one FLT3 inhibitor recently approved, more options would be welcome.

In CML [ph], there are 5 tyrosine kinase inhibitors approved to treat the disease, and we as oncologists want them all and we use them all. The more drugs that we have to attack the driver oncoprotein, the more useful options we have for our patients, particularly for those with the worst prognosis like the ones that we're discussing.

Another important benefit of quizartinib therapy is that responses are generally as rapid as with intensive chemotherapy but with longer duration. Shown here, are [indiscernible] plots for the time to first remission and duration of CRc. It should be noted that there were no

responses in the patients treated with low-intensity chemotherapy.

As you can see on the left, the quizartinib patients achieved remission quickly with a median time to CRc of less than 5 weeks, which is similar to the timing of response with high-intensity chemotherapy, and they did this with an oral outpatient therapy. On the right, you can see the median duration of CRc was greater in the quizartinib arm at 12 weeks compared to 5 weeks in the chemotherapy arm.

For these patients, transplant remains the best option for cure and is typically considered for younger patients who achieve significant reduction in leukemic blast burden, are fit to receive the conditioning regimen, and have an identified donor. The longer duration of CRc with quizartinib is important to allow the necessary time to find a match for transplant before the patient relapses.

It is no surprise, then, that with a higher CRc rate, including Cr's and Cri's, a longer

duration of response, and less of a negative impact of the treatment on their performing status, more patients in the quizartinib arm were able to undergo transplant without additional therapy.

Not only is quizartinib an effective treatment option, it is also one that has a favorable safety profile and is suitable for outpatient administration. In over 650 patients to date, quizartinib has been well tolerated. The adverse events that Dr. Choi described are mostly the typical events experienced by patients with relapsed/refractory AML: infection, neutropenic fever, and nausea.

Regarding QTc prolongation and cardiac toxicity in general, I think we need to look at the big picture. We are talking about patients with relapse or refractory FLT3 ITD AML. These patients are facing imminent death potentially within days or weeks.

There's no question that QTc prolongation is an important issue, but as you saw in this story and in my experience from the early stages of the

quizartinib program, it can be readily managed, and the risk of cardio toxicity with quizartinib is small relative to the risk of uncontrolled leukemia. In my opinion, the sponsor recommendations for risk mitigation, which are based on the steps used in the QuANTUM-R study, are effective and easily adhered to in the typical clinical setting.

This is an incredibly exciting time in the field of AML. After years of having no new treatments to offer to these patients, we now have several new molecularly targeted agents approved, including 2 FLT3 inhibitors. We have shown you today that the patients with very aggressive disease experience clinical benefit with quizartinib. They can receive outpatient therapy. You can expect a longer survival, a better probability of responding, a longer response duration, and a better chance of getting to a transplant, which offers then the possibility of a cure.

We are confident that quizartinib can be an

important new addition to our arsenal as we thrive to improve the outcomes for our patients with these very challenging subtypes of AML. I thank you for your attention, and this concludes the sponsor presentation.

DR. RINI: Thank you. We'll now proceed with presentations from FDA.

FDA Presentation - Kunthel By

DR. BY: Good afternoon. This is FDA's presentation of NDA 212166, quizartinib. My name is Kunthel By. I am the statistical reviewer for this application. My colleague Dr. Krauss and I will be presenting FDA's evaluation of the safety and efficacy of quizartinib. FDA's presentation agenda will be as follows. I will discuss the efficacy review, and Dr. Aviva Krauss will follow with the safety review and a summary of the issues.

For the efficacy presentation, I will briefly remark on the requirements for the marketing approval of AML therapies. I will then review the efficacy of quizartinib in the context of study AC220-007, which the applicant referred to

as QuANTUM-R, the pivotal study upon which this submission is based. This review will center around the first issue, namely the uncertainty and the estimated treatment effect.

Per the Food, Drug, and Cosmetic Act, the primary requirements for marketing approval of an application to market a drug for human use is that the application must provide substantial evidence of safety and effectiveness, and that the evidence should come from adequate and well-controlled clinical studies. This includes the use of endpoints that are considered to be clinically relevant and the use of study designs that enable the determination of a treatment effect that is free from bias.

FDA has accepted the following endpoints as clinically relevant for establishing the effectiveness of drugs to treat AML. These include overall survival; event-free survival; durable, complete remission; and complete remission or complete remission with partial hematological recovery supported by evidence of transfusion

independence.

I will now begin the discussion of the first overarching issue, which is the uncertainty and the estimated treatment effect. As presented earlier by the applicant, study 007 is an open-label, randomized, active control study of quizartinib versus chemotherapy in patients who are at least 18 years of age with FLT3 ITD-positive AML and who are refractory or relapse within 6 months of first remission.

Randomization is stratified by two factors, one of which is pre-randomization. Investigators selected chemotherapy whose levels include intensive chemo, which consists of MEC and FLAG-IDA and low-intensity chemo, which consists of LDAC. The primary endpoint is overall survival with event-free survival as the key secondary endpoint. A total of 367 patients were randomized with 245 in the quizartinib arm and 122 in the chemotherapy arm.

Although study 007 is a randomized study, we have the following concerns. First is the lack

of internal consistency across endpoints; second is the impact of subsequent therapies on overall survival; third, there are a differential number of patients who were randomized but not treated with study therapy; and fourth, there are differential numbers of patients early censored, which could be informative if patients who were early censored are systematically more likely or systematically less likely to die earlier than patients who are not early censored.

Each of these concerns is a source of additional uncertainty, which in turn raises questions about the overall uncertainty and the interpretability of the estimated treatment effect. I will go over each of these points in my subsequent slides.

This table summarizes the treatment effect based on the overall survival primary endpoint. Note that although the OS is statistically significant, the treatment effect as quantified by the hazard ratio is borderline in the sense that the upper 95 percent confidence limit is 0.99.

I want to emphasize that when we consider evidence of efficacy in the context of a single trial, we generally require supporting evidence from other clinically relevant endpoints. We refer to this as having internal consistency.

This brings us to our first concern with study 007, namely the lack of internal consistency across endpoints that FDA considers as relevant to AML. As shown here, EFS, the key secondary endpoint, as analyzed by FDA does not suggest a quizartinib advantage over chemotherapy, as the hazard ratio is 0.9 with a 95 percent confidence interval that spans points 0.71 to 1.16.

While the CR rates seen here show a numerically higher value for quizartinib, they are less than 5 percent in both arms, the confidence intervals overlap, and in absolute terms, it is not clear that these magnitudes could explain the OS advantage observed in the primary analysis.

The second concern that we have with this application is the impact of subsequent therapies on overall survival. In the pivotal study,

patients in both arms initiate subsequent therapies, but of particular concern to FDA is that of allogeneic hematopoietic stem cell transplant or HSCT.

As shown in this table, most patients who initiated Allo HSCT did so without achieving CR. Of note, we observed an imbalance in the rate of HSCT not only between the quizartinib treatment arm and the control chemotherapy arm, but also an imbalance between the intensive stratum and the low-intensity stratum.

Across both of these intensity strata, 83 or 34 percent of patients in the quizartinib arm initiated HSCT while not in CR, and 21 or 17 percent of patients in the chemotherapy arm initiated HSCT while not in CR. In the intensive stratum, 37 percent of quizartinib patients initiated HSCT without CR, while 23 percent of chemotherapy patients initiated HSCT without CR.

Note in the low-intensity stratum, the difference is larger. In particular, 23 percent in the quizartinib arm initiated HSCT while not in CR,

but no patients in the chemotherapy arm initiated HSCT. What's driving this imbalance is not clear, but we cannot rule out the possibility that the imbalance is induced by the open-label nature of the study.

In order to explore the effect of HSCT on overall survival, we examined the treatment effect within the intensive stratum, which is roughly 75 percent of the study population and where the difference in HSCT use between quizartinib and chemotherapy appears less dissimilar as compared to the low-intensity stratum.

As noted in the previous slide, 37 percent of quizartinib patients initiated HSCT while not in CR, and 23 percent of patients in chemotherapy initiated HSCT while not in CR. The survival curves are shown on the left. Note that the hazard ratio is 0.83 with a 95 percent confidence interval of 0.62 and 1.1. This result suggests the possibility of no quizartinib survival advantage if use of HSCT among patients who did not achieve CR is more similar between the treatment arms.

FDA fully recognizes that study 007 is not adequately powered to make statements about the treatment effect within subgroups, and that this apparent lack of efficacy may be due to inadequate sample size. However, the emphasis here is that there is an imbalance in the number of patients who initiated HSCT while not in CR, and as HSCT extends survival, the observed OS advantage could be due, in whole or in part, to this imbalance.

Our third concern is the number of patients who were randomized but were not treated with study therapy. In this study, a substantial proportion of patients in the chemotherapy arm were randomized but not treated. In particular, 28 patients or 23 percent in the chemotherapy arm were randomized not treated, and 4 patients or 1.6 percent in the quizartinib arm were randomized not treated.

This imbalance is possibly due to the open-label nature of the study, and because the randomized not treated is prevalent mainly in the chemotherapy arm, it raises the question about how much impact these patients would have had on the

estimated treatment effect had they been treated with study therapy.

The fourth concern stems from the fact that there is differential early censoring between arms. For the remainder of my presentation, the phrase "early censoring" will refer to censoring before 8 weeks after randomization and will be abbreviated as EC8.

The phrase "early death" will refer to death before 8 weeks after randomization and will be abbreviated ED8. Patients with at least 8 weeks of survival follow-up will be abbreviated as GE8, and they include patients who died on or after 8 weeks and patients who were censored on or after 8 weeks.

In general, patients who are early censored provide little to no information about the treatment effect. In the pivotal steady, 9 or 7.4 percent of patients from the chemotherapy arm were early censored while only one or 0.4 percent of patients from the quizartinib arm were early censored.

Due to the imbalance and the potential for informative early censoring, it raises the question about how much impact these patients would have had on the estimated treatment effect had these patients had longer follow-up.

The following table jointly summarizes patients according to treatment arm; stratum based on the preselected chemotherapy stratification factor; early censoring status; and randomized not treated status. In this table, we see that 9 patients in the chemotherapy arm are early censored, 7 of whom are randomized not treated and 2 of whom are randomized treated.

In the quizartinib arm, one randomized treated patient was early censored. And as noted earlier, a total of 28 patients were randomized and not treated in the chemotherapy arm as compared to only 4 in the quizartinib arm.

FDA performed the stress test analysis to assess the robustness of quizartinib OS advantage under differential randomized not treated and early censoring. The approach is to impute the survival

times and statuses of early censored and randomized not treated patients from those who were randomized treated and having at least 8 weeks of survival follow-up. We used an approach similar to the applicant but under a different set of assumptions.

To illustrate, consider the set of chemotherapy patients who were preselected for intensive chemotherapy. There are 6 patients who were randomized not treated and early censored. The red arrow from 57 indicates that their survival information is replaced by those of 6 randomly selected patients from the set of 57 who are randomized treated with at least 8 weeks of survival follow-up, and similarly for the 2 patients who were early censored but were randomized and treated.

For the 12 randomized not treated patients whose survival times was at least 8 weeks, we consider three scenarios. The first scenario is to impute the survival times for all 12 patients, the second scenario is to impute the survival times of half of these patients, and the third scenario is

to not impute the survival times of these patients.

This slide shows the range of treatment effects obtained from the stress test under FDA's assumptions. Please note that the full details of the imputation analysis are provided in the briefing document. I would just like to point out that the first row of this table corresponds to Pi equals zero using the notation of the briefing document. The second row corresponds to Pi equals 0.5, and the third row corresponds to Pi equals 1.

What's important to note is that within the range of assumptions that FDA considers, this last row represents the most conservative scenario and is most favorable to quizartinib.

Even with this conservative scenario, we see that the hazard ratio is 0.78 with an upper 95 percent confidence limit of 1.0, a value indicating no statistical difference in the treatment effect. As shown in the third column, this is consistent with the fact that 50 percent of our imputations failed to show that quizartinib is superior to chemotherapy.

In general, it is extremely difficult to perform imputation analysis, as it depends on difficult to verify assumptions. But to the extent that our assumptions are reasonable, the range of hazard ratios shown here lead us to question whether the observed quizartinib OS advantage is robust and whether it truly reflects the uncertainty caused by differential early censoring and randomized not treated.

I also want to point out that the stress test results do not reflect the uncertainty induced by differential rates of HSCT among patients who did not respond. The purpose of a stress test is to only examine what can happen to the estimated treatment effect if we assume that the survival times of patients randomized not treated and early censored resemble those who are randomized treated and have follow-up for at least 8 weeks.

To summarize, the overall survival analysis based on the submitted data suggest an OS advantage with a hazard ratio of 0.77 and an upper 95 percent confidence limit of 0.99. The estimated difference

in median overall survival is 6.5 weeks. But as described earlier, we are concerned that these results do not adequately account for all the uncertainty, and thus may not reflect the actual treatment effect. Our concern stems mainly from the following.

First, there was a lack of internal consistency across endpoints. In general, when we evaluate efficacy based on a single trial, we expect that the primary results are supported by other clinically relevant endpoints. In this pivotal study, both EFS and CR show a lack of efficacy.

Second, it is not clear that the observed OS advantage is not due to subsequent therapy; in particular, post randomization HSCT. In the pivotal steady, we observed an imbalance in HSCT use between arms notably in patients who did not achieve CR, and that more quizartinib and chemotherapy patients initiated HSCT while not in CR. As HSCT extends survival, it is possible that the observed OS advantage is due, in whole or in

part, to the HSCT imbalance.

Third, there were differential randomized not treated and early censoring prevalent mainly in the chemotherapy arm. When the choice to not be treated or the decision to leave the study early is due to knowledge of the assigned treatment arm, it is well known that an analysis based on the observed data can be bias. The goal of the stress test was to assess the impact of differential randomized not treated and early censoring on the estimated treatment effect. The results of our stress test indicate a lack of robustness in the estimated treatment effect.

With all these concerns in mind, we have doubts about the existence of a quizartinib OS advantage and that the estimated treatment effect is likely to be biased, the extent of which is unknown. Given the certainty in the estimated treatment effect due to the reasons just mentioned, we ask the committee to please discuss whether the results of OS analysis of study AC220-007 are persuasive evidence of effectiveness of quizartinib

and the reasons for your opinion.

I now turn the presentation over to Dr. Krauss to discuss the safety findings.

FDA Presentation - Aviva Krauss

DR. KRAUSS: Thank you, Dr. By.

Good afternoon. FDA's analysis of the safety of quizartinib focuses mainly on the results of the pivotal trial 007, but we will also highlight relevant findings from the integrated safety population of patients with relapsed or refractory AML who received quizartinib monotherapy across the clinical development program, as well as limited safety data from the ongoing phase 3 trial of quizartinib in combination with intensive chemotherapy in patients with newly diagnosed FLT3 ITD-positive AML.

The median duration of treatment with quizartinib was approximately 3 cycles on a pivotal trial and 2 cycles in the integrated safety population, so the bulk of these safety analyses are limited by a short duration of exposure.

FDA's analysis of safety across the

development program focused on the unique cardiac toxicity associated with IKs blockade; identification of a new safety signal for differentiation syndrome and acute febrile neutrophilic dermatosis; and prolonged cytopenias associated with quizartinib monotherapy.

Typical safety concerns related to quizartinib and associated cardiac toxicity in context. This slide and the next reviewed the physiology of the cardiac action potential and associated pathophysiology that can be seen with agents that prolong QT through inhibition of the outward potassium current.

The cardiac action potential begins in the sinoatrial node. Depolarization and repolarization are controlled by ion channels through which sodium and calcium flow in and potassium flows out of cardiac myocytes. Specifically, repolarization is controlled mainly by the outward delayed rectifier currents IKr, the rapid component, and IKs, the slow component.

When the potassium channels are blocked by

a drug, for example, as depicted in the red line of the middle figure on the left, the decrease in potassium east efflux through the delayed rectifiers delays repolarization, and the action potential is prolonged. This is reflected in the EKG as prolongation of a QT interval.

The increased relative influx of sodium or calcium through their ion channels may result in early after depolarization and triggers torsade de pointes, or TDP, that can be fatal or self-resolve and results in palpitations, dizziness, dyspnea, near syncope, or syncope.

As far as we are aware, to date, approved agents associated with QT prolongation do so through inhibition of the IKr current. This leads IKs intact to provide repolarization reserve, although a patient's risk of developing TDP is influenced by this repolarization reserve as well as confounding clinical risk factors.

Since there is currently no approved non-cardiac drug that blocks IKs and we have no clinical data for other IKs blockers, insights

regarding blockade of IKs are taken from the relatively rare autosomal recessive long QT syndrome type 1, which has decreased IKs activity resulting from a loss of function mutation in the KCNQ1 gene.

The greatest risk for cardiac arrhythmias and sudden death in these patients occurs when the QT, or corrected QT, QTc, is prolonged beyond 500 milliseconds. But patients with autosomal recessive long QTS1 [ph], who have normal QT intervals at rest, are still at risk of life-threatening or fatal arrhythmias. Since QTc becomes prolonged, IKs function is blunted even further in the setting of beta adrenergic stimulation, such as during emotional or physical stress.

Such patients than typically present with syncope or loss of consciousness that's precipitated by abrupt onset tachycardia. Consequently, prophylactic beta blockade is recommended even when they have a normal resting QTc. Finally, some patients with long QTS1 are

only diagnosed as such when they're treated with drugs that block IKr, leaving them without the reserve necessary to prevent the later repolarization.

The converse is manifest in the clinical context of approved agents that prolong QT. Since they do so through inhibition of IKr, the concomitant use of two of these agents leaves IKs intact. In contrast, if an IKs blocker such as quizartinib is given concomitantly with a drug that inhibits IKr, the lack of a collateral pathway for repolarization may potentially result in a heightened increased pro-arrhythmic risk.

The ICH E14 guideline discusses the design, conduct, analysis, and interpretation of clinical studies to assess a drug's ability to delay cardiac repolarization. Per ICH E14, substantial prolongation of QT/QTc, even without documented arrhythmias, could be the basis for non-approval of a drug, or just discontinuation of its clinical development, particularly when it has no clear advantage over available therapy.

However, in general, the outcome of the risk-benefit assessment will be influenced by the size of the prolongation effect whether it is seen in most patients or only in identifiable outliers, the overall benefit of the drug, and the utility and feasibility of risk management options.

With regard to the size of the prolongation of the QT/QTc effect, E14 states that drugs that prolong the mean QT/QTc interval by more than 20 milliseconds have a substantially increased likelihood of being proarrhythmic and might have clinical arrhythmic events captured during drug development.

Regulatory decision-making uses QTc prolongation as a surrogate marker for the risk of TDP. The greater the extent of QTc prolongation, the greater the risk. This surrogate, combined with clinical events that occur, allows for delineation of general categories of low, increasing, or definite concern for TDP.

In vitro studies showed that quizartinib is a predominant IKs blocker. The applicant

calculated the quizartinib IC50 to be less than 300 nanomolar for IKs blockade, and based on the PK studies, such concentrations of quizartinib may be reached in Vivo with the proposed 60-milligram dose.

Given this predominant IKs blockade in the nonclinical studies, FDA evaluated the effect of quizartinib on the QTcF interval in the pivotal study 007, as well as study 2689-CL-2004. Results from 2004 are depicted here with cycle number, day and hour, and post-quizartinib depicted on the X-axis.

As shown in both the 30 in blue and 60 in red milligram cohorts, the mean delta QTcF increases over time. Using the thresholds from the previous slide alone, even without clinical context, it is clear that the mean delta QTcF as early as 2 hours after the first dose of quizartinib is in the range that has been associated with arrhythmias. In patients receiving the proposed dose of quizartinib, the mean delta QTcF is above the 20-millisecond threshold that is

considered to be a risk for TDP by day 8, and this prolongation is concentration dependent.

To assess whether the IKs blockade and QTc prolongation of quizartinib was associated with clinical manifestations, FDA first looked at acute or subacute cardiac deaths. We identified 4 patients on the pivotal trial who experienced a fatal event that was assessed to be possibly cardiac in origin and at least possibly related to quizartinib. In 3 of these 4 cases, FDA's assessment was that the deaths were likely related to quizartinib.

In the 724 patients with relapsed or refractory AML treated with quizartinib monotherapy across the clinical program, FDA identified an additional 3 deaths that were considered at least possibly related to quizartinib therapy with a cardiac event as the root cause of death.

Lastly, in the ongoing phase 3, randomized placebo-controlled trial in which quizartinib is administered with intensive chemotherapy as first-line treatment, FDA identified 5 cardiac

deaths all in the quizartinib arm that were considered at least possibly related to quizartinib. No such events were identified on the placebo arm.

In many of the cases summarized above, electrolyte abnormalities, anemia, sepsis, or other complications, as well as concomitant use of other QT prolonging agents, may be implicated as confounding factors in the cause for the arrhythmias or fatal cardiac events.

We note that although these confounding circumstances may contribute to these adverse events, given the preclinical and clinical data above, a causal relationship to quizartinib is biologically plausible and cannot be excluded definitively.

Further, the unique clinical manifestation of IKs blockade, as gleaned from insights into long QTc syndrome type 1, suggests that patients treated with quizartinib, and IKs blocker, may be predisposed to fatal cardiac events that are manifest with the occurrence of anemia or sepsis

and their accompanying tachycardia or with hyperkalemia. The fact that some of these cardiac events occurred early in the treatment course also supports the notion that these risks are not merely theoretical.

In addition to looking at cardiac deaths across the quizartinib development program, depicted at the top of this slide is an FDA analysis of safety data from the pivotal study 007, using a standard screening tool for QT propagation arrhythmia events also discussed in ICH E14.

Over the course of treatment, QT prolongation, falls, and syncope occurred at a higher rate on the quizartinib arm compared to the control arm. Since exposure on the quizartinib arm was longer than that on the chemotherapy arm in both preselected chemotherapy substrata, FDA also performed an analysis of cardiac events during cycle 1 only.

The cardiac events occurring at a higher rate in the quizartinib arm during cycle 1, and the rates at which they occurred in each arm in

substratum, are detailed in table 11 and 12 of the FDA briefing document. Whether the comparison is made to low-dose or intensive chemotherapy, cardiac related events occurred at a higher rate on the quizartinib arm, even just during cycle 1.

Additionally, since quizartinib is administered chronically, there's a potential for cumulative toxicity over time, so an estimate of the risk of these events over multiple cycles of quizartinib is also critical and relevant. However, due to the short exposure to quizartinib in study 007, the safety of long-term administration remains uncertain.

In summary, quizartinib is associated with IKs blockade, and at steady-state exposures results in mean changes in the QTcF on baseline that are in the proarrhythmic range. This was borne out in the pivotal study with over 20 percent of patients experiencing QTcF prolongation on the quizartinib arm compared to less than 5 percent in the control arm.

On treatment, fatal cardiac events occurred

in 1 to 2 percent of patients. In the ongoing randomized, phase 3 study, there has been an imbalance in cardiac death with 5 on the quizartinib arm and none on the placebo arm. These events occurred despite dose modifications and concomitant medication instructions on the pivotal trial.

Among the potential strategies to manage these risks are the contraindication for use with other agents associated with prolonged QT, since with dual blockade of IKr and IKs, repolarization reserve may be lost. Although not incorporated as a strategy on 007, the model of long QTc syndrome type 1 for IKs blockade, which is the additional recommendation for administration of beta blockers concomitant with quizartinib therapy similar to the prophylaxis recommended for patients with this syndrome.

With all of this in mind, we ask the committee to please discuss the need for and feasibility of A, a contraindication for use with drugs that prolong QT via the complementary IKr

channel; and B, a recommendation for administration of beta blockers to prevent arrhythmias, as means to reduce the risk of life-threatening and fetal cardiac events resulting from IKs blockade if quizartinib is marketed.

Much of the FDA review of safety focused on unique cardiac risk I just discussed. While FDA largely agreed with the applicant with regard to common treatment-emergent adverse events on the pivotal study, as they have described during their presentation, FDA's analysis of safety also identified a new safety signal for differentiation syndrome and acute febrile neutrophilic dermatosis, as well as prolonged cytopenias associated with quizartinib monotherapy.

Differentiation syndrome, or DS, is a clinical syndrome characterized by dyspnea, unexplained fever, weight gain, unexplained hypertension, acute kidney injury, and pulmonary infiltrate or pleural pericardial effusion. Montesinos, et al. described objective criteria that could be applied to identify what we would

call classic DS.

Since it was first described in the context of the treatment of acute promyelocytic leukemia, or APL, with the differentiation agent all-trans retinoic acid or ATRA, it has also been reported with the use of targeted therapies for non-APL AML, including approved IDH and FLT3 targeted therapies. Fatal cases have occurred in both of these clinical contexts.

Cutaneous manifestations are not one of the criteria of classic DS. Acute febrile neutrophilic dermatosis, or Sweet's syndrome, was first described by Dr. Robert Douglas Sweet in 1964 as a syndrome of fever, skin lesions, and neutrophilia, with the findings of dermal neutrophil infiltration.

It has since been mostly recognized in the context of malignancy as a paraneoplastic syndrome and also as manifestation of leukemia cutis, or with associated medications, infections, inflammatory disease, or pregnancy. It too has been reported in the literature in the context of FLT3

targeted therapies, in which the lesions were biopsied proven to be mature neutrophils and not blasts.

Steroids are the mainstay of treatment of AFND in conjunction with or as part of treatment of the underlying associated condition, and drug associated cases may require withdrawal of the offending agent.

FDA identified classic DS in 5 percent of patients on the pivotal study. In the integrated safety population overall, and on 007 in particular, AFND was reported in 3 percent of patients. On 007, FDA identified an additional 4 patients who only partially fulfilled Montesinos' criteria but who also had the cutaneous manifestations.

When considering that AFND may be an additional manifestation of DS, 7 percent of patients on quizartinib in the pivotal study experienced an event on the spectrum. Among these were 3 fatal cases; 2 of these 3 cases did not have quizartinib interrupted or steroids administered

such that these manifestations appear to be underrecognized in the proposed population.

Finally, to assess the risks of quizartinib in comparison to available therapy, FDA performed an analysis of adverse reactions on study 007 using narrow standardized MedDRA queries by preselected chemotherapy substratum. This slide shows the adverse reactions with the risk difference between study arms of at least 15 percent for patients preselected for the LDAC stratum. FDA noted that in addition to cardiac events described previously, cytopenias and gastrointestinal conditions occurred at a higher rate in the quizartinib arm than with low-dose cytarabine.

In those preselected for intensive chemotherapy, only cardiac AEs and shock occurred at higher rates on the quizartinib arm, while the gastrointestinal conditions in particular had a lower incidence than with intensive chemotherapy.

Given the 26 percent higher incidence of hematopoietic cytopenias in the quizartinib arm on 007, FDA analyzed absolute neutrophil counts of

platelet counts over the course of therapy in patients who achieved a CR or CRh separately from those who achieved CRi or CRp and non-responders. These analyses are depicted in figure 3 of the FDA briefing document and summarized here.

Even patients who achieved a CR or CRh experienced both neutropenia and thrombocytopenia, and these trends continued beyond cycle 1. The duration of grade 3 to 4 neutropenia, lasting through cycle 3, appear to be more protracted than that of thrombocytopenia, which appear to be of lower grade, 2 to 4, and recover by the end of cycle 2 in patients who achieved a CR or CRh.

In summary, quizartinib therapy is associated with significant and unique safety concerns in the proposed population, including the risk of fatal cardiac events that cannot be predicted with certainty using routine QTc measurements. These cardiac events occurred on study 007 despite dose modifications and concomitant medication guidelines in the protocol. Administration of prophylactic beta blockade and a

contraindication for the use of concomitant QT prolonging medications may be necessary, and it is unclear to what degree these will mitigate the cardiac risks.

Quizartinib is also associated with events on the differentiation syndrome, acute febrile neutrophilic dermatosis spectrum, which can be fatal, as well as gastrointestinal toxicities. Lastly, despite being a targeted agent rather than a cytotoxic, quizartinib monotherapy is associated with prolonged neutropenia and thrombocytopenia even in patients who achieve a CR or CRh.

The data presented as substantial evidence of effectiveness for quizartinib therapy in the treatment of relapsed or refractory FLT3 ITD-positive AML are based on a single pivotal trial that demonstrated a 6.5-week overall survival benefit. The credibility of these results are challenged by the concern described by Dr. By, namely confounding imbalances between the treatment and control arms in patients randomized not treated and those censored early, and the impact on the

treatment effect by the imbalance between study arms in post-study therapies such as allogeneic hematopoietic stem cell transplantation that might affect survival.

Lastly, the lack of supportive evidence for other endpoints such as EFS, CR rates, or CRh rates detract from the confidence in the study results. We emphasize that none of these issues can be used to conclude definitively that quizartinib does not have activity in the proposed population. However, the uncertainties they introduce raise questions about whether this single study represents substantial evidence of effectiveness that meets the statutory requirements for marketing approval.

Bearing all of this in mind, we ask the committee to first please discuss whether the results of the OS analysis of study AC220-007 are persuasive evidence of effectiveness of quizartinib and the reasons for your opinion.

Second, please discuss the need for and feasibility of a contraindication for use of drugs that prolong QT via the complementary IKr channel

and the recommendation for administration of beta blockers to prevent arrhythmias as means to reduce the risk of life-threatening and fatal cardiac events resulting from IKs blockade if quizartinib is marketed.

And finally, the voting question for the committee is presented here. Do the results of study AC220-007 demonstrate that treatment with quizartinib provides for a benefit that outweighs the safety risks for patients with relapsed or refractory FLT3 ITD-positive AML.

This slide lists the members of FDA's multidisciplinary review team who are available for input in the event that the committee has any questions regarding the review of efficacy or safety. Thank you. This concludes the FDA presentation.

Clarifying Questions

DR. RINI: Thank you. We'll now take clarifying questions for any of the presenters. And remember, for this session and throughout the rest of the day to state your name in the record

before you speak, and if you'd like, direct your questions to a specific presenter.

We'll start with Dr. Halabi, and just wave at Jennifer or myself if you want to ask.

DR. HALABI: Susan Halabi. I have a question for the sponsor. Can you clarify why when you conducted for EFS analysis, how did the results end up being statistically significant? And more importantly, can you describe in the protocol how the assessments were done during the study?

MR. RICHARDS: First, I'll have Dr. Koch speak to how the corrected analysis was done as opposed to the original analysis of EFS.

Dr. Koch?

DR. KOCH: Gary Koch, biostatistics department, University of North Carolina at Chapel Hill. My only financial relationship with the sponsor is that I'm principal investigator of a cooperative biostatistical agreement that the sponsor has with the University of North Carolina.

The nature of EFS is that it has three components. One is the occurrence of response or

not, CRc response. The other one is how long that response lasts, and the third one is related to death. The issue with its analysis is that patients who do not have any follow-up to judge whether a response and occurs or not are not at risk for failing to achieve response, so they are necessarily censored. But the stipulation of the method is that anyone who actually was followed for response and failed to achieve it is going to be classified as having an EFS or then on day 1, the day of randomization.

The patients with no assessment are neither at risk for failing to achieve it, so they should actually be censored one day before the day at which patients who failed to achieve it are classified as having the event.

The corrected analysis, which is shown on ST-4, basically invokes that. It essentially censors patients with no assessments of response, because they were essentially censored early, are censored one day before the day at which patients who failed to achieve response are actually

classified as having a failure event. That essentially is what is happening.

So the corrected analysis is essentially removing the patients who had no data from the risk set so that you do not overestimate the EFS avoidance rate for the control group, and this then makes the two results consistent with one another.

The sponsor also did a resampling analysis, where for the patients that did not have any post-baseline assessments to judge EFS, they resampled them from the other patients to make a judgment as to what that analysis would do. It agreed basically with the corrected analysis.

DR. RINI: Dr. Lincoff is next.

DR. LINCOFF: Yes, to the sponsor. You've asserted, which to some extent, it potentially make sense, that the higher rates of stem cell transplantation in the patients on active treatment were in effect a consequence of better response or partial response, and that shouldn't be looked at as a deficiency in the ability to assess the effectiveness of the drug but is a consequence of

that.

Do you have any data that you can provide to help sort that out in a little bit more detail in terms of which patients went on to transplant in the two groups, to help support that assertion?

MR. RICHARDS: I can ask Dr. Levis to speak to this point. The study didn't have any a priori criteria in terms of which patients would be candidates for transplant. Dr. Levis may be able to enlighten us on this based on institutional standards.

DR. LEVIS: Mark Levis, Johns Hopkins University. This is obviously a complex issue for who goes to transplant and who doesn't. I'll start with some very basic numbers. Yes, there clearly were a group of patients who were selected for the low-intensity arm and then randomized to get low-dose ARA-C, who regardless, no one achieved a response and no one went to transplant.

It is my task as a clinician to assess who goes to transplant. The patient's there in my office, and I have to make a decision on that, and

a number of factors go into that. First, the patient's got to have a good performance status. Basically, they've got to walk into clinic virtually talking to me like they're looking like an outpatient. They have to have good organ function.

Their leukemia has got to be controlled. They can't have rising blasts. They can't have circulating blasts. They can have blasts, 11 percent or 1 percent. I'd prefer none, but that isn't the final decision on going to transplant. They've got to not be in essentially a wheelchair.

Again, a good example of this is a patient of mine who's on the control arm who got MEC, and her ejection fraction was reduced to 15 percent even though she got a complete remission. Hallelujah, you're in remission, but you can't go to transplant because you would not survive the transplant.

If you look at the patient's strata randomized to low-intensity treatment and they got LoDAC, we looked at those patients as not fit

enough to get any kind of intensive therapy like a transplant, and they got a treatment that did not improve them. They still had just as much leukemia after the treatment. Quizartinib would take those patients and very gently, in the clinic, make their blasts drift on down to where it was sort of controlling the blasts so that I can make a T cell swim up and kill it with a transplant.

All of this goes into play when I'm deciding who goes to transplant, and there's no question quizartinib was so reliable, I literally was scheduling the transplant on day 60 of starting day 1 of quizartinib because the patient would come in each week saying, "What are you doing about my transplant? Are you scheduled? I've got my donors lined up."

The patient who's getting induction chemo or salvage chemo is in the hospital, still dealing with infections, getting IV antibiotics, and is in no shape to go to transplant. And when they emerge, their organ function frequently is gone, so I can't transplant them.

So these numbers look very stark. We cheated somehow. We chose patients because we were biased. No. Actually, we have pretty clear institutional standards who goes to transplant. I can't just transplant anybody. I've got to choose according to our policies, and the quizartinib patients routinely would meet those qualifications. So that's why.

DR. RINI: Can I just ask maybe a quick follow-up to that? You just mentioned a number of things that are criteria for transplant: performance status, circulating blasts, et cetera. Are there actual data -- which is I think what was the question being asked -- are there actual data from patients in the trial saying that the 22 percent of the low intensity who made it to transplant had improvement in those parameters or met those parameters?

Do you know what I'm asking?

DR. LEVIS: No, I understand what you're saying, and there actually are no data. But what we do have I think is a very useful -- suppose we

were choosing patients just because I wanted to transplant them, and I'm cheating. I'm taking somebody who really isn't fit for transplant. If that were the case, then somebody who got a remission or a response from chemo would potentially do better than someone who got a response from quiz. In other words, I'm cheating and taking patients who really shouldn't go to transplant on quiz.

But this slide I think is very striking. This shown here is survival for patients who went to transplant on the study versus those who didn't. If you went to transplant from the chemotherapy arm, you did just as well as going to transplant on the quiz arm. So I think this at least illustrates that the decision for patients taking a patient on quizartinib to go to transplant is essentially the same as what was used for the chemotherapy arm. Their outcomes were better. But this is really the only hard data that can kind of support that.

DR. RINI: Thank you.

DR. SUNG: Sorry. Can I just respond

directly?

DR. RINI: Sure. Dr. Sung?

DR. SUNG: As a fellow transplanter, I do acknowledge that there are institutional standards, but I do also think that there is an art to selecting the right transplant. I have colleagues who will transplant patients that I won't, and vice versa. I do think there still remains the possibility that if you have someone who is aggressive and recruits patients to participate in clinical trials and study drug, that they may be more likely to take that patient to transplant, and then they have better results with transplant.

I don't disagree with you that the transplant results are equivalent, but I do think there is a possibility for bias there since there was no prespecified separation or analysis.

DR. LEVIS: May I respond?

DR. RINI: Sure.

DR. LEVIS: But if that were the case, if I'm taking patients who really shouldn't go to transplant, would you not expect the quizartinib

arm to be lower than the chemotherapy arm?

DR. SUNG: Well, in that case, you have transplant, which cures everything.

(Laughter.)

DR. LEVIS: Well --

DR. SUNG: Transplant cures all sins, of course.

DR. RINI: Dr. Hunsberger?

DR. HUNSBERGER: Sally Hunsberger. I just wanted to follow up on the EFS a little bit more. Dr. Halabi had asked about the assessment. How often is the assessment for EFS made? The assumption you're making, then, in your analysis was that if you didn't have EFS measured, they're going to do worse than the people who did have it because you're making it a day earlier. And if you put it at randomization, isn't that like excluding them from the analysis? I might be wrong. I'm just trying to think through.

MR. RICHARDS: Dr. Koch can address both questions.

Let me address your first question first.

This probably is a simple question. If we can have the slide up?

The assessments were made at screening for central testing, cycle 2 day 1, cycle 3 day 1, and at end of visit.

Does that answer your question?

DR. HUNSBERGER: So cycle 2 begins when?

MR. RICHARDS: Cycle 2 at day 1. Is that your question?

DR. HUNSBERGER: So you evaluate at day 1 -- they're randomized, and then you would evaluate -- when is the next time you would evaluate, day 1?

MR. RICHARDS: I'd have to invite Doctor Gammon to speak to that. He's more familiar with the assessment schedule.

MR. GAMMON: Guy Gammon. I'm a paid consultant of Daiichi Sankyo and a former employee of Daiichi Sankyo and Ambit Biosciences, the original sponsor of this study.

The assessment is at day 29? When it says cycle 2, day 1, it's the end of cycle 1, and

likewise, cycle 3.

DR. HUNSBERGER: So unless they died, the first time you could really have an event would be at day 29.

MR. GAMMON: The first time you assess response is at day --

DR. HUNSBERGER: Right. So you could censor people at day 29 rather than at day zero or day 1.

MR. GAMMON: I'd leave that question to Dr. Koch.

DR. KOCH: So achieving the CEC response is a good thing.

DR. HUNSBERGER: Right.

DR. KOCH: That's actually the objective. The failure event is failing to achieve a response. So a patient who had the assessments that have just been described and never achieved CEC response was, by convention, identified as being a failure on day 1. The patients who never had any assessments in the original analysis plan were identified as being censored on day 1 as if they were at risk for

failing to achieve response. But they were never at risk for that because they never had any assessments.

So the corrected analysis simply censored them on day zero, and that's the difference between the original analysis and the corrected analysis.

Now, the sponsor also did an analysis with resampling, and that's ST-7, where they imputed an EFS for the patients that did not have any follow-up to judge whether or not they would ever have a CEC event, and the results from that are shown on ST-8, which is the next slide, and that basically, by multiple imputation, produced a confidence interval for EFS if you did it as a stratified resampling from 0.6 to 0.98, and if it was unstratified, 0.6 to 0.99.

That's the distinction in the resampled analysis where the effort is being made to identify an EFS failure time for these patients agrees with the corrected analysis. And all the corrected analysis is doing is moving the patients who had no assessments to judge whether they had a response to

being censored one day before the first day at which a patient is classified as having an EFS event.

DR. RINI: You can go ahead, Dr. By.

DR. BY: I just want to clarify, I think the EFS analysis censoring at day zero is essentially throwing out the 18 patients that were not assessed.

DR. KOCH: Well, it's excluding them because they're not in the risk set. And the reason why the resampling analysis was done was to avoid that exclusion, so they actually could be accounted for in an analysis. The assumption of that analysis is that they would have EFS like all of the other patients who had data to judge EFS.

DR. BY: Right. We go by the ITT analysis, and throwing out patients who were not assessed actually harkens back to the issues that I've alluded to earlier in the presentation, which is the idea that knowing which arm you were assigned to leads you to either not receive treatment in the study or to be early censored, and in this case, it

is possible that not having post-baseline assessment is a function of knowledge of that treatment assignment as well. So it goes back to that.

DR. KOCH: The analysis that's not correct, however, is the analysis that was originally planned because that analysis operates as if those 17 patients were at risk to have an EFS failure event when they had no data with which to judge that. So the resampling analysis tries to identify what their EFS outcomes might have been had they actually had data. The corrected analysis essentially removes them from consideration. There are other types of resampling analysis that could also be applied to them, but what we presented is what we currently have.

DR. RINI: Dr. Klepin?

DR. KLEPIN: Heidi Klepin, Wake Forest. This is a question for the sponsor. I just wanted to circle back to the discussion around the relationship between quizartinib, being on quizartinib and getting a transplant and the

suggestion and the observed experience that possibly quizartinib resulted in the higher likelihood of receiving a transplant, so that being a potential outcome.

I know that the analysis wasn't done that way, but you mentioned you don't have data to show the mechanistic support of that with respect to some of the outcomes that we might look at that were mentioned. But I was wondering if you could show us the percent of patients who went to transplant in the quizartinib arm by CRc.

So if they achieved a CRc, that's those 48 percent of patients versus those quizartinib patients who didn't achieve that, so the 52 percent. The percentage of transplant just in that strata would be helpful.

MR. RICHARDS: Sure. Just a second.

DR. KLEPIN: Those strata.

MR. RICHARDS: Perfect. I'd like to ask Dr. Cortes to come and present this now since we do have it for the transplanted patients' best response.

DR. CORTES: Thank you. One important thing to remember is that to go to a transplant nowadays, we don't necessarily need a CR. We can transplant patients that are in CRi, or in CRp, or in CRh, in one of the responses, the recovery of the counts for these purposes, it's not as relevant.

We show this slide, TR-22, it shows I believe what you were trying to get to, which is the best response for the patients who were transplanted. As you can see, a large percentage of the patients who were transplanted did have a CRi. So CRi does get you to a transplant -- does give you that ability to go to a transplant.

The big imbalance in the transplant is that since we have such a big difference between the two arms in the probability of achieving a CRc with a CR, CRp, or CRi, we did get more patients to transplant with quizartinib mostly because they had that. Even patients with PR, sometimes we are more likely to consider them for a transplant because, after all, they may have 6 or 7 percent blasts, and

on a patient who has refractory or relapsed leukemia, that has not many other treatment options, that could be the best alternative that we have available.

Then we can follow up that with TR-25, and that shows that the patients who were transplanted with CRi, it is not a meaningless transplant. It is a transplant that is valuable. If you have a CRi and you get a transplant, you have a better outcome.

So in general -- then in conclusion, what I'm trying to say is that, yes, we did have most of the patients who went to transplant went to transplant because they had a good response, CRc and even some PRs. And certainly the patients who went with a CRi, which is the biggest group, did benefit from the transplant. So it was an appropriate transplant.

DR. RINI: Hold on one second.

DR. KLEPIN: The percentage that went to transplant that did not have a CRi or CRc, was that -- I'm just trying to get that breakdown.

DR. CORTES: We can go back to the TR-22, please. It's a small percentage of patients. You can see there are 11 patients in the quizartinib arm and 3 patients on the ITT arm. That's the bottom row on this slide.

DR. RINI: Dr. Sung first, and then --

DR. SUNG: Sorry; just responding to that. Again, the fact that you have 25 patients in this quizartinib group going to transplant who did not fit the traditional CRc definition for transplant criteria, for transplant, and only 3 in the salvage group does speak about the potential of bias to me in the absence of prespecified criteria for who goes to transplant or not.

I'm not saying there is bias. I'm just saying normally in a study -- I'm a transplanter. If you can get patients to transplant, I think about that as a good thing. But without prespecified criteria, I can't interpret this data, and I can't say are you getting more patients to transplant because quizartinib is good and it works, or are you getting more patients to

transplant because of potential bias? I just can't say.

MR. RICHARDS: Dr. Levis, would you like to respond? And then you can go. Do you want to respond first?

DR. RINI: Let him respond.

DR. LEVIS: Yes. On my counter, how would you like it if the trial ordered you to transplant a patient based on trial criteria? In other words, as a transplanter you're going to use your institutional criteria, so we didn't stipulate that any institution had to or could not transplant a patient.

DR. SUNG: So two things. One option would be -- I guess you couldn't necessarily blind patients in the study because you're doing an oral drug versus low-dose Cytarabine, but you could have each institution prespecify their criteria. So on an institutional level, they would already prespecify and say, okay, this is how we transplant patients at Duke, versus Hopkins, versus et cetera.

DR. LEVIS: I will concede that, but that

would be a challenging thing to do, given we barely know -- can make an agreement at times at our own institutions, as I'm sure is the case at your institution.

DR. RINI: Thank you. Dr. Taylor?

DR. TAYLOR: I guess I really just had kind of the same question, is that you said the CRi is a good criteria to consider transplant. Then why was there such a discrepancy in the quizartinib versus the salvage? I guess that's what you were talking about. I still think -- I'm surprised there weren't more from the salvage group that went to transplant if CRi is good enough criteria.

MR. RICHARDS: I think Dr. Levis might be able to clarify that point.

DR. LEVIS: Again, I apologize. It's hard to convey this. But a patient who's gotten chemotherapy usually has a lot more going on than just the patient who's gotten the oral drug. They frequently are coming in with organ dysfunction, cardiac dysfunction, active infections, which simply wasn't the case with

quizartinib.

We didn't entirely expect that this was going to happen, but as the clinician with this patient in front of you, what you're trying to do is cure -- this is my patient. I don't care about a trial. I don't care about the drug. The patient is asking "How am I going to get cured?" "Well, I'm going to transplant you." "Can I be transplanted?" "Yes."

The quizartinib patients would come in well, basically, and that's a patient that has a performance status and meets the criteria. So a CR patient who's got that from chemotherapy is frequently just not in the physical shape to undergo a transplant. I don't have any specific criteria other than that.

DR. TAYLOR: So would you say that quizartinib is a good tool as a bridge to transplant? Is that what you're saying?

DR. LEVIS: Yes. FDA didn't like that term.

(Laughter.)

DR. LEVIS: As a clinician, that's what we use it as. In fact, I do not regard -- a patient with relapsed/refractory AML, most of these patients are going to die. They're going to succumb to this disease. I'm only going to get 1 in 5 through this. In fact, what's interesting about CRi, why is CRi good enough to go to transplant versus a CR?

A CR with a drug like gilteritinib or chemo would still often lead to what we call measurable residual disease. I can still detect some of the disease in their marrow. Those patients going to transplant with a CR that I can still detect the FLT3 mutation do identical to someone who goes into transplant with an NR, or a PR, or a CRi, according to published studies. And I think Dr. Sung will agree with me, there's no difference.

So I don't distinguish a CRh, a CR, a CRi. It's really more do I have a donor, a performance status, organ function that determines whether they can go to transplant. I would love a CR with no measurable residual disease. You can't count on

that in this setting.

DR. RINI: Thank you. Dr. Nowakowski?

DR. NOWAKOWSKI: Greg Nowakowski. I have a question for the sponsor. Twenty-three percent of the patients which were randomized to the control arm, did not receive the therapy in this arm, can you comment what therapy they actually received in the salvage setting, or are they just on palliative care? What happened to those patients?

MR. RICHARDS: I'd like to invite Dr. Cortes to speak to what likely happened to those patients, subsequently.

DR. CORTES: Thank you. We don't have the information for all the patients because they withdrew consent, and it's not easy then to obtain that type of information. We were able to take survival, but this is more than we can obtain from public records and other elements.

We do have a little bit of information that I can show you on EF-1 or 2. What that shows you is some of what you would expect. Some of these patients decided to get the chemotherapy, the same

chemotherapy but off protocol. Protocols have restrictions and requirements that patients don't necessarily like. If they're going to get the standard chemotherapy, they might as well get it closer to home or something like that.

Others got FLT3 inhibitors, among those that we have information, a couple of them, FLT3 inhibitors. Other protocols were available. There are drugs that you can prescribe off label, sorafenib, for example, that people are used to prescribing. I suspect that that split carries on to those 23, but that's speculation because I don't have information. But I suspect it's a split between the same standard chemotherapy off protocol, and some got FLT3 inhibitors on another protocol or off protocol.

DR. NOWAKOWSKI: Was the retention of the patients in the study the same across the center, or was the center a specific issue that in your analysis?

MR. RICHARDS: No, it was distributed. There was no center effect.

DR. RINI: Thank you. Dr. Sung?

DR. SUNG: This is actually a two-part question. Looking at the sponsor brochure on page 87, it notes in the quizartinib group that -- sorry. Looking at page 121, it notes that, "Although generally the same, TEAEs were grade 3 or greater in both groups. Proportionally more female patients than male patients were reported with grade greater than or equal to 3; ECG QT prolongation, 6.9 percent versus 1.5 percent, respectively."

I'm not a cardiologist, so I'll defer to my cardiology colleague. I do understand that, in general, women are more likely to develop QT prolongation than men, especially drug-induced QT prolongation. As I recall, it's of a 2-fold increase as opposed a greater than 4-fold increase seen in these results.

I also noted that on page 128 of the sponsor briefing document, they noted there was a 54-year-old woman who developed cardiac arrest in the setting of grade 3 hypokalemia while on

quizartinib, again, hypokalemia being common in these patients.

I wonder, it didn't comment on the other cardiac events or deaths, what the gender split was, and if there may be a concern that women may be at greater risk, especially from cardiovascular complications with this drug.

MR. RICHARDS: I'd like to invite Dr. Choi to speak. We did run a covariate analysis, and in the covariate analysis, no distinction by sex, but I'll let Dr. Choi run us through that analysis.

DR. CHOI: Youngsook Choi, clinical safety and pharmacovigilance. In the subgroup analysis by sex, generally the treatment-emergent adverse events were quite similar between sex, and based on the categorical QTcF findings, you were right. There were higher rates among women than men. But as you also point out, there is a higher baseline among women than men.

In our CQTc ER analysis -- if I could have the prior one back. In the CQTc ER analysis -- sorry. I'm having a bit of trouble.

In the concentration to CQTc analysis, sex was not found to be a covariate. And if I could also have Dr. Kowey come up and comment on potential sex and other factors.

DR. KOWEY: My name is Peter Kowey. I'm a cardiac electrophysiologist and arrhythmia doctor in Philadelphia Jefferson Lankenau Heart Institute. I am paid by the sponsor for my time and my expenses.

Yes, you're absolutely correct. The women are more susceptible to QT prolonging drugs as well as to the chances of developing a malignant arrhythmia from QT prolongation. The magnitude of that differences is rather small, but it's consistent across lots of trials.

But I'm very grateful to have the opportunity to make a couple of other comments about the QT and how it's been measured. There are several things that you heard that I think need to be clarified. One is the magnitude of the QT effect size that you're seeing here is over 20 milliseconds, but it's not unprecedented for drugs

to have approval with QT effect sizes like that, especially in the oncology arena.

The other thing that you need to know is that you heard about heart rate and concomitant use of drugs that block IKr. The data clearly show, in this particular project, that there was no interaction for con-meds with regard to QT prolongation; that is there were just as many people who got con-meds who had the same amount of QT prolongation as if they didn't get the IKr blockers.

They also need to know that heart rate was not a covariate for changes in QTc. In fact, curiously, people who receive beta blockers in this trial experience actually had a higher chance of having a QTc greater than 500 than people who didn't get beta blockers. Extrapolating from a congenital long QTc syndrome, such as long QT1, to and acquired long QT syndrome is hazardous.

The other thing that you need to know is that there is a precedent for IKs blockade. It's a drug called azimilide, which was actually reviewed

by the FDA in rather detail several years ago, a relatively pure IKs blocker that behaved exactly the same as we would have expected from an IKr blocker in human beings. The data that you heard about this morning differentiating IKr from IKs is almost all based on preclinical information, guinea pigs and rabbits.

So I'm really grateful for the opportunity to be able to say that I think after going through these cases very carefully, there was QT prolongation, and some of the cases of cardiac arrest and death that you saw did occur. But it did not occur at a level of greater than 500 milliseconds, and 500 milliseconds is the value that we really care about.

Then finally, there was a statement made in the FDA slides that somehow you can develop a cardiac arrest in a proarrhythmia without a QT prolongation. I'm having a hard time understanding that. Torsade by definition is an arrhythmia, a polymorphic ventricular tachycardia associated with QT prolongation.

Not having QT prolongation means it's not torsade, and we did not detect that signal in QuANTUM-R actually worked. And the reason we didn't is because the company implemented a strategy that actually worked. The risk mitigation in QuANTUM-R, and as you saw, there were no cases of torsade or arrhythmias that we suspect to have been torsade in QuANTUM-R with the risk mitigation strategy that was put into place.

I really appreciate the opportunity to opine, and I apologize for going a little over.

DR. RINI: Appreciate it. Thank you.

Dr. Lincoff?

DR. LINCOFF: Michael Lincoff from Cleveland Clinic. I'd like to go back to the statement of the 23 patients in the control arm who were not treated, randomized but not treated, that they were withdrawn consent. In general, when we expect a proportion -- and it may be higher in the control group and in an open-label trial. We expect proportion patients not to be on the treatment regimen, but we really, in general,

fundamentally with clinical trials, try to get full data on all these patients.

So what was it about your trial design or the way that it was conducted that that 23 of 23 patients who chose not to take the salvage chemotherapy also withdrew consent? Because if that was the way the protocol was written, then I say that's a flaw in the protocol that really now you have to deal with the consequences.

MR. RICHARDS: I can invite Dr. Cortes to speak to the milieu, to the conduct of the study when the withdrawal consent happened.

DR. CORTES: Thank you. Jorge Cortes from MD Anderson, in Houston. I think part of what happened with this study is that by the time the study was initiated, the benefit of the FLT3 inhibitors, and quizartinib in particular, there had been already 3 or 4 studies with quizartinib, and some with other drugs, that showed that there was some benefit for these drugs.

They were not randomized, and they were single arm, et cetera, as I described on the phase

2. Some of these drugs were available for patients, either on clinical trials or off-label prescription. So that made -- despite the efforts of investigators, and the sponsor, and everybody, some patients could choose to go to try to get one of those drugs. I think mechanistically that became appealing, and based on the data that was available from some of these other studies, that made them do that.

So I think that the study was well conducted and tried to minimize this, but it wasn't available, and you have to respect the patient's decisions.

DR. LINCOFF: Can I ask a clarifying?

DR. RINI: Sure.

DR. LINCOFF: But that's really not what I was getting to. Of course you can't stop a patient from asking for or a clinician for giving what they think is the best therapy. So we commonly have, as part of a trial, patients get something different for whatever reason. But we generally try to follow those patients and get information on them.

We don't require that if you don't do what we tell you, we kick you out of the trial, or you, de facto, have withdrawn consent.

So again, why was the structure of this that you got no further data on what else they got, et cetera, aside from survival that you could get from other statistics, on those patients who chose, or either their physicians chose, to put on another therapy?

MR. RICHARDS: Sure. I can invite Dr. Gammon to come and speak. Part of this does relate to the additional data that we got in the follow-up, which we were able to get a subset of those patients that were censored. Some of those patients, we did try to find them, and we were prevented by local laws and regulations. They said no. They said because they've withdrawn the consent, even though our understanding of the consent is, yes, we can follow, they disagreed in XYZ countries.

MR. GAMMON: Guy Gammon, consultant for Daiichi Sankyo. Obviously, it is important,

whenever possible, to get as much follow-up data on patients who withdraw from the study as possible. When we realized that some patients were withdrawing in the study, we made numerous efforts to communicate with all investigators, and specifically investigators when they had a patient who did withdraw, to emphasize the importance of the need to have a control arm and the integrity of the control arm, and to, during the consent process, make sure the patient understood the chance of being randomized to chemotherapy.

Also, that even if they withdrew from therapy, I didn't mean that they would necessarily -- they could still be followed. A lot of efforts were made to collect as much follow-up data as possible, and we have follow-up survival data on 21 of the 28 patients. But as you indicate, I wish we were able to get more.

DR. RINI: Thank you. Dr. Sung?

DR. SUNG: Tony Sung from Duke. I'm sorry to turn my back to you. Following up on response to my question earlier about the gender differences

and cardiac risks, you had mentioned the bradycardia associated QT prolongation and sex hormones do modulate cardiac, potassium, and calcium ion channels involved in ventricular repolarization. Estrogen can facilitate bradycardia induced QT prolongation.

So I was wondering if you had looked at -- again, just delving further into those male versus female differences -- either estrogen levels or maybe proxies for estrogen such as oral contraceptive use, which we often give in women who are menstruating, and we're concerned about bleeding or age of the female and potential estrogen levels, and how they may impact their cardiovascular risk.

The other part of my original question was also what I wanted to know is the patients who had sudden cardiac death across all quizartinib studies, what is the ratio of male to female, both in the sponsor and adjudicated analysis of cardiac deaths, as well as in the FDA adjudicated analysis of cardiac deaths?

The reason I bring this up is, again, interestingly, although females are at high risk of having QT prolongation, males are at higher risk of developing sudden cardiac death. So even if you're seeing similar rates of sudden cardiac deaths in males and females, that seems a little surprising since males should be twice as likely to have cardiac death.

MR. RICHARDS: I'd like to invite Dr. Kowey to speak to this point. As he approaches the podium, I can tell you that we did do a covariate analysis, and con-meds was not something that came up as a significant variable.

Dr. Kowey?

DR. KOWEY: I have to go back and look at that specifically. My recollection is that it was pretty close in terms of male/female, but I'd have to look at the numbers. If you'd like, we could look at that at the break and come back and give you the exact number.

DR. SUNG: Sure. I guess what I meant is if it's pretty close, males should be dying of

sudden cardiac death at twice the rate of females.

DR. KOWEY: Yeah, yeah.

DR. SUNG: So if the rates are pretty close, that means females are dying at an increase, a greater than expected rate.

DR. KOWEY: Your point is extremely important. I don't want anybody on the committee to believe that this drug, under some set of circumstances in some people, is not going to cause torsade. It is. It's a QT prolonging drug, and it's going to cause an arrhythmia, in some patients, at some time, under some circumstances, perhaps more commonly in women than in men.

We're not arguing about that. What we're saying is you have a drug that prolongs the QT interval. You did your early studies. You gave big doses. You weren't paying a whole lot of attention maybe because you weren't sure what the effect size was, and then you saw it. And then you said, no, we're going to cut the dose back. We're going to start at a lower dose. We're going to monitor the patients. We're going to limit all the

drugs. We're going to do all the things you're supposed to do, maintain electrolytes, and then we're going to see what happens.

What happened -- this is a really interesting turn in this clinical development program -- is they have data now in a very large randomized trial saying that we did it. They didn't have any torsade cases. And when we went back and looked at those cases of people who died, their QTc's were not at a level where we would have suspected; it was torsade, and that's to me a very unique aspect.

With regard to the hormonal stuff, it's very interesting because people have tried to manipulate hormones, as you can imagine, in various clinical -- preclinical as well as clinical models. The only thing that seems to work, that works consistently, is testosterone; that is, administering testosterone in people or to animals seems to attenuate the QT prolonging effective of IKr blockers. I can't say much about IKs blockers.

So there clearly is a hormonal dependency,

but manipulating estrogens and progesterones don't seem to be as effective as manipulating testosterone.

Does that help?

DR. RINI: Thank you. We're running short on time. Dr. Hoffman?

Did you want to comment about that? Sure, go ahead.

DR. KRAUSS: Aviva Krauss, FDA. I just want to answer your question in terms of our adjudication of the deaths. Looking at the integrated safety population of relapsed/refractory AML, it was 7 deaths altogether; 4 were male and 3 were female. So the numbers are small; more males.

On the ongoing phase 3, the randomized trial of quizartinib versus placebo in combination with intensive chemotherapy, there were 5 cardiac deaths as I stated. One of them, the sex is unknown, but the other 4 were all male.

DR. RINI: Thank you. Dr. Hoffman?

DR. HOFFMAN: Either for Dr. Cortes or Levis. What would you say the advantage this drug

will bring to the table compared to the availability of gilteritinib?

MR. RICHARDS: I'd like to invite Dr. Levis to address this first.

DR. LEVIS: Mark Levis, Johns Hopkins University. I will confess, I'm deeply involved with the development of both drugs and like both of them, but they are very different, and would politely ask you, could I please have this one, too? But they are very different drugs. It's kind of interesting; in fact, I find it very interesting.

Shown here are these funny chi-nome [ph] plots that we look at kinase inhibitors with. For those of you who aren't familiar with this, the background spiky thing is actually every kinase in the human genome, 500 or so, and the ability of the given drug to inhibit that kinase is represented by a red ball. The bigger the red ball, the more it inhibits it.

A so-called dirty drug, like the one up in the left corner, lestaurtinib, inhibits everything

in the genome. And if you look down at the opposite end of the spectrum, quizartinib, pretty much focuses just on the FLT3 family, if you will. This activity also confers its potency.

So if you look at gilteritinib, the one you referenced, up in the upper right, it's actually a pretty dirty drug. Mind you, I'm very fond of gilteritinib, and I'm going to say mean things about it. But in fact, I like it. It complements quizartinib and vice versa.

Gilteritinib, by virtue of its being what we call a type 1 and less selective, lacks potency, and we actually do find that clinically. Quizartinib focuses just on the FLT3 family. You get a very rapid specific response.

Gilteritinib, a slower response, longer duration of response. The mechanisms of resistance are different. We know that, gilteritinib, you're going to get a RAS mutation that's going to make you resist it. With quizartinib, you're going to get a FLT3 TKD mutation, usually pretty quick.

So the FLT3 TKD mutations come out rapidly,

which is why the responses are shorter; the duration responses are shorter with quizartinib, and a little longer with gilteritinib. To get to the response takes longer with gilt. So I actually had a hard time getting those patients to transplant. They weren't quite ready. Their blasts were still kind of going down, and the end result for both drugs was the same.

If you look at the survival curves for both -- and you're talking about a 55-year-old patient, they're less interested in give me 2 more months. They want to know what you're going to do to cure them. The results are the same with both drugs. Quiz will work I think in gilt-resistant patients and vice versa. I might choose quiz if I'm going to move a patient rapidly to transplant and I've got the donor lined, because it's going to be more reliable.

On the other hand, if there are going to be delays, or if there's a preexisting FLT3 TKD, no way I'm using gilt -- I'm sorry. No way I'm using quiz; I'm going to gilt. If there's a preexisting

RAS mutation, I'm not using gilt; I'm going to quiz.

I want choices. I've used both of these drugs. I really can't distinguish the two. They both work. They each have their warts, gilt a little less potent. It's caused me LFT abnormalities. I'm definitely having that as a problem; take that into account when you're going to transplant. We don't like elevated liver enzymes.

So these drugs complement each other. I will use both of them. I want both of them. I regard them pretty much as equal. And I think going into the future, we're going to be able to use them. I don't want to treat these patients with one drug. We're already doing multiple trials where we're combining these drugs with other agents, folding them in.

I think quiz will be better up front. I think gilt will be better perhaps as a maintenance drug afterwards, but this all remains to be worked out.

DR. RINI: Thank you. Much like this morning, we have more questions and less time. We're going to do a 10-minute break now, and then we'll come back and do the open public hearing. We just have about three more questions, and then we'll proceed to the discussion. So we'll take a 10-minute break. It's 3:22.

(Whereupon, at 3:22 p.m., a recess was taken.)

Open Public Hearing

DR. RINI: Both FDA and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationships you may have with the sponsor, its product, and if known,

its direct competitors.

For example, this may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have such relationships. If you choose not to address this issue, it will not preclude you from speaking.

FDA and this committee place 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 are 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 and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by myself. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself, and state any name and organization you're representing?

MS. SCHILDER: My name is Dorothy Schilder. I do not represent any organization. I was brought here, paid for by a car service. That's the only thing that was paid for me.

I thank you for this opportunity to speak to you today and share my story. On December 16, 2011, at age 47, I left my exercise class to go to a doctor's appointment. Having had a series of minor but nagging symptoms, such as bruising, rash, sinus infection, and feeling generally tired, I expected my doctor to tell me I had an infection and prescribe a course of antibiotics. I did not expect to receive a diagnosis of acute myeloid leukemia, and be admitted to the hospital three days later, to begin a 21-day round of intensive HiDAC chemotherapy.

Subsequent to my release, I began a grueling 4-month course of additional chemotherapy, which I was told was the gold standard of

treatment. Throughout my chemotherapy, I suffered severe side effects. I experienced chronic nausea, vomiting, diarrhea, bleeding, excruciating headaches, mouth sores, loss of appetite, loss of taste, dry mouth, drastic weight loss, bruising, bone pain, neuropathy, hair loss, lethargy, neutropenia, just to name a few. And I suffered two infections that required week-long hospital stays.

Upon my completion of treatment in May of 2012, I was deemed to be in remission, but shortly thereafter, I developed a large rash on my neck, and my follow-up blood work showed that my platelets were plummeting. I had relapsed. I was told by my Kaiser oncologist there was nothing more they could do.

Fortunately, my oncologist had been in contact with Johns Hopkins. I was admitted to Johns Hopkins Hospital in July of 2012. It was there that my genetic testing results confirmed I had AML with FLT3 ITD. Despite conventional treatment with extensive chemotherapy, my relapse

was all but guaranteed with this genetic mutation, and my chances of survival were near zero.

At Johns Hopkins and after an unsuccessful trial with another drug, I met Dr. Mark Levis in August and was introduced to his clinical trial using quizartinib. In September with this drug in tow, I was able to leave the hospital, where I had been for months, and return home to be with my family; to be with my husband, my 10-year-old son, my 12-year-old daughter, my 85-year-old mother, and my father, who was 100 at the time.

I did so well with quizartinib that I was able to obtain remission and qualified for a bone marrow transplant. I reentered Johns Hopkins on Halloween Day, had my transplant on November 6, and on January 5, 2013 I was released from the Johns Hopkins inpatient/outpatient facility, and I went home.

During my entire treatment with quizartinib, I never experienced any other negative side effects. All my numerous EKGs were normal, my previous symptoms resolved over time, and my lab

work was normalized. Clearly, I was well enough to be selected for, undergo, and recover from bone marrow transplant with quizartinib.

The one wonderful side effect I did experience so far from treatment with quizartinib is life, this beautiful, healthy, long life. This drug works. It's lifesaving. I'm proof. I'm here. In fact, it seems to me that the only negative side effect from this drug would occur by not taking it.

I urge you to approve the use of quizartinib and prevent the seemingly certain and unnecessary death for patients like me who would be denied its use. Thank you very much.

DR. RINI: Thank you. Speaker number 2, can you approach the podium?

DR. SRINIVASAN: Thank you for the opportunity to speak today. My name is Dr. Varuna Srinivasan. I'm a physician with a masters in public health from Johns Hopkins University. I'm speaking today as a senior fellow with the National Center for Health Research, which analyzes

scientific and medical data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug and medical device companies, so I have no conflicts of interest.

Let me start by saying that we understand that AML with positive FLT3 IDT is a deadly disease. However, we share concerns expressed by the FDA about the efficacy of the drug quizartinib. We question why quizartinib was compared to chemotherapy rather than to one of the treatments in the same drug class or even placebo. If physicians believe that this is a disease that relies on multiple drugs, it might be helpful to understand how quizartinib will perform in the context of other drugs from the same class.

While difference in overall survival was significant, a more important indicator to the patients and their families, event-free survival was not. Additionally, the sponsors provided no information about quality of life of patients on quizartinib compared to chemo. Quality of life is

especially important considering that this treatment is neither a high success rate for overall survival, nor a high success rate in terms of complete remission.

The FDA also reported 1 to 2 percent of quizartinib patients died from cardiac related causes. The unique and understudied mechanism of action of this drug on the potassium channels of the heart make this seem fairly dangerous for some patients, potentially leading to arrhythmias and cardiac arrest. Doubts still remain about which patients are most likely to die.

Patients with this disease do not live very long on average after diagnosis. Current treatments with chemotherapy often leaves patients with low quality of life with an extension of only a few months as part of their overall survival. We need treatments for this deadly disease, but we need to know if a new drug is actually proven to be efficacious.

While it appears that there are some patients who seem to have benefited from this drug

with minimal to no side effects, we can't help but wonder if these patients are outliers. The fact remains that we still do not know the actual profile of persons who stand to benefit from this drug, keeping in mind the facts presented by the FDA experts today.

Are we willing to gamble that all AML patients in the real world will respond in a similar manner? At the very least, we asked the sponsor to determine which patients are most likely to benefit from the drug and which patients are most likely to die from cardiac toxicity. We urge the panel today to consider these points while discussing and voting. Thank you.

DR. RINI: Thank you. Speaker number 3.

MS. LEWIS: Good afternoon. My name is Patricia Lewis. I usually go by Pat, mom, or grandma. I am here today with Stan, my best friend, husband, and last four years, my caregiver. I want to thank the Food and Drug Administration for holding this open hearing and allowing patients and others to tell their story. I also want to

thank Daiichi Sankyo for their development of quizartinib and help share the expense for my trip from Michigan. Without them, I would not be able to be here today.

I'm a leukemia patient and a stem cell transplant patient. Our journey began February 22, 2015 when I was diagnosed in a local ER with acute myeloid leukemia, and within 6 hours was on the cancer floor with traditional chemo IV. My white blood count was 126,000.

In July of 2015, I went to University of Michigan Hospital in Ann Arbor for the transplant, where I received more traditional chemo, and then a day of rest, and then given my brother Tim stem cells. I spent 5 weeks in the transplant unit before my white blood count finally got up to 700, and I was released to a nearby hospital-approved apartment for two more months. Stan gave me daily IVs, kept track of my many meds, and several weekly visits to the U of M clinic in the hospital.

Within 3 months, Halloween of 2015, my blood count tests revealed my leukemia had

returned. One of the doctors told me I had a very stubborn FLT3. That's when we met Dr. Dale Bixby, Department of Internal Medicine, Division of Hematology and Oncology, and was told about quizartinib and the trial program. Dr. Bixby entered us into a computer drawing, and we were blessed enough to be 1 of 3 chosen.

I was taken off for 50 days within 2 months because of a serious reaction to the highest dose of the regimen. On March 11, 2016, my blood work showed the leukemia came back. Dr. Bixby put me back on quizartinib and eliminated the leukemia within days.

To this date, the leukemia has not returned, and I have been in remission for 3 years next month. I remain on quizartinib 20 milligrams, which seems to be working great for me with very few side effects. I have been blessed through the entire journey with an excellent husband and caregiver, who has met every challenge head on. I have also been blessed with the best doctors and one of the best hospitals to fight leukemia.

The quizartinib has allowed me to attend my oldest grandson's graduation from Michigan Tech University with an electrical engineering degree, move to North Carolina, get married, and start their life. It has allowed me to see my son get married in downtown Chicago to a wonderful girl.

I am able to live a relatively normal life with just a few side effects, mainly from the bone marrow transplant. I am on 19 pills a day for maintenance. I remain on quizartinib because it is still in study drug form. If I chose to stop the pill and the leukemia came back, I could not get back into the study program.

Experience with both induction therapy and therapy treatment with quizartinib has given me a perspective of the quality of life with both treatments. There is a huge difference. My four traditional treatments involved a hospital stay with many side effects and cost to insurance and co-pays to the patient. Also, some patients would need assisted living. I was blessed enough to have my husband and be able to go home.

The quizartinib gave me a chance at a normal life at home while taking treatment and being self-sufficient as possible. As an active participant in family life, there is much less burden on my caregiver. I would not be here today if I had to remain on traditional chemotherapy. It's just too degenerating on the body.

My prayer is that this pill will be available and approved to oncologists everywhere to help acute myeloid leukemia patients that do not have access to the drug study and my quality of life. Thank you again for this opportunity.

DR. RINI: Thank you. Speaker number 4?

MR. OH: Hi. My name is Justin Oh, caretaker and son to my mother, who was diagnosed with AML.

MS. OH: My name is Chung Oh.

MR. OH: About 2 and a half years ago -- my mom's been an active, healthy person all her life -- I received a phone call from my sister that she had just collapsed out of nowhere. I guess the pessimistic side of me said we need to go to Penn,

University of Pennsylvania -- thankfully it's in our backyard -- and within 24 hours received a diagnosis that she had AML, FLT3 ITD positive.

At the time for me, it was basically hearing a death sentence for my mother. It was hard because 5 grandkids all under the age of 5 at the time -- I've got three; my sister had two -- she was set to retire and live the American dream, and immigrating here 30 years ago, this wasn't the way it was supposed to end, is what I thought. But my mother's a fighter, so we started 7-plus-3 induction treatment right away.

Mom, how did you feel with the 7-plus-3 when we started chemotherapy?

MS. OH: Physically, I was very tired. I got fever, slightly nausea and vomiting, but the medicine helped me. My hemoglobin and my platelet was very low, so I got blood and platelet transfusion I think about 30 times during treatment.

I know AML FLT3 is very aggressive and poor progress, difficult to treatment, and not many

medications for me. So at that time, anything, any medicine, I want to try. So the doctor introduced quizartinib. I signed right away, and then medicine, I think is a mild side effect.

I was able to take the medicine with induction 7 to 3 days, I was a very active lady, so I said I'm going to stay active before I got diagnosis. At 6:00, I get up and make the bed. I run to the nurse station, 1 mile every day. I ask a young patient, "Come on. Follow me. We have to go."

Every day, I took a patient -- I was the leader. I know I'm a petite size, but I'm a mother and I'm a grandmother. So I know God gave me strength. I was minding them with Mighty Mouse; so Mighty Mouse can do it.

(Laughter.)

MR. OH: Yes, very inspiring, and it was funny because I had read a lot of articles on quizartinib, John Hopkins, as anyone would do. And I absolutely believed it was a drug, a bridge to transplant. I don't believe my mother would be

here with us today without quizartinib. Again, when I think about the induction 7-plus-3, the HiDAC, and the other things that her body tolerated, quizartinib, again, I would say the side effects, at least in my humble opinion, were pretty moderate, just like a little fatigue and metallic tasting.

MS. OH: Yeah, yeah, funny tasting, kind of a metallic. My appetite has decreased, but the doctor said, "Chung, you have to make 100 pounds. Right now, it's 82 pounds." So I got 3 meals, 2 snacks every --

(Laughter.)

MS. OH: -- a 2 to 3-hour drink. So I made 85 pounds, so doctor said, "Okay, you can do this." I did it.

MR. OH: At the end of the day, I heard a lot about overall survival, EFS, and all these statistics that all the physicians here look at, but what quizartinib represents to us and the fellow patients in this room -- the pollen count in here is pretty high, I think --

(Laughter.)

MR. OH: -- is hope. There's was no cure yet today, so we need these kinds of therapies because hope and faith is what got us through and our families through this. And again, wholeheartedly I want to say thank you to the company, the physicians that have studied this drug, the patients and the caregivers in this room because, again, an unbelievable struggle to survive when you've got this kind of disease. But drugs like these provide that hope and that spark to keep moving forward. Thank you.

MS. OH: I'm pleased that FDA -- approval for quizartinib for me and other patients. Thank you.

Clarifying Questions (continued)

DR. RINI: Thank you both.

The open public hearing portion of this meeting is now concluded and we'll no longer take comments from the audience. We're going to take 10 minutes here to finish up some questions from the panel.

Ms. Preusse, you can go. Did you have a question? You want me to go?

Actually, I think I'll add a question, and it's for both the sponsor and I think maybe for FDA. The elephant in the room that we haven't talked about is obviously the survival benefit. And I heard in the different presentations different sensitivity analysis, and I was told that there were different assumptions.

The sponsor's conclusion is that the hazard ratio is fairly consistent at 0.76 with the upper bound close to 1, but FDA's conclusions were different in terms of the hazard ratio. So maybe help me as a non-statistician to understand the differences between the analyses because I think that's really the heart of the issue here. I don't know who wants to start.

MR. RICHARDS: Sure. We can start. I'd like to invite Dr. Koch to come up and walk us through. I think one important thing -- there are probably two important things to note, as Gary approaches the podium. The estimate for

quizartinib is reliable and robust, especially the updated. We're only missing one patient. So that estimate is robust.

What we're talking about is the effect size on the salvage chemotherapy arm and the assumptions of how that salvage chemotherapy arm behaved in the absence of data and with the updated data, and then with the sensitivity analyses.

I'll allow Dr. Koch to speak to the juxtaposition of those sensitivity analyses.

DR. KOCH: The sponsor did three sensitivity analyses as was indicated in the core presentation. One of them resampled the 28 randomized, not treated patients from the 94 that were randomized and treated. That analysis addressed the question of if the randomized not treated patients off study got something less effective than what their assigned treatment was, what would their outcome potentially be? The 28 are sampled from the 94, and that's the question that's being addressed by that analysis.

The second question that they addressed

related to if the randomized not treated patients actually had better treatment than what they might have gotten with their assigned therapy and 21 of them were followed, what would have happened if the 7 had outcomes like the 21? And again, that was reinforcing as well.

The FDA analysis -- and I can try to use an FDA slide if I'm able to have it; I think it's FDA-16 -- sampled these patients from the randomized treated patients, whose survival was at least 8 weeks. If you look at the bottom row, the analysis that the sponsor did, you see where the 7 are being randomly sampled from the 21 on the bottom row. The other one the sponsor did is you take all 28 on the bottom row and you sample them from the 94 that are to the right on the bottom row. That's what the sponsor did.

What the FDA did was illustrate it on the next slide of the FDA, where they sampled from the patients who were having survival that was at least 8 weeks. What that did not allow for, for the randomized not treated, was the fact that for the

randomized not treated, had they been treated, they could have been an early death.

Also, if they had been treated, their survival could have actually been less than what they were observed to survive on their on-study treatment. Basically that stress test, which is of use to do, to understand where it takes you, optimistically imputes a survival time for the control group.

Now again, the quizartinib group doesn't have really any missing data. Only one patient was censored before 8 weeks. There were 4 randomized not treated patients. They were all followed, and they actually died relatively early. So the quizartinib group gives you a survival curve in which one can have a moderate level of confidence.

The sponsor has done relatively neutral imputations, one being the sample of the 7 from the 21, the other being the 28 from the 94, to try to understand what the implications of that would be. The FDA has done a stress test where they basically sample the patients who were randomized and not

treated from the survivors of at least 8 weeks, and that creates a somewhat better profile for them than what they might have gotten had they gotten chemotherapy because, among other things, had they gotten the chemotherapy, their survival could have been less than what they were observed to have, and also they could have been an early death.

DR. RINI: Dr. By, do you want to comment?

DR. BY: Sure. The characterization of how we sample by Dr. Koch is correct. I would just like to point out that originally when the data came in, there was a lot more patients early censored, and after the survival update were down to 9, early censored in the chemotherapy arm.

With the survival update, we were able to learn about what the survival statuses of those people who were previously classified as early censored. Four of them were censored originally on day 2; one of them was censored on day 1. A few more were censored around day 4, and one was censored around 1.5 weeks after the data update.

A lot of these people, most of them, I

think 7 out of 8, had survival status that was well beyond 8 weeks. Some of them were 48. Some of them were -- let me give you the exact numbers. The distribution is patients that were previously early censored before 8 weeks after the survival update, one had a death at week 12; 4 of them had deaths after week 17. One of them was censored at 34 weeks.

So to say that we imputed in an optimistic way I don't think is a fair characterization. I think based on this data that we were able to obtain, imputation based on follow-up time beyond 8 weeks I think is fair. That's one clarification.

The other clarification is when we were thinking about how to impute, while we have -- for example, if a patient was randomized and not treated and, for example, had follow-up beyond -- let's say he had follow-up at 14 weeks, censored at 14 weeks. For us to impute in the sense that we allow this patient to have less survival time, given that currently he has a survival time up to 14 weeks, doesn't make a whole

lot of sense, and for that reason, we impute early.

For those patients who were randomized not treated and had follow-up for at least 8 weeks, we impute from the set of randomized treated who had follow-up for at least 8 weeks but who also had survival time that is at least as high as the patient that's being considered for imputation. So that I think is clarification of the difference.

DR. RINI: Okay. I think we have one more question. Dr. Sung, we'll give you the last question. Use your microphone, please.

DR. SUNG: Thank you. Tony Sung from Duke. Would you please show sponsor slide EC-10, or CE-10?

MR. RICHARDS: CE-10?

DR. SUNG: Yes, thank you. Sorry. I appreciate the input from the open comments and speakers 1, 3, and, 4, especially given that they were female. But at the same time, when I look at this data and the subgroup of women, that hazard ratio of 0.94 in that confidence interval is very unimpressive.

That gets to my earlier questions about sex differences and potential risk associated with this drug. Are there sex differences and potential benefit or absence of benefit? Could this be a drug where men may develop clinical benefit and be a lower risk, but women may not derive clinical benefit and may be at higher risk?

MR. RICHARDS: We're not aware of any -- I'll offer Dr. Levis' opinion, but we're not aware of any biological reason that females respond different than males. There's variability in these subgroup analyses. I'm not sure that we can ascribe any sort of causality to the variability that we're seeing here between males and females.

Dr. Levis?

DR. LEVIS: Mark Levis, Johns Hopkins University. This male/female thing quickly caught attention with the midostaurin data, where midostaurin subgroup analysis seemed to imply that women did not do as well as men. Those of us who pointed that out, we quickly had stones thrown at us for doing subgroup analysis after the trial, so

we apologized. And we noted that in this study, we saw kind of the same thing, and we looked at that.

But again, I have to step back and say, no, actually -- I think I'm going to be a little more disciplined here. I would like to think that there might be something to this, but I don't think there is. As you can see, in fact, no, I think I saw the same number of women as men benefiting from it.

So I'm going to step back and be disciplined and say, no, I think I need much more data than doing subgroup analysis. Tom Fleming whacked me on the head when I brought up this. So I said, "I'm sorry, Tom." So I concede to this kind of interesting observation, but I think these numbers are just too small to make a statement on that. That's been our opinion.

DR. RINI: Thank you. One more, Ms Preusse?

DR. PREUSSE: Courtney Preusse, consumer rep. Sorry about earlier. The patients' stories shook me up a little bit.

Prior to listening to the patient reports,

my question was going to be in what instance would we recommend the use of quizartinib when on slide CS-4, they showed that the serious adverse events, the drug discontinuation due to adverse events, the association with fatal outcome are all higher in the quizartinib group versus salvage therapy.

After listening to the patients talk about their experience with this drug, I'd actually like to rephrase that question and not say in what instance would I recommend this to others, but rather, the assumption that the prevailing benefit of quizartinib in its ability to target the FLT3 ITD mutation, if so, how does quizartinib compare against other FLT3 positive targeting drugs that are already on the market?

MR. RICHARDS: I can invite Dr. Levis to speak to that last point. There probably is some clarification needed in terms of CS-4. This is for the full study period, and part of the problem in interpreting this data is that the safety follow-up is very much different between the quizartinib arm and salvage chemotherapy, where salvage

chemotherapy was just one cycle of 28, where you had 97 days was the median follow-up in the monotherapy.

So it's a bit of an apples to orange comparison. But in terms of comparing the other FLT3 inhibitors, I will invite Dr. Levis to speak to that.

DR. LEVIS: Mark Levis, Johns Hopkins University. Dr. Cortes and I were looking at this slide, and we were actually pretty startled. We were wondering what trial that was. These weren't the patients we were seeing.

This paints a picture of havoc in the clinic, and yet, my colleague at Penn, Sasha Perl, [indiscernible], Dr. Cortes, and sort of a collection of us around the country, we shared notes. We easily treated many dozens of these patients, and it was a very eye-opening experience, where I'm sorry, they came into clinic. They didn't have any of this stuff.

I get it that there were these EKG things, and the patients were asking, "Why am I having EKGs

done anyway? What's going on?" No, you're begging them for a symptom. I do remember the metallic taste. They actually did have that. I got one. We have a side effect, finally. So the picture shown here does not paint the true picture of what you're actually seeing in the clinic.

As to your question on comparing it to other approved FLT3 inhibitors, you can ask my patient about how she likes sorafenib, the off-label drug that we use. I have patients that are on chronic opiates for the pain that that drug causes. This is sorafenib. That's an off-label choice. Yes, it does work. It doesn't work as well as gilt or quiz.

Midostaurin is approved for FLT3 mutant AML diagnosis. It does not work any way as a monotherapy. It's a little use. It's not potent enough. And it smells really bad, and patients don't like it. It causes nausea. Really, it's gilt and quiz. Those are the two big players in this field right now. I'm working on some more, but gilt and quiz. Again, they are different.

Just again pointing out how I see these drugs moving forward, this is a data that we presented at ASH a couple years ago. Gilt doesn't work that well after chemo. It loses potency. This is FLT3 inhibition. You're totally losing that inhibition in the setting following chemo. There are a number of explanations for this, which we fully understand. But this just illustrates these drugs are different.

This is getting the FLT3 inhibitor after chemo. This is gilt. And now look at quiz, giving it after chemotherapy. You still blank out the target; potency. No question, definite side effects, different -- and it has to do with, again, the structure of this one. There are different types of inhibitors.

As an oncologist, I want both. We actually didn't see a difference. I've treated an equal number of patients. We saw no difference in what it was doing to the patients. But they behaved differently, and I would simply ask to give us the option. Give us the options, because there's no

question, there are patients that are going to want to use and patients that are going to want to use the other.

Questions to the Committee and Discussion

DR. RINI: Thank you.

We'll now proceed with the questions to the committee and the panel discussions. I'd like to remind the public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. There are two discussion questions; if we could put up the first one. Thank you.

Please discuss whether the results of the overall survival analysis of study AC220-007 are persuasive evidence of effectiveness of quizartinib and the reasons for your opinion. So here we're just obviously talking about the benefit side of the equation centered around the OS analysis.

Are there any questions about the question? It's pretty straightforward. If I could maybe lean on the statisticians to get back to the questions that I asked them. I'm still struggling with the

sensitivity analysis, A, B, C and D, and the different assumptions and the different numbers. I'm still struggling with that, so I'd be interested in your opinions.

DR. HALABI: Susan Halabi, Duke University. Overall, when we look at the results from this randomized trial, the hazard ratio, based on the ITT analysis, was 0.76 with a 95 percent confidence interval ranging from 0.58 to 0.98. The sponsor did three types of analyses, whereby they did show in each of the analyses the robustness of the treatment effect, the benefit of the treatment.

Now, with the FDA, they did more of the conservative -- they did a different types of analyses, and one of them was not very conservative when they looked at the proportion is equal to zero, which means none of the patients were imputed. And based on those results, the upper bound of the confidence interval was above 1. Based on the simulation, I believe it was about 50 percent of the times, the results were not significant, which suggests that the results were

not as robust as they appear to be.

This is something obviously that I also struggled with. It seems that based on the simulations, that perhaps FDA did not take into account updated OS --

DR. BY: We did [off mic].

DR. HALABI: -- you did? Okay. Thank you for that clarification.

The questions remain whether -- so let me step back here. The important question remains whether this really translates to a tangible benefit to the patient. And while the results are clearly significant based on what's been reported by the sponsor, the thing that's troubling me is the fact that the upper bound of the confidence interval is very close to 1.

The fact that if you believe the assumptions that the FDA did, which basically takes into account the patients that were randomized and not treated, to have the same sort of survival distribution like the patients who were randomized and treated, and the salvage chemotherapy, then the

results are not as robust as they appear to be.

DR. RINI: Sally?

DR. HUNSBERGER: Sally Hunsberger. To me, the level of evidence we have in this study is about like phase 2 evidence. I think it's interesting. I think there's something here, but I don't know that we know how to use it. I think there's enough unanswered questions with the not treated, with the censored that -- I think the FDA's analysis is a legitimate analysis, and it pretty much takes away the survival advantage.

I think it almost seems like the use for this is to get people to transplant, so maybe we need to do a study that actually asks that question in a rigorous way. But I don't think we can look at this data and say that that's what this is doing.

So I think it's phase 2 type data; that there's an interesting thing here, but we need to study it more, especially given the safety issues. So I'm not saying we should throw it out, but I don't feel comfortable that it's strong enough to

say yes, it should be approved.

DR. RINI: Dr. Pazdur?

DR. PAZDUR: I wanted to get back to a concept that Dr. Sung brought up, and that is potential bias here. I think it deserves some discussion. When you have an imbalance in randomized patients of 23 percent versus 1.6 percent, that is quite bothersome of whether this is an adequate and well-controlled trial.

Here again, when we talk about randomization, we talk about the concept of an equipoise, and I think we have to have a discussion is and was there equipoise during this randomization process? Because this is quite bothersome. I've been here 20 years. I haven't seen this discrepancy here of randomized but not treated, to this extent. Then you get into other confounding issues of the censoring issues that also demonstrate a potential imbalance here that's quite bothersome, as well as on the transplant.

So for the question that I have, rather than discussing -- is there a survival advantage in

my mind? And that's what comes up given all of these. And I think we could do all the sensitivity analysis under the sun and pick which ones are favorable and which ones are not. As you can see, there is a discrepancy. But was there an existence of equipoise here during the randomization process in the conduct of the trial?

That concept of equipoise is very important because it really underlines the concept of an adequate and well-controlled trial. And if you don't have it -- and it's not meaningful or a situation where somebody did something wrong; it just creeps into the process, basically, because you have other therapies that are being developed at this time and the availability of other therapies.

So can people talk about this issue of 23 percent versus 1.6 percent? I haven't seen that in 20 years.

DR. RINI: Did you want to comment? Dr. Lincoff, please?

DR. LINCOFF: Michael Lincoff. That was

part of what I was going to address. I am bothered by the 23 percent, not with the 23 patients -- not that they came off the intended intensive chemotherapy, because I think that that's a normal part of intention to treat; that if you're now confronted with what that chemotherapy involves, you may make a decision not to do that, or if there's availability of other agents that may or may not be allowed as concomitant medications.

I think it's very unfortunate that the protocol and the way the trial was designed didn't allow full follow-up on those patients. Choosing not to be on the designated therapy does not mean you don't remain in the trial. That's for all kinds of trials. Cardiovascular trials, I'm familiar with that, and that's missing data that's a big problem. I think that's the biggest challenge here.

I don't think it necessarily reflects a lack of equipoise because it may represent what you're asking patients to do when you say full chemotherapy versus an oral agent.

But that point aside, the other two sort of legs upon which the question of whether or not this is a robust result, or based upon, was the apparent lack of internal consistency, and then the question of the disproportion, or the differences in proportions based on the stem cell transplant. In both of those cases, I'm much less bothered.

I think the internal consistency issue, to a great extent, depends upon whether or not you think it's legitimate to use a CRc definition, and that is whether persistence of transfusion requirements still represents a benefit, and I think that there's mechanistic reasons that were put forth by the sponsor with the c-Kit partial suppression that may make that reasonable. If you do accept that, then the numbers do look very different between the treatment groups in favor of the active treatment.

Then the issue of the imbalance in or the much greater use of stem cell transplant I think is -- although there's no strong pathway where you can point to each patient and say by guidelines, I

think it's not far from common sense based upon what was seen with these patients, that they ended up being better candidates for transplants.

Although you may say there's a bias or lack of equipoise within the two treatments, I think presented with a patient, the clinician is going to, if possible, do a stem cell transplant. And the fact that more patients were presenting in a way that made them suitable, it does say something about the drug.

So for two of the three reasons of robustness, I'm less concerned. I don't know how to get around the issue of the missing data. I just think we have to decide in the overall, holistic of everything that's there, is that enough to say that we don't believe the statistically significant primary endpoint?

DR. RINI: Thank you. Dr. Sung?

DR. SUNG: Tony Sung from Duke. I was trying to refresh myself on the midostaurin data and found a 2017 Blood paper by one Mark Levis. The thing in my mind is with midostaurin, you had a

very strong and clear statistical benefit to it, and you also had a very significant clinical benefit. In that setting, the gender difference, I'm more willing to kind of say, okay, we'll think about it later or we won't invest too much time on it.

In this setting, where the statistically significant benefit is unclear, there's at least a lot of debate over the statistical significance of the findings, where the clinical benefit, 1 and a half months is a little underwhelming. It makes me a little bit more uncomfortable, and it makes me really question what the benefit is here.

I do agree that I think CRi is a clinically meaningful endpoint. And again, I agree the inhibition of c-Kit makes CRi particularly irrelevant in this setting. I guess it's too late to ask, but I wonder if there are gender differences or if there's data on CRi responses by gender. But at least from what I see, I have doubts.

DR. RINI: Do you have a comment on the

high dropout rate given that you take care of these patients, in terms of why it might have been higher in this study versus other studies that you do?

DR. SUNG: I have to say as a caveat, I'm primarily a transplanter, so I will take care of leukemic patients, but I usually take care of the leukemic patients who relapse after transplant. They usually come to me already in remission or ready for transplant, or some of them have active disease, and they're trying to get into remission.

To that extent, that's why I was saying I favor quizartinib or anything that can get patients to transplant or looking at bridge to transplant as endpoint because I do think that's clinically meaningful. I was facetious when I said earlier transplant cures all, but it does cure a lot of people, as seen from the open comments.

As to the high dropout rate in this study with the 23 percent, I have to say I can't comment very well to that.

DR. RINI: Other discussion about the OS analysis or anything on the benefit side of the

equation, or the high dropout rate, if anybody wants to comment further?

(No response.)

DR. RINI: I think to summarize this part of the discussion, I think there still remains a lot of uncertainty around the overall survival analysis, and the question of benefit, and the magnitude of benefit. I think it's been articulated, high dropout rate seems to be perhaps the most concerning and lack of follow-up in those patients for whatever reason.

I think there's some uncertainty about the clinical benefit of the other endpoints, like increased transplant rate, CRi as an end point, et cetera, that are not necessarily standard but would complement the OS benefit if there is one.

I think you can go to question 2. The second question, just to read it, please discuss the feasibility and adequacy of, A, contraindication for use of drugs that prolong QT via the complementary IKr channel. Secondly, a recommendation for administration of beta blockers

to prevent arrhythmias as a means to reduce the risk of life-threatening and fatal cardiac events resulting from IKs blockade if quizartinib is marketed.

Questions about the question? I think I'm going to start with cardiologists for this one.

DR. LINCOFF: I am not too bothered by the QTc issue. No question that in some patients this can be a problem and some combination of concomitant electrolyte abnormalities from everything else that's going on, that there are going to be some patients that the QT will be prolonged, and there is the potential, as there is with any mechanism of QT prolongation, for them to have arrhythmias.

Looking over as much as I was able to find in all the briefing books, the narratives on all of the events that were questioned, it's really hard to find many, if any, that are even -- as an adjudicator in some trials, it would be likely to have been associated with QT prolongation or arrhythmia.

I think we're left with a developmental effort here that has clearly a potential, theoretical issue, that with this QTc prolongation that is real, that you could have patients that ultimately would have a cardiac arrest or a deadly arrhythmia from it, but we really didn't see it. In this trial, it's net clinical benefit. If they died from it, that would be subtracted from the patients who survive. So we're looking at survival, which should smooth that out, so I should take that into account.

As an issue, to offset the seriousness of this disease, I really don't think it's an issue. I think it would clearly be ideal to try relatively or contraindicate use of drugs that also prolong QT. The fact that in this relatively small effort, there wasn't a clear interaction, it was demonstrable, still does not rule out that in some patients it would be, although, the problem of course is some antifungals and some other agents for which -- this is not my oncologic expertise, but it would seem that some of these drugs, there

are no alternatives in some of these patients, but to the extent that you could.

I'm much less enthusiastic about the beta blockers. Yes, for congenital long QT, that's one thing, but I think the potential differences here, the downside of beta blockers in a group of patients who could be hemodynamically unstable and dehydrated, et cetera, I think may outweigh the potential benefits of what I think is a low risk.

So I would do what you could do to contraindicate drugs that prolong QT, and monitor I think the dosage regimen that was used in the trial. But otherwise, I just don't think this is that big of an issue. And I know that's what I'm supposed to be here for --

(Laughter.)

DR. LINCOFF: -- but I just can't get that upset about this QT.

DR. RINI: Thank you. Please?

DR. NOWAKOWSKI: Greg Nowakowski, Mayo Clinic. Just a comment as a hematologist. I think the awareness of QT and the drugs that prolong QT

and the importance of electrolytes management has improved greatly in hematology words. I'm running right now with a team that before I even ask, they're already running with the ECGs, and they are telling me this, we should not start this antibiotic because of this potential.

I echo what you're saying. I think in the modern era, we are used to it, particularly with some of those new targeted agents, and this will be less of a concern.

Forgive me for not commenting about beta blockers, but I will abstain from this part.

DR. RINI: Dr. Taylor?

DR. TAYLOR: Wayne Taylor, patient representative. I agree having a boxed warning or parameters for monitoring electrolytes, and volume status, and all that. I have a problem as an internist making a blanket recommendation that people should be on beta blockers because I think there's going to be a lot of variation of individuals. I think recommending that for all people, if this drug gets approved, I wouldn't

support that.

DR. RINI: Dr. Sung?

DR. SUNG: I was going to say the same thing. Relapsed/refractory patients are the ones who are more immunosuppressed. They're at high risk of developing invasive mold infections like aspergillus or antifungals that do not prolong to QT; like micafungin don't cover for that. We do this all the time. Patients have a prolonged QT; we put them on micafungin, and then they get aspergillus pneumonia.

So a warning is appropriate, but I think an absolute contraindication just wouldn't fly in the clinical setting, not to mention the Zofran, and the Compazine, and all the other agents that we give; the ciprofloxacin levofloxacin, antibiotic prophylaxis.

With regard to item B, I would disagree as well, both, as Dr. Lincoff was saying, because of the potential for hypertension and other adverse events. I remember when I was at Hopkins, Judy Karp, one of the other physicians there, we would

smack the intern who started beta blockers just because we need to know when these patients get tachycardic, they're at high risk of getting septic. Beta blockers can blunt these things or make events worse.

In addition, as alluded to by one of the other members here, there's the risk of bradycardia induced QT prolongation. So I think just putting beta blockers on these patients is not a great idea.

DR. RINI: Other comments from many of the non-cardiologists about this?

(No response.)

DR. RINI: Okay. Maybe just to summarize, I think the general sense, from what I heard mostly from Dr. Lincoff, was that there's a relatively lower concern about this, about QT prolongation in that I think a contraindication for use of QT prolonging drugs is probably not realistic, although maybe should be avoided or something as much as possible. But in the clinical context, it sounds like those are the drugs that are used in

this context, and that there was little to no enthusiasm for a recommendation about a blanket recommendation for beta blockers.

If there's no further discussion, we will now proceed with the voting process. Let me read the question first.

Do the results of study AC220-007 demonstrate that treatment with quizartinib provides a benefit that outweighs the safety risks for patients with relapse or refractory FLT3 ITD-positive AML? Any questions about the voting question?

(No response.)

DR. RINI: So we'll now begin the voting process. We'll be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in and then be displayed on the screen. The DFO will read the vote from the screen into the record, and then we'll go around the room and each individual who voted will state their name and how they voted into the record. Please also state the reason why you voted as you did if you want to.

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

(Voting.)

LCDR SHEPHERD: For the record, the vote is 3 yes; 8 no; zero abstain; and zero no voting.

DR. RINI: Thank you. Now that the vote is complete, we'll go around the table and have everyone who voted state their name and their vote.

If you'd like, please state the reason why you voted as you did into the record, and we'll start at that end of the table.

DR. LINCOFF: Michael Lincoff. I voted yes. As I said, I'm less concerned about the risk, and I do think on the balance, there is benefit within the constraints of the magnitude being difficult to estimate precisely. But I think that most of the concerns still do not remove, in my mind that, that there is a benefit.

DR. SUNG: Tony Sung from Duke. As Dr. Pazdur has heard at every meeting I've been at, I think, I hate this process of voting on this question because I believe in the drug. I think it works. I think it benefits patients. I think it should be approved. But the language of the question is do I believe the benefits outweigh the risks?

I do think that CRi is an important endpoint in this population. As I mentioned before, I do think we need to have drugs with multiple classes; that this complements

gilteritinib. I think this should help get patients to transplant, and I think it has the potential to improve quality of life, although as open comment speaker number 2 noted, we don't have any data on that.

My main concern, as I was stating earlier, I believe that in women, who may be at higher risk for adverse events and may be at lower risk for benefit, I'm not convinced that the benefits outweigh the risks in that patient population. I know that is a subgroup, but that's half the population. That's an important subgroup, while there are clearly several women who have benefited, as seen in the audience.

Just in terms of the data that I'm shown, and that's why my vote is based purely on the data that I'm shown, my vote is no. But I want the FDA to know that I believe in this drug, and I think it should get approved, and I want to use it.

(Laughter.)

DR. RINI: Thank you. Dr. Taylor?

DR. TAYLOR: Ditto. Wayne Taylor, patient

representative. If I have a bias, it's to move things quickly from bench to bedside. But also, as I sit on this committee, my job is to vote on the evidence, and I don't think that this study has enough robust evidence. I think the FDA has done a lot to advance the speed from bench to bedside, but the standard for maybe leukemia of always having maybe just one clinical trial isn't always what we need. Sometimes we need more than one study.

I also believe in the targeted small molecule approach. I like the analogy to BCR-ABL and CML, that maybe we're going to have different tools. I think this will be a tool. I just think we need more study.

MS. PREUSSE: Courtney Preusse, consumer rep. My answer isn't so much no, as not right now. I think Dr. Hunsberger summarized it really well, that this makes for really good phase 2 data, and I would love to see this in a phase 3 trial that answers some of these questions around the interpretability, around longevity, around gender differences, around con -- I can never pronounce

that word -- medications.

I think, based on public comment, this drug is providing clinical benefit to some, but I think there are still a lot of questions that still need to be answered before bringing this to market.

DR. HOFFMAN: Philip Hoffman, University of Chicago. Strictly on the wording of the question, which do the results demonstrate that treatment provides for benefit that outweighs the safety risk, I do believe the answer is yes to that. I think that in the realm of hematology/oncology, there are no patients sicker than acute leukemia patients and no physicians more intensely watching the details than leukemia doctors.

So I'm not particularly worried that this cardiac safety question will somehow fall through the cracks if it is a major issue. I agree with some of the others that I don't get the sense, at least based on the data right now, that this is a blockbuster, but it does seem like it's one more agent in the armamentarium that will be and can be useful in leukemia patients, and perhaps as a way

to get patients in sufficient remission to move toward a transplant, I think that's a worthwhile end as well.

DR. KLEPIN: Heidi Klepin, Wake Forest. I voted no. I share the same struggles that others have already mentioned. I voted based on the data available. My primary reasons, the efficacy results that we were shown are modest, so a modest 6 weeks.

If I felt confident in those data, that would have been enough for me in the setting of AML. But a lot of the questions that were raised with respect to bias, confounding -- I do think the issue of equipoise is a real one in the setting of this particular study. It raises questions about whether or not that survival benefit is real.

So taking that into the context of some of the concerns about cardiotoxicity, which might not have been a deal breaker, I think are still significant and warrant attention, and that's the reason why I voted no.

I do wish we had some additional data that

really supported the clinical observations that were being discussed, both with respect to the mechanistic potential link between getting folks to transplant and then also some quality-of-life data that might have really helped us understand this a little bit better.

DR. RINI: Thanks. I'll go last. Greg, if you want to go.

DR. NOWAKOWSKI: Greg Nowakowski. I voted no. I did not have many safety concerns in the target populations, which is a high-risk population, as we all agreed here. My concerns were mainly in the efficacy of this therapy and the real change in the overall survival in this study, considering that many patients in the control arm did not receive from intended treatment. And unfortunately, we did not have data on really what happened to those patients afterwards.

In the big picture, I think if you look at the practice gap, with some of the other inhibitors in this space, the practice gap is not so big. And I hope that in the meantime, other studies of this

compound can actually substantiate those initial findings and maybe come back with a stronger data.

DR. ULDRICK: Thomas Uldrick, Fred Hutchinson Cancer Research Center. I voted no. I agree with most of the previous comments. There was clearly -- this is an interesting drug with some activity. I think the use of this drug in this population has not been well defined in this study, and I'm left with, really, substantial questions about the overall survival benefit given the differential in the early censoring and randomized not treated data, and the negative intent-to-treat EFS data.

So I think a better understanding of how to use this drug will require additional studies.

DR. HALABI: Susan Halabi, Duke University. I was mainly concerned with the estimate of the clinical benefit and the potential bias in that estimate. Also, as mentioned by others, I was concerned about the high proportion of patients who were randomized but not treated. Clearly, that would lead to questions about the conduct of the

trial, and that leads to issues regarding the strength of evidence.

I was also concerned about the lack of internal consistency when we look at the event-free survival and whether that endpoint really is a good endpoint to measure clinical benefit to the patients. I know this endpoint has been used in other AML studies.

I think I would have been more impressed if there were more data, and another trial would have been really nice to substantiate the evidence from this trial. But clearly, having said all that, I think there is some signal there is clearly a subgroup of patients who are benefiting from the drug, but we're not sure whether this estimate is measured without bias.

DR. HUNSBERGER: Sally Hunsberger. I voted no. I don't really have anything else to add. I think it just needs more research.

DR. RINI: Thank you. Brian Rini. I voted yes. I don't disagree with anything that the no or yes voters have said, and I think you can tell that

when the no voters say that they want to use the drug, that tells you how close it is.

I do believe there's an OS signal. Obviously, if it were a more substantial OS signal, we wouldn't be sitting here. I think I probably put a little more stock into some of the softer endpoints about getting people to transplant and the CRi maybe than others did, and I think I was reassured by the risks that this, on a day-to-day basis, seemed to be a reasonably well-tolerated drug.

What Dr. Lincoff said about not worrying too much about QT, obviously it's a serious problem, but not being rate limiting. I think probably one of the biggest take-homes, and this really relates to the large dropout rate, which I agree is concerning, is that it seems like it's a really difficult population to do studies in because they're just really sick patients, and now they may have other alternatives. So that equipoise and that true randomization that we want to answer questions is seemingly very difficult.

Adjournment

DR. RINI: If there are no more comments, I will now adjourn the meeting. Panel members, leave your name badge on the table so they may be recycled and take all your personal belongings. You can leave your meeting materials on the table. Thank you.

(Whereupon, at 4:41 p.m., the afternoon session was adjourned.)