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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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4 Division of Advisory Committee and Consultant  
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1       **FDA PARTICIPANTS (Non-Voting)**

2       **Richard Pazdur, MD**

3       Director, Oncology Center of Excellence, FDA

4       Acting Director, Office of Hematology &

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19      **Donna Przepiorka, MD, PhD**

20      *(Afternoon Session Only)*

21      Cross-Discipline Team Leader

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*(Afternoon Session Only)*

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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

1 DR. BY: Kunthel By, FDA.

2 DR. HUNSBERGER: Sally Hunsberger, NIH.

3 DR. HALABI: Susan Halabi, Duke University.

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

6 DR. NOWAKOWSKI: Gregorz Nowakowski, Mayo  
7 Clinic.

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

10 DR. RINI: Brian Rini, Cleveland Clinic.

11 DR. KLEPIN: Heidi Klepin Wake Forest.

12 DR. HOFFMAN: Philip Hoffman, University of  
13 Chicago.

14 MS. PREUSSE: Courtney Preusse, consumer  
15 rep.

16 DR. TAYLOR: Wayne Taylor, patient  
17 representative.

18 DR. SUNG: Anthony Sung, Duke.

19 DR. LINCOFF: Michael Lincoff, Cleveland  
20 Clinic.

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

22 DR. RINI: Thank you.

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

11           In the spirit of the Federal Advisory  
12 Committee Act and the Government in the Sunshine  
13 Act, we ask that advisory committee members take  
14 care that their conversations about the topic at  
15 hand take place in the open forum of the meeting.  
16 We are aware that many members of the media are  
17 anxious to speak with FDA about these proceedings.  
18 However, FDA will refrain from discussing details  
19 of this meeting with the media until its  
20 conclusion. Also, the committee is reminded to  
21 refrain from discussing the meeting topic during  
22 any breaks. Thank you.

1 I'll pass it to Lieutenant Commander  
2 Jennifer Shepherd, who will read the Conflict of  
3 Interest Statement.

4 **Conflict of Interest Statement**

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

15 The following information on the status of  
16 this committee's compliance with federal ethics and  
17 conflict of interest laws, covered by but not  
18 limited to those found at 18 U.S.C. Section 208, is  
19 being provided to participants in today's meeting  
20 and to the public.

21 FDA has determined that members and  
22 temporary voting members of this committee are in

1 compliance with federal ethics and conflict of  
2 interest laws. Under 18 U.S.C. Section 208,  
3 Congress has authorized FDA to grant waivers to  
4 special government employees and regular federal  
5 employees who have potential financial conflicts  
6 when it is determined that the agency's need for a  
7 special government employee's services outweighs  
8 his or her potential financial conflict of interest  
9 or when the interest of a regular federal employee  
10 is not so substantial as to be deemed likely to  
11 affect the integrity of the services which the  
12 government may expect from the employee.

13 Related to the discussion of today's  
14 meeting, members and temporary voting members of  
15 this committee have been screened for potential  
16 financial conflicts of interest of their own, as  
17 well as those imputed to them, including those of  
18 their spouses or minor children and, for purposes  
19 of 18 USC Section 208, their employers. These  
20 interests may include investments; consulting;  
21 expert witness testimony; contracts, grants,  
22 CRADAs; teaching, speaking, writing; patents and

1 royalties; and primary employment.

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

10           This is a particular matters meeting during  
11 which specific matters related to Daiichi Sankyo's  
12 NDA will be discussed. Based on the agenda for  
13 today's meeting and all financial interests  
14 reported by the committee members and temporary  
15 voting members, no conflict of interest waivers  
16 have been issued in connection with this meeting.  
17 To ensure transparency, we encourage all standing  
18 committee members and temporary voting members to  
19 disclose any public statements that they have made  
20 concerning the product at issue.

21           With respect to FDA's invited industry  
22 representative, we would like to disclose that



1 Dr. P.K. Morrow is participating in this meeting as  
2 a nonvoting industry representative, acting on  
3 behalf of regulated industry. Dr. Morrow's role at  
4 this meeting is to represent industry in general  
5 and not any particular company. Dr. Morrow is  
6 employed by Amgen.

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

18 DR. RINI: Thank you. We will now proceed  
19 with FDA's introductory comments from Dr. Donna  
20 Przepiorka.

21 **FDA Introductory Comments - Donna Przepiorka**

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

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

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

1 remission rates.

2           Lastly, although there are 8 kinase  
3 inhibitors with activity against FLT3 on the  
4 market, only gilteritinib has an approved  
5 indication for treatment of relapsed or refractory  
6 FLT3 positive AML. FDA's review of gilteritinib  
7 showed that 12 percent of patients achieved CR;  
8 21 percent achieved CR with full or partial  
9 hematologic recovery; and the median survival was  
10 9 months. Clearly, new safe and effective  
11 treatments are needed for patients with relapsed or  
12 refractory FLT3 mutation-positive AML.

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

1           The FDA analysis shown here demonstrated a  
2 statistically significant improvement in overall  
3 survival in study 007 with a median OS of  
4 6.2 months for the patients treated with  
5 quizartinib versus 4.7 months on the control arm,  
6 a difference of 6 weeks. However, FDA also noted  
7 that the treatment effect in this study was  
8 borderline with an upper 95 percent confidence  
9 interval of the hazard ratio being 0.99.

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

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

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

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

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

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

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

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

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

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

20               Dr. Rini?

21               DR. RINI: Thank you.

22               Both FDA and the public believe in a

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

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

21 **Applicant Presentation - Eric Richards**

22 MR. RICHARDS: Good afternoon, Chairman,



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

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

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

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

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

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

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

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

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

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

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

9 Dr. Levis?

10 **Applicant Presentation - Mark Levis**

11 DR. LEVIS: Thank you, Mr. Richards.

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

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

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

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

14 In relapsed AML, the duration of first  
15 remission is highly predictive of outcomes. Shown  
16 here is a recent compilation of data from ECOG  
17 studies demonstrating that AML patients who relapse  
18 with a duration of first CR less than a year have a  
19 median survival of less than 5 months compared to  
20 11 months in patients who have a CR of greater than  
21 a year.

22 These data on the right are from patients

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

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

22 The ITD mutation is found in approximately

1 25 percent of newly diagnosed AML and controls a  
2 dismal prognosis. And just like with many solid  
3 tumors, FLT3 ITD leukemia evolves from diagnosis to  
4 relapse. The leukemia cells in patients who have  
5 relapsed/refractory disease are often much more  
6 dependent upon FLT3 signaling.

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

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

22 I have studied, both in the lab and in the

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

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

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

22 The result is complete clearance of



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

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

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

1 is an effective treatment strategy across multiple  
2 clinical scenarios.

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

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

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

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

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

8 Dr. Cortes?

9 **Applicant Presentation - Jorge Cortes**

10 DR. CORTES: Thank you, Dr. Levis.

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

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

1 with significant comorbidities, and those with more  
2 severe diseases.

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

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

19 We observed a higher rate of QTc  
20 prolongation than we anticipated, so we initiated a  
21 second phase 2 study to evaluate where the lower  
22 doses would reduce the incidence of QTc

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

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

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

1 chemotherapy were not eligible.

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

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

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

1 transplant rate.

2 Dosing was initiated at 30 milligrams per  
3 day and up to 2 weeks. If the QTc was below 450  
4 milliseconds, the dose was escalated to 60  
5 milligrams daily. Dose adjustments were indicated  
6 for those events, including QTc prolongation.  
7 Because quizartinib is primarily metabolized by  
8 CYP3A, doses were reduced from 30 to 20 or 60 to  
9 30 milligrams when administered with strong CYP3A  
10 inhibitors to provide consistent drug levels.

11 563 patients were screened and 367 patients  
12 were randomized in a 2 to 1 ratio. Of the 245  
13 patients randomized to quizartinib, 4 did not  
14 receive treatment, and they were followed for  
15 overall survival. For the 122 patients randomized  
16 to salvage chemotherapy, 28 did not receive  
17 treatment.

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

1 FLT3 inhibitors that had rapid disease progression.

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

1 assumes they are different. We will focus on the  
2 28 randomized not treated patients in the  
3 chemotherapy arm.

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

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

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

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

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

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

16 We have carefully examined analyses  
17 conducted by the FDA, and our interpretation of  
18 these analyses. For the patients censored within  
19 8 weeks, She's as follows for the patient's sensor  
20 within 8 weeks, 7 of the 9 which are randomized not  
21 treating, the agency assumed that they could not  
22 have died before 8 weeks. Therefore, they

1 resampled these patients only from the patients  
2 treated on study with survival of at least 8 weeks.  
3 However, we know that 22 percent of the patients  
4 treated with salvage chemotherapy died within  
5 8 weeks.

6 Second, for the 21 randomized not treated  
7 patients in the control arm with known survival  
8 dates beyond 8 weeks, the agency assumes that these  
9 patients would have survived as long or longer than  
10 they did had they received study treatment.

11 However, based on the data from the patients  
12 actually treated on the control arm, it is equally  
13 possible that these randomized not treated patients  
14 could have had a shorter survival had they received  
15 the salvage chemotherapy on the study.

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

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

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

4 In the original analysis, the censoring  
5 treated these patients as if they did not have an  
6 event-free survival event of failure to achieve  
7 CRc, even though in fact we do not know their  
8 response to therapy. This artificially inflated  
9 the outcome of the salvage chemotherapy arm because  
10 17 of these 18 patients were on the chemotherapy  
11 arm.

12 Among chemotherapy patients with response  
13 assessment, we know that 60 percent had an event of  
14 failure to achieve a CRc. So we corrected the  
15 analysis by more appropriately timing the censoring  
16 of these 18 patients. The hazard ratio is then  
17 0.78 and the one-sided p-value is 0.0147. These  
18 results are again consistent with the overall  
19 survival analysis.

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

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

9 In quizartinib treated patients, the time  
10 to remission was fast at 4.9 weeks and the median  
11 duration of CRc was 12.1 weeks. As expected with a  
12 difference in response rate, there was a difference  
13 in the transplant rate between the two arms,  
14 32 percent in the quizartinib arm and 12 percent on  
15 the salvage chemotherapy. This difference in  
16 transplant reflects the treatment effect of  
17 quizartinib, resulting in more patients being  
18 considered eligible for transplant based on the  
19 reduction disease burden in the bone marrow and the  
20 good performance status.

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



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

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

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

1 quizartinib in this patient population.

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

5 Dr. Choi?

6 **Applicant Presentation - Youngsook Choi**

7 DR. CHOI: Thank you, Dr. Cortes.

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

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

1 age.

2 As you see, the treatment duration for the  
3 two groups were different in the QuANTUM-R study.  
4 241 patients received quizartinib for a median of  
5 four 28-day cycles with some patients receiving  
6 therapy for over 1000 days. In contrast, 94  
7 chemotherapy patients received a median of 1 cycle  
8 and a maximum of 2 cycles. Treatment-emergent  
9 safety analysis includes events while on study  
10 treatment plus 30 days.

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

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

22 Commonly occurring events in cycle 1 are

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

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

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

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

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

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

17 Differentiation syndrome was discussed in  
18 the FDA briefing document. There were no events  
19 reported by the investigator. However, in a  
20 retrospective analysis, we identified  
21 12 quizartinib treated patients as having possible  
22 differentiation syndrome. Among 8 patients with

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

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

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

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

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

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

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

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

22 Now let's review the frequency and degree

1 of QTc prolongation based on the standardized  
2 central ECG reading. QTcF greater than  
3 500 milliseconds, a threshold that is clinically  
4 significant, occurred in 8 patients. None had  
5 ventricular arrhythmias. In 7 of these 8 patients,  
6 QTcF normalized with dose interruption or  
7 reduction. The other patient had presented  
8 quizartinib withdrawn due to AML disease  
9 progression.

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

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



1 ventricular fibrillation, cardiac arrest, or sudden  
2 death.

3 Thirteen patients had syncope or loss of  
4 consciousness. One patient with loss of  
5 consciousness had prolonged QTcF of  
6 503 milliseconds. Documented hypotension and  
7 severe anemia was thought to result in this  
8 patient's fall and loss of consciousness. In the  
9 remaining 12 patients, there was no QT prolongation  
10 or arrhythmias. There was one non-serious event of  
11 ventricular tachycardia, and this patient continued  
12 in the study for more than 1000 days without a  
13 recurrence.

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

22 Turning now to the overall relapsed or

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

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

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

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

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

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

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

1 for patients and education material for  
2 prescribers.

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

6 **Applicant Presentation - Jorge Cortes**

7 DR. CORTES: Thank you, Dr. Choi.

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

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

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

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

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

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

1 responses in the patients treated with  
2 low-intensity chemotherapy.

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

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

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

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

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

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

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

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

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

22           We are confident that quizartinib can be an



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

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

8 **FDA Presentation - Kunthel By**

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

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

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

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

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

1 independence.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

10           Our third concern is the number of patients  
11           who were randomized but were not treated with study  
12           therapy. In this study, a substantial proportion  
13           of patients in the chemotherapy arm were randomized  
14           but not treated. In particular, 28 patients or  
15           23 percent in the chemotherapy arm were randomized  
16           not treated, and 4 patients or 1.6 percent in the  
17           quizartinib arm were randomized not treated.

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



1 estimated treatment effect had they been treated  
2 with study therapy.

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

9 The phrase "early death" will refer to  
10 death before 8 weeks after randomization and will  
11 be abbreviated ED8. Patients with at least 8 weeks  
12 of survival follow-up will be abbreviated as GE8,  
13 and they include patients who died on or after  
14 8 weeks and patients who were censored on or after  
15 8 weeks.

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

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

6           The following table jointly summarizes  
7           patients according to treatment arm; stratum based  
8           on the preselected chemotherapy stratification  
9           factor; early censoring status; and randomized not  
10          treated status. In this table, we see that  
11          9 patients in the chemotherapy arm are early  
12          censored, 7 of whom are randomized not treated and  
13          2 of whom are randomized treated.

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

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

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

6 To illustrate, consider the set of  
7 chemotherapy patients who were preselected for  
8 intensive chemotherapy. There are 6 patients who  
9 were randomized not treated and early censored.  
10 The red arrow from 57 indicates that their survival  
11 information is replaced by those of 6 randomly  
12 selected patients from the set of 57 who are  
13 randomized treated with at least 8 weeks of  
14 survival follow-up, and similarly for the  
15 2 patients who were early censored but were  
16 randomized and treated.

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

1 to not impute the survival times of these patients.

2 This slide shows the range of treatment  
3 effects obtained from the stress test under FDA's  
4 assumptions. Please note that the full details of  
5 the imputation analysis are provided in the  
6 briefing document. I would just like to point out  
7 that the first row of this table corresponds to  $P_i$   
8 equals zero using the notation of the briefing  
9 document. The second row corresponds to  $P_i$  equals  
10 0.5, and the third row corresponds to  $P_i$  equals 1.

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

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

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

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

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

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

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

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

1 part, to the HSCT imbalance.

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

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

1 and the reasons for your opinion.

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

4 **FDA Presentation - Aviva Krauss**

5 DR. KRAUSS: Thank you, Dr. By.

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

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

22 FDA's analysis of safety across the



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

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

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

22 When the potassium channels are blocked by

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3 To assess whether the IKs blockade and QTc  
4 prolongation of quizartinib was associated with  
5 clinical manifestations, FDA first looked at acute  
6 or subacute cardiac deaths. We identified  
7 4 patients on the pivotal trial who experienced a  
8 fatal event that was assessed to be possibly  
9 cardiac in origin and at least possibly related to  
10 quizartinib. In 3 of these 4 cases, FDA's  
11 assessment was that the deaths were likely related  
12 to quizartinib.

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

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

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

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

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

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



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

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

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

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

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

6 Additionally, since quizartinib is  
7 administered chronically, there's a potential for  
8 cumulative toxicity over time, so an estimate of  
9 the risk of these events over multiple cycles of  
10 quizartinib is also critical and relevant.

11 However, due to the short exposure to quizartinib  
12 in study 007, the safety of long-term  
13 administration remains uncertain.

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

22 On treatment, fatal cardiac events occurred

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

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

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

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

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

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

1 call classic DS.

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

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

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

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

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

9 FDA identified classic DS in 5 percent of  
10 patients on the pivotal study. In the integrated  
11 safety population overall, and on 007 in  
12 particular, AFND was reported in 3 percent of  
13 patients. On 007, FDA identified an additional  
14 4 patients who only partially fulfilled Montesinos'  
15 criteria but who also had the cutaneous  
16 manifestations.

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

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

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

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

20 Given the 26 percent higher incidence of  
21 hematopoietic cytopenias in the quizartinib arm on  
22 007, FDA analyzed absolute neutrophil counts of

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

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

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



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

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

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

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

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

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

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

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

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

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

#### 18 **Clarifying Questions**

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

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

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

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

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

14 Dr. Koch?

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

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

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

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

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

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

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

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

14 DR. RINI: Dr. Lincoff is next.

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

1 that.

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

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

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

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

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

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

13 Again, a good example of this is a patient  
14 of mine who's on the control arm who got MEC, and  
15 her ejection fraction was reduced to 15 percent  
16 even though she got a complete remission.

17 Hallelujah, you're in remission, but you can't go  
18 to transplant because you would not survive the  
19 transplant.

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



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

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

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

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

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

19          Do you know what I'm asking?

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

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

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

21 DR. RINI: Thank you.

22 DR. SUNG: Sorry. Can I just respond

1 directly?

2 DR. RINI: Sure. Dr. Sung?

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

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

18 DR. LEVIS: May I respond?

19 DR. RINI: Sure.

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

1 arm to be lower than the chemotherapy arm?

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

4 (Laughter.)

5 DR. LEVIS: Well --

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

8 DR. RINI: Dr. Hunsberger?

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

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

22 Let me address your first question first.

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

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

6 Does that answer your question?

7 DR. HUNSBERGER: So cycle 2 begins when?

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

10 DR. HUNSBERGER: So you evaluate at day  
11 1 -- they're randomized, and then you would  
12 evaluate -- when is the next time you would  
13 evaluate, day 1?

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

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

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

1 likewise, cycle 3.

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

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

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

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

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

14 DR. HUNSBERGER: Right.

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

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

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

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

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



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

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

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

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

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

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

5 DR. KOCH: The analysis that's not correct,  
6 however, is the analysis that was originally  
7 planned because that analysis operates as if those  
8 17 patients were at risk to have an EFS failure  
9 event when they had no data with which to judge  
10 that. So the resampling analysis tries to identify  
11 what their EFS outcomes might have been had they  
12 actually had data. The corrected analysis  
13 essentially removes them from consideration. There  
14 are other types of resampling analysis that could  
15 also be applied to them, but what we presented is  
16 what we currently have.

17 DR. RINI: Dr. Klepin?

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

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

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

12 So if they achieved a CRc, that's those  
13 48 percent of patients versus those quizartinib  
14 patients who didn't achieve that, so the 52  
15 percent. The percentage of transplant just in that  
16 strata would be helpful.

17 MR. RICHARDS: Sure. Just a second.

18 DR. KLEPIN: Those strata.

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

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

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

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

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

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

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

19 DR. RINI: Hold on one second.

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

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

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

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

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

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

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

6 DR. RINI: Let him respond.

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

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

22 DR. LEVIS: I will concede that, but that

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

5 DR. RINI: Thank you. Dr. Taylor?

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

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

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



1 quizartinib.

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

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

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

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

22           (Laughter.)

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

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

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

1 that in this setting.

2 DR. RINI: Thank you. Dr. Nowakowski?

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

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

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

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

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

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

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

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

1 DR. RINI: Thank you. Dr. Sung?

2 DR. SUNG: This is actually a two-part  
3 question. Looking at the sponsor brochure on page  
4 87, it notes in the quizartinib group  
5 that -- sorry. Looking at page 121, it notes that,  
6 "Although generally the same, TEAEs were grade 3 or  
7 greater in both groups. Proportionally more female  
8 patients than male patients were reported with  
9 grade greater than or equal to 3; ECG QT  
10 prolongation, 6.9 percent versus 1.5 percent,  
11 respectively."

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

19 I also noted that on page 128 of the  
20 sponsor briefing document, they noted there was a  
21 54-year-old woman who developed cardiac arrest in  
22 the setting of grade 3 hypokalemia while on

1 quizartinib, again, hypokalemia being common in  
2 these patients.

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

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

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

12           DR. RINI: Appreciate it. Thank you.

13           Dr. Lincoff?

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

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

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

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

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

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

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

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

14               DR. LINCOFF: Can I ask a clarifying?

15               DR. RINI: Sure.

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

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

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

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

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

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

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

19 DR. RINI: Thank you. Dr. Sung?

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

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

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

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

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

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

14          Dr. Kowey?

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

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



1 sudden cardiac death at twice the rate of females.

2 DR. KOWEY: Yeah, yeah.

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

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

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

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

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

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

22 So there clearly is a hormonal dependency,

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

4 Does that help?

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

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

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

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

20 DR. RINI: Thank you. Dr. Hoffman?

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

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

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

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

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

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

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

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

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

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

22 So the FLT3 TKD mutations come out rapidly,

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

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

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

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

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

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

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

1 DR. RINI: Thank you. Much like this  
2 morning, we have more questions and less time.  
3 We're going to do a 10-minute break now, and then  
4 we'll come back and do the open public hearing. We  
5 just have about three more questions, and then  
6 we'll proceed to the discussion. So we'll take a  
7 10-minute break. It's 3:22.

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

#### 10 **Open Public Hearing**

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

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



1 its direct competitors.

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

10 FDA and this committee place great  
11 importance in the open public hearing process. The  
12 insights and comments provided can help the agency  
13 and this committee in their consideration of the  
14 issues before them. That said, in many instances  
15 and for many topics, there are a variety of  
16 opinions. One of our goals today is for this open  
17 public hearing to be conducted in a fair and open  
18 way, where every participant is listened to  
19 carefully and treated with dignity, courtesy, and  
20 respect. Therefore, please speak only when  
21 recognized by myself. Thank you for your  
22 cooperation.

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

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

8 I thank you for this opportunity to speak  
9 to you today and share my story. On December 16,  
10 2011, at age 47, I left my exercise class to go to  
11 a doctor's appointment. Having had a series of  
12 minor but nagging symptoms, such as bruising, rash,  
13 sinus infection, and feeling generally tired, I  
14 expected my doctor to tell me I had an infection  
15 and prescribe a course of antibiotics. I did not  
16 expect to receive a diagnosis of acute myeloid  
17 leukemia, and be admitted to the hospital three  
18 days later, to begin a 21-day round of intensive  
19 HiDAC chemotherapy.

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

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

10           Upon my completion of treatment in May of  
11 2012, I was deemed to be in remission, but shortly  
12 thereafter, I developed a large rash on my neck,  
13 and my follow-up blood work showed that my  
14 platelets were plummeting. I had relapsed. I was  
15 told by my Kaiser oncologist there was nothing more  
16 they could do.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

15 DR. RINI: Thank you. Speaker number 3.

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



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

5               I'm a leukemia patient and a stem cell  
6       transplant patient. Our journey began February 22,  
7       2015 when I was diagnosed in a local ER with acute  
8       myeloid leukemia, and within 6 hours was on the  
9       cancer floor with traditional chemo IV. My white  
10      blood count was 126,000.

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

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

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

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

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

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

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

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

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

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

13           DR. RINI: Thank you. Speaker number 4?

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

17           MS. OH: My name is Chung Oh.

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

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

4 At the time for me, it was basically  
5 hearing a death sentence for my mother. It was  
6 hard because 5 grandkids all under the age of 5 at  
7 the time -- I've got three; my sister had  
8 two -- she was set to retire and live the American  
9 dream, and immigrating here 30 years ago, this  
10 wasn't the way it was supposed to end, is what I  
11 thought. But my mother's a fighter, so we started  
12 7-plus-3 induction treatment right away.

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

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

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

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

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

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

17 (Laughter.)

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

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

8 MS. OH: Yeah, yeah, funny tasting, kind of  
9 a metallic. My appetite has decreased, but the  
10 doctor said, "Chung, you have to make 100 pounds.  
11 Right now, it's 82 pounds." So I got 3 meals,  
12 2 snacks every --

13 (Laughter.)

14 MS. OH: -- a 2 to 3-hour drink. So I made  
15 85 pounds, so doctor said, "Okay, you can do this."  
16 I did it.

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

1 (Laughter.)

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

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

16 **Clarifying Questions (continued)**

17 DR. RINI: Thank you both.

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



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

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

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

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

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

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

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

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

22 The second question that they addressed

1 related to if the randomized not treated patients  
2 actually had better treatment than what they might  
3 have gotten with their assigned therapy and 21 of  
4 them were followed, what would have happened if the  
5 7 had outcomes like the 21? And again, that was  
6 reinforcing as well.

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

18           What the FDA did was illustrate it on the  
19 next slide of the FDA, where they sampled from the  
20 patients who were having survival that was at least  
21 8 weeks. What that did not allow for, for the  
22 randomized not treated, was the fact that for the

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

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

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

17 The sponsor has done relatively neutral  
18 imputations, one being the sample of the 7 from the  
19 21, the other being the 28 from the 94, to try to  
20 understand what the implications of that would be.  
21 The FDA has done a stress test where they basically  
22 sample the patients who were randomized and not

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

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

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

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

22 A lot of these people, most of them, I

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

9 So to say that we imputed in an optimistic  
10 way I don't think is a fair characterization. I  
11 think based on this data that we were able to  
12 obtain, imputation based on follow-up time beyond  
13 8 weeks I think is fair. That's one clarification.

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

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

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

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

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

15 MR. RICHARDS: CE-10?

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

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

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

15           Dr. Levis?

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



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

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

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

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

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

22 Prior to listening to the patient reports,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4 **Questions to the Committee and Discussion**

5 DR. RINI: Thank you.

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

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

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

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

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

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

1 not as robust as they appear to be.

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

6 DR. BY: We did [off mic].

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

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

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



1 results are not as robust as they appear to be.

2 DR. RINI: Sally?

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

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

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

1 say yes, it should be approved.

2 DR. RINI: Dr. Pazdur?

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

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

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

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

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

17 So can people talk about this issue of 23  
18 percent versus 1.6 percent? I haven't seen that in  
19 20 years.

20 DR. RINI: Did you want to comment?

21 Dr. Lincoff, please?

22 DR. LINCOFF: Michael Lincoff. That was

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

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

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

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

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

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

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

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

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

18           DR. RINI: Thank you. Dr. Sung?

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

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

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

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

22 DR. RINI: Do you have a comment on the

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

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

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

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

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



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

3 (No response.)

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

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

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

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

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

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

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

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

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

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

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

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

16 (Laughter.)

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

19 DR. RINI: Thank you. Please?

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

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

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

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

13 DR. RINI: Dr. Taylor?

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

1 support that.

2 DR. RINI: Dr. Sung?

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

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

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

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

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

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

13             (No response.)

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

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

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

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

13 (No response.)

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



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

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

17           (Voting.)

18           LCDR SHEPHERD: For the record, the vote is  
19 3 yes; 8 no; zero abstain; and zero no voting.

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

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

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

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

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

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

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

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

20 (Laughter.)

21 DR. RINI: Thank you. Dr. Taylor?

22 DR. TAYLOR: Ditto. Wayne Taylor, patient

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

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

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

1 that word -- medications.

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

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

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

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

4 DR. KLEPIN: Heidi Klepin, Wake Forest. I  
5 voted no. I share the same struggles that others  
6 have already mentioned. I voted based on the data  
7 available. My primary reasons, the efficacy  
8 results that we were shown are modest, so a modest  
9 6 weeks.

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

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

22 I do wish we had some additional data that

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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### **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.)