FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUG ADVISORY COMMITTEE (ODAC) MEETING

Wednesday, March 7, 2018

8:01 a.m. to 11:44 a.m.

FDA White Oak Campus

Building 31 Conference Center

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:01 a.m.)

Call to Order

Introduction of Committee

DR. ROTH: Good morning. Why don't we get started? Welcome to the March 7, 2018 meeting of the Oncology Drug Advisory Committee. I'm Bruce Roth. I'm chair of the committee. I think we'll start by going around the table introducing our full-time members, our guests, and staff as well. So let's start at this end.

DR. GORDON: Gary Gordon, vice president for oncology development at AbbVie.

DR. HOURIGAN: Chris Hourigan. I'm an investigator with National Heart, Lung and Blood Institute.

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

DR. SUNG: Anthony Sung, bone marrow transplant from Duke University.

MR. FLATAU: Hi. Art Flatau, the patient representative.

MS. PREUSSE: Courtney Preusse, consumer rep.

DR. HALABI: Susan Halabi, biostatistician, Duke University.

DR. PAPADIMITRAKOPOULOU: Vali Papadimitrakopoulou, MD Anderson.

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

DR. TESH: Lauren Tesh, designated federal officer for ODAC.

DR. HOFFMAN: I'm Philip Hoffman, medical oncologist, University of Chicago.

DR. NOWAKOWSKI: Greg Nowakowski, medical oncologist, Mayo Clinic, Rochester.

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

DR. BOLLARD: Cath Bollard, Children's National and The George Washington University.

DR. XU: Qing Xu, statistical reviewer from FDA.

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

DR. PRZEPIORKA: Donna Przepiorka,

cross-discipline team leader, FDA.

DR. FARRELL: Ann Farrell, division director, FDA.

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

DR. ROTH: Thank you.

I'd like to first remind everyone to please silence your cell phones, smartphones, and any other devices if you've not already done so. I'd also like to identify the FDA press contact, Sandy Walsh. If you're present, please stand. Thank you.

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

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

I'll now pass it on to Dr. Lauren Tesh, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. TESH: The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or

regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the service which the government may

expect from the employee.

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

Today's agenda involves supplemental biologic license application 125557/S-013 for Blincyto, blinatumomab, injection for intravenous use, application submitted by Amgen, Inc. The proposed indication, use, for this product is for the treatment of minimal residual disease positive B-cell precursor acute lymphoblastic leukemia. This is a particular matters meeting during which specific matters related to Amgen's supplemental BLA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

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

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the

participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. ROTH: Thank you, Dr. Tesh.

We'll begin with remarks from the FDA, and these will be given by Dr. Donna Przepiorka.

FDA Opening Remarks - Donna Przepiorka

DR. PRZEPIORKA: Thank you, Dr. Roth, and good morning. The topic for discussion today is a supplement to BLA 125557 for blinatumomab, a bispecific, CD19-directed T-cell engager that is currently approved for treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia or ALL.

All told, FDA has granted approval for over 20 drugs for treatment of ALL. For most of these drugs, the approval was for treatment of patients in morphological relapse, and the endpoint used to assess efficacy was morphological complete

remission, or CR, that is durable.

The supplement under discussion today is for a paradigm-shifting new indication, treatment of minimal residual disease or MRD positive B-cell precursor ALL. The intended population is patients in morphological CR or remission with only molecular evidence of leukemia, and efficacy is based on a molecular response.

The proposed indication was based in part on the results of studies MT103-203 or study 203, a single-arm trial of blinatumomab monotherapy for treatment of patients with ALL in remission with minimal residual disease greater than or equal to 0.1 percent by a molecular assay of cells in the marrow. This eligibility criterion brings up the first issue for discussion by ODAC today; that is, do the available data support the cutoff of an MRD level of greater than or equal to 0.1 percent as describing a subpopulation of patients with ALL in remission who have a need for preemptive therapy?

To support the criterion used for selection of these patients for the protocol, the applicant

will describe for you study 20120148 or study 148, a retrospective analysis of patients with ALL having MRD greater than 0.01 percent after intensive chemotherapy. This is the historical control group. None of these patients are treated with blinatumomab.

FDA identified 268 patients with Philadelphia chromosome negative B-cell precursor ALL in this cohort for analysis. Relapse-free survival or RFS was used as the analysis endpoint by FDA, and RFS was assessed in contiguous subgroups by MRD quantitation. The results are shown in the table here. It is clear that the patients with ALL in first remission with MRD greater than or equal to 0.1 percent have a poor prognosis with relapse-free survival 10.6 months or less.

The primary efficacy endpoint of the pivotal study, study 203, was a laboratory measurement, absence of detectable MRD using an assay with sensitivity less than 0.01 percent, and it was assessed after 1 cycle of blinatumomab. FDA

identified 87 patients in the study who fit the intended population, and in this group 79 percent had a reduction of MRD to lower than the target level. There was however no patient-level data for FDA to review to determine the clinical meaningfulness of a reduction in MRD independently for this patient population.

Therefore, to address whether blinatumomab treatment confers a benefit, the applicant will also describe for you their propensity score analysis from the patients of study 203 and the historical controls to assess the effect of blinatumomab on relapse-free survival and overall survival or OS.

They concluded that the blinatumomab treatment was associated with a significant effect on RFS. The FDA statistician however identified numerous confounding issues in the propensity score analysis, and she will describe the reasons why the results are not considered wholly credible. Nonetheless, the clinical reviewer will opine the RFS of 22.3 months for the patients with

blinatumomab in study 203 might be remarkable in the context of the rather short RFS in the historical control population.

Lastly, the clinical reviewer will provide an overview of the key safety outcomes for patients with MRD-positive ALL treated with blinatumomab. In general, the toxicity profile was similar to that established for blinatumomab in relapsed/refractory ALL populations and notably included fatal events in addition to the adverse drug reactions of cytokine release syndrome and neurotoxicity. This leads to the second question for ODAC to discuss; that is, considering the results of study 203 for patients with ALL in CR who have MRD greater or equal to 0.1 percent, does treatment with blinatumomab provide a potential benefit that outweighs the risks?

This concludes the FDA's introductory remarks. Thank you. I will now hand the podium over to Kathy Kross from Amgen for the applicant's presentation.

DR. ROTH: Both the Food and Drug

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

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interest and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the applicant's

presentations.

Applicant Presentation - Kathy Kross

MS. KROSS: Good morning. I'm Kathy Kross, and I'm the executive director in global regulatory affairs at Amgen. I would like to thank the FDA and members of the advisory committee for your time today.

Amgen is working to advance the science and evolve the treatment of patients with acute lymphoblastic leukemia. We are here today to discuss a potential paradigm shift for the treatment of patients with MRD-positive ALL using blinatumomab to achieve a complete minimal residual disease response and to improve clinical outcomes.

I will cover briefly the blinatumomab mechanism of action, regulatory history, and summary of the MRD-positive development program, then Dr. Radich will present an overview of MRD-positive ALL and describe the unmet medical need. This will be followed by my colleagues Dr. Franklin who will review the efficacy and

safety of blinatumomab and Dr. Friberg who will summarize the benefit-risk profile. We will conclude with a clinician's perspective from Dr. Logan. In addition, Dr. Richard Simon has joined us today to address your questions along with the Amgen team.

Blinatumomab, also known by its commercial name as Blincyto, is currently approved to treat relapsed or refractory B-cell precursor acute lymphoblastic leukemia in adults and children. Blinatumomab is a first-in-class bispecific T-cell engager also referred to as a BITE. It is an antibody construct that directs cytotoxic T cells to CD19 positive cells. CD19 is a highly specific B-cell marker that is expressed throughout B-cell development and in greater than 90 percent of B-cell lineage cancers.

Blinatumomab was engineered to target two markers. One end recognizes CD3 on cytotoxic T cells. The other end recognizes CD19 on leukemic B cells. By bridging T cells to the leukemic B cells, blinatumomab elicits the production of

inflammatory cytokines leading to the proliferation of cytotoxic T cells and lysis of CD19 expressing leukemic cells. This first-in-class bispecific antibody received orphan and breakthrough therapy designation for the treatment of ALL in 2008 and 2014, respectively.

Blinatumomab was granted accelerated approval in December 2014 for the treatment of Philadelphia chromosome negative relapsed or refractory B-cell precursor ALL. It was the first immunotherapy approved for the treatment of ALL and the first bispecific antibody approved by the FDA. This was based upon a single-arm trial with a primary endpoint of hematologic complete remission known as CR, a direct measure of leukemic burden. The approval was supported by supplementary historical data showing that blinatumomab-treated patients had CR rates approximately double those observed with standard of care chemotherapy.

In 2017, blinatumomab was converted to full approval in relapsed or refractory ALL, and the indication was expanded to include both

Philadelphia chromosome positive in pediatric patients. In the confirmatory phase 3 study, the CR rate in the blinatumomab arm was more than double the rate for the standard of care cytotoxic chemotherapy arm.

These results also demonstrated that blinatumomab's ability to reduce leukemic burden correlated with a significant overall survival advantage in a randomized controlled setting. In doing so, this confirmed the benefits predicted by the earlier single-arm study and historical comparisons.

Amgen is working to address the unmet medical need in ALL patients who had an incomplete response to their induction chemotherapy as indicated by the presence of minimal residual disease in the bone marrow; therefore, we submitted supplement BLA in September 2017 that is the topic of our discussion today.

The proposed indication is for patients who achieved a complete remission determined by conventional hematologic assessment but who still

have minimal residual disease present. MRD is a measure of leukemic burden at lower levels than those detected by conventional hematologic assessments. These patients still have leukemia and have a very poor prognosis as we will discuss today. This is a very rare patient population with only a few hundred patients identified per year in the U.S.

MRD is a direct measure of disease and refers to the presence of leukemic cells below the detection of conventional morphologic measures, meaning by light microscopy. Techniques to measure MRD have become more sensitive over the past few decades allowing clinicians to measure disease at much lower levels. Our understanding and detection of ALL has evolved over the years, and patients who are classified as being in hematologic complete remission and are MRD positive should not be considered in full remission. Dr. Radich will discuss these concepts and methods in his presentation.

An essential goal of ALL treatment is to

prevent relapse because patients who relapse have a poor prognosis. The presence of MRD after achieving hematologic remission is the single strongest prognostic factor for relapse, and thus overall outcomes for these patients are also quite poor. There is no standard treatment approach for MRD-positive patients, and there are no currently approved therapies to treat this residual leukemia. Therefore, MRD-positive ALL patients have a need for additional therapy.

To address this unmet need, we evaluated complete response as a primary endpoint in the development program to determine the clinical efficacy of blinatumomab in patients with MRD-positive ALL. The development program consisted of study 202, an exploratory phase 2 trial which demonstrated a promising ability of blinatumomab to induce complete molecular remissions in patients with MRD-positive disease.

To confirm and extend these findings, we conducted study 203, a single-arm phase 2 trial. Study 203 was designed in collaboration with key

European investigators and is the largest trial conducted to date in this patient population. The results of study 203 confirm the observations in study 202 demonstrating induction of complete molecular remission in nearly 4 out of every 5 patients treated.

Additionally, we conducted study 148, the historical comparator study of patients with ALL treated with standard chemotherapy as a supplementary assessment for effectiveness to substantiate the relevance of our single-arm trial, study 203.

To compare the results of study 203 and 148, we conducted a propensity score analysis to control for difference in baseline characteristics that could affect the outcome between blinatumomab and historically treated patients. My colleague Dr. Franklin will discuss these studies in more detail in our efficacy presentation.

Today we will show you the data that support the following. Blinatumomab is efficacious in MRD-positive ALL. Data from study 203 show that

78 percent of patients achieved complete MRD response after 1 cycle, meaning disease was completely undetectable by the molecular method. Median relapse-free survival for complete MRD responders was 23.6 months as compared to 5.7 months for patients who did not achieve a complete MRD response. Relapse-free survival was favorable compared to historical data and was supported by the propensity score analysis.

A large meta-analysis has demonstrated that clinical outcomes are better for ALL patients who achieved MRD negativity. There's a large volume of data supporting the benefit-risk of blinatumomab in the relapsed/refractory setting and adverse events are well characterized and managed through product labeling and the existing REMS. In totality, the evidence supports a favorable benefit-risk for blinatumomab as a single-agent therapy to treat this rate subset of patients with MRD-positive ALL.

Now, I would like to introduce Dr. Radich who will address the unmet medical need in MRD-positive ALL.

Applicant Presentation - Jerald Radich

DR. RADICH: Hi. Good morning. First, by way of disclosure, I'm getting paid for this consultancy role. I have no financial stake in any of the proceedings herethereafter and have not been involved in any of the blinatumomab studies that will be discussed here. I'm going to talk here in summary of MRD, how we measure it and what it means, and I'm going to do this from the standpoint of two roles that I have. One is as a physician who takes care of these kind of patients and also as a bench scientist who's been studying MRD for almost three decades now.

First, let's quickly discuss ALL. It's a very rare disease. There are about 7,000 cases in total in this country. About a third of those are adults. In adults, it's a very rare disease. We all know the treatment story in pediatric ALL where, really, 90 percent of the kids we cure, but we don't do nearly that well with adults. We can get people into complete remission about 80 percent of the time, but really the overall survival has

been stuck at around 40 percent for some time now. We do know that of those 40 percent, most of the failures are predominantly from relapses after they obtain complete remission. And for patients who relapse after remission, it's a very bleak picture.

So if you go to the stop slide there, this is a study of people who relapse after first remission, looking at males and females. And you can see that the overall survival, despite whatever type of therapy you want to give them, is less than 10 percent. The bottom is that same group of people fashioned out depending on what kind of therapy they receive.

For patients, if you look at that bottom curve, who relapse after complete remission and get just chemotherapy, their 5-year survival is 4 percent. You can salvage some of them with an allogeneic transplant in relapse, and the survival there is a little bit over 20 percent. So people who relapse are in really dire straits.

To discuss the molecular monitoring and the impact in ALL, I want to go back first to another

very rare disease, chronic myeloid leukemia, because this is really the model of how we can use molecular monitoring to really guide therapy and has made a huge impact on how we actually treat patients.

On the left is looking at the result after allogeneic transplant. For those of you who are as old as I am, allo transplant was really the primary way we treated CML for quite a while. In CML, every patient has the BCR-ABL translocation. That's a completely disease-specific marker that we can monitor by PCR.

On the left is looking at 12 months after a transplant and saying what's your risk of relapse if you have any BCR-ABL positivity? As you can see for people who have a negative test, your risk of relapse is about 4 percent, but it marches on upwards whether we have one copy detected, 1 to 100, or greater than 100, so kind of a dose response of minimal residual disease and outcome.

Times have changed and we now have tyrosine kinase therapies. On the right is the landmark

IRIS trial, which is the randomized registration trial for imatinib. What we've done here, we've now basically labeled BCR-ABL levels in a little bit different way now using this international scale. This is looking at event-free survival again at 12 months based on BCR-ABL level, and you can see that the top two curves there, which have spectacular survivals, are people with zero or vanishingly small amounts of BCR-ABL, and as you get increasing amounts, your relapse risk is higher and higher.

Really, in CML, now BCR-ABL is used as the only way we do monitoring before we dispense morphology and the like and has really embedded itself in both treatment algorithms for the NCI and the NNL [ph], and in actual studies so that virtually every second generation drug has now used BCR-ABL level at 12 months as one of the primary study outcomes. So it's really revolutionized and is a model of how we can use molecular biology and genetics to really monitor disease in the leukemias.

The bullet points I'm going to raise here is that with chemotherapy, roughly 30 to 50 percent of adult ALL patients who have CR by morphology still have residual disease by some other sophisticated tests. We'll show that MRD really is just a measure of disease burden, and it's really the strongest prognostic factor for relapse after CR.

This is a cartoon showing the relative sensitivities of these assays. On the Y-axis, we've put the proportionate malignant cells. We have to apologize for the field. You'll read in the literature here various ways to represent disease burden; sometimes they'll say log reduction and sometimes they'll say 10 to the minus something, which relates to log reduction; and then sometimes they'll put it in percentages. We've talked a bit about a 3-log reduction, which is equal to 10 to the minus 3, which is equal to 0.1 percent. Sometimes it's a bit confusing, but that's how they all equal.

In this chart, you start off, and the green is the level of disease burden that we can measure

by morphology by looking at a microscope and trying to find leukemic cells that are backed out of normal cells. Remission is usually described as having 5 percent or less blasts, and that really just reflects how hard it is when you have low level of disease to find a leukemic cell and discriminate it from a normal cell. That's really the low level of sensitivity.

The blue there is the level of disease that is undetectable by morphology, but you can pick up by other sensitive assays. The ways that we usually do this in ALL. There are three of them. There's flow cytometry, which looks at the distribution and amount of antigens on cell surfaces, and that has a detection in most labs of somewhere between 10 to the minus 3 to 10 to the minus 4.

PCR of immunoglobulin gene rearrangements, and what that means is that each B cell in its development has a unique VDJ rearrangement, and if a leukemia stems from that B cell, that whole clone will have that VDJ rearrangement. You can actually

isolate that and then make patient-specific primers that then become a patient-specific fingerprint of the disease that you can then use for PCR monitoring. That sensitivity is usually 10 to the minus 4 or 10 to the minus 5. And now there are next-generation sequencing techniques that use multiple sets of primers, and one assay can determine all the VDJ rearrangements. There you can get down to 10 to the minus 5 to even 1 in a million sensitivity.

Let's imagine that you have ALL and come in sick to the emergency room. You probably have around a diagnosis of 10 to the 12 leukemia cells. Just for sake of reference, there are 10 to the 11 stars in the Milky Way, so you have a lot of disease burden when you get treated. We're going to give you conventional chemotherapy, then roughly around day 30 we're going to do a bone marrow and see where you're at. If you have still, by morphology, blasts, then you really need alternative therapy. That could be immunotherapy, that could be a try-to-salvage transplant, and some

other experimental therapy.

If you are in a CR, then you have the two paths of the green or the blue. What we're going to be hoping is you go down the green pathway by either transplantation or continuing of the chemotherapy that got you to a morphological complete relapse or complete remission, but we know the national proportion of patients will take the blue curve and subsequently relapse. When those people relapse, they're going to have roughly a thousand-fold disease more, and they often come in rather sick. So your ability to salvage those patients, as I showed before, is relatively low.

What we're trying to do with MRD detection is really detect in a better way which people are going to go on the green pathway to remission and which ones are going to go the blue pathway and structure therapy based on that result. So we're going to use MRD in two ways, both as an indicator of relapse risk and really as a measure of a therapeutic target.

This is an example of many studies. This is

a study from Germany where they measured VDJ rearrangements by immunoglobulin PCR rearrangements. What this shows is that at the end of induction therapy, on the left the probability of continuous CR and on the right the probability of survival, based on whether you are MRD positive or not. The dark blue curves show the relapse rate or the survival and continuous CR if you're MRD positive, and the top teal is if you're MRD negative. You see there is a substantial difference between those survival curves.

About two years ago, a group was financed by the FNIH. They were members of academia, NCI and the FDA. We were tasked with looking and performing a meta-analysis to show what the effect of MRD was in both pediatric and ALL. Don Berry was the lead statistician and the first author of the paper. I was the person who was responsible for the clinical and molecular analysis.

What you have on the left is the overall survival for the pediatric studies, and on the right for the adult studies. In the gray are those

who have no MRD, and in the pink, positive MRD. What you can see is the kids do better than the adults; we know that. But if you look at the effect size of MRD, the hazard ratio is identical, 0.28 in both groups. This looks at the event-free survival, and you get the same story; basically, the hazard ratios are highly significant and are virtually the same for adults and kids.

This just shows the study one by one. If you look at anything left of the horizontal dotted line, there is a hazard ratio that basically shows that MRD positivity is bad and associated with poor event-free survival. What's really remarkable about this -- kids on the left, adults on the right -- is the absolute consistency of the data over many, many studies. These are studies that are done a decade apart, many different types of regimens. It really doesn't matter. The MRD is consistently bad. In the last two rows, there are the aggregate results based on two different statistical approaches, and that's where the 0.28 comes from, so a remarkably consistent effect of

MRD and outcome across all studies.

You can look at it a different way looking at specific variables. We have pediatric in the orange triangle there and adults in the black. If you look at different variables, for instance, how do you do the MRD assessment for cytometry or PCR, it doesn't make a difference. It doesn't make a difference in adults or kids. The MRD cutoff, 10 to the minus 4 and above or below, no difference; whether you measured it at induction and consolidation, no difference; and whether you are pH positive or pH negative, no difference. Basically MRD, no matter how you cut it, is associated with a bad outcome.

It's also associated with a bad outcome in transplant. These are patients out of my own institution of Fred Hutch, about 160 patients. These are patients who are all morphologically in remission, and you do a flow cytometry assessment of MRD. And if you have any MRD, your relapse-free survival and overall survival is significantly inferior to people who are MRD negative.

You can see the hazard ratio on the left. MRD impact was not influenced by CR1 or CR2 status. The impact is exactly the same. In fact, in this study, how much MRD you had did not influence impact of survival. In this context, even in transplantation, it would be an ablative regimen. Any MRD positivity is still extremely bad.

This is a more user friendly version of the NCCN guidelines, and we can take you through what they recommend. You get multiagent chemotherapy and then you assess your response. If you go down to the gray with no CR, this is obviously the worse outcome. You have to use something different. This could be different experimental therapy. This can be blinatumomab. This can be, if you're really bold, a salvage transplant.

The group we're interested in is the group that gets the complete remission. The NCCN basically says that you should use some assay that has a sensitivity of 10 to the minus 4. It doesn't care what that is. If you're MRD negative, the green, this is obviously the best group. This is a

group that can go on to get a transplant with relatively high success or continue on your regular chemotherapy. The group we're concerned about is the MRD-positive group. These are patients who obviously have a poor risk and you could go to transplant, but they have inferior outcomes. This is a group that the NCCN actually recommends blinatumomab for in their guidelines.

In summary, what I want to leave you with is that there is nothing minimal about residual disease. In fact, the field is changing to the term "measurable residual disease" because the presence of MRD is not associated with a minimal amount of leukemia burden. It's thousands if not millions of leukemia cells with MRD positivity. There are not minimal consequences of MRD; it's bad, so there's nothing minimal about the clinical consequence.

What we're trying to do here in this setting is look at these patients who we know have a substantial amount of leukemia burden, a substantial risk of relapse, and to offer some

different tools to reduce this leukemia burden. With that, I'm going to go to Janet Franklin to talk about clinical efficacy and safety. Thanks.

Applicant Presentation - Janet Franklin

DR. FRANKLIN: Thank you, Dr. Radich. I would now like to turn your attention to the efficacy of blinatumomab in the context of our MRD-positive ALL clinical development program. I'll begin by providing some context from the relapsed/refractory ALL program, then I'll review the clinical trials and MRD-positive ALL, which include our exploratory study 202, which has 5 years of follow-up data and the phase 2 trial, study 203.

Study 148 provides an historical comparator for the study 203, and then I'll discuss the propensity score analysis, which allows for comparison of the clinical study data to historical outcomes in patients with MRD-positive ALL.

Our relapsed/refractory ALL development program included both clinical and historical comparator studies. The clinical studies enrolled

711 adults and 93 children. For adult relapsed/refractory ALL, the accelerated approval was based on the 206 and the 211 single-arm clinical studies along with the historical comparator data from study 310. Later, a full approval was granted on the basis of the randomized control study 311, which is also known as the TOWER study.

Results from the TOWER study confirmed blinatumomab's ability to reduce disease burden compared to standard of care chemotherapy. These results established that disease reduction correlates with overall survival as demonstrated by the overall survival benefit over standard of care chemotherapy with a hazard ratio of 0.71 and a p-value of 0.012. This benefit was predicted by the earlier single-arm studies and the historical comparator study.

Here is an overview of our MRD-positive ALL development program. Study 202 explored safety and efficacy of blinatumomab in a small number of ALL patients with an N of 21. Study 203 is a

single-arm phase 2 study which enrolled 116 patients. We also conducted study 148, a historical comparator study that analyzed a retrospective cohort of 287 MRD-positive ALL patients. Lastly, we conducted a propensity score analysis of relapse-free survival and overall survival results in studies 203 and study 148.

Let's begin with the exploratory study. Study 202 established the early safety and efficacy profile of blinatumomab for an MRD-positive ALL patient population. The outcome results are shown on this slide. This proof-of-concept study had several key outcomes including 80 percent of patients achieving an MRD-negative response and 45 percent of patients going on to transplant.

It also provides 5-year long-term follow-up outcomes with a medium follow-up time of 50.8 months. The expected 5-year survival rate for MRD-positive ALL literature are all stating 20 percent or less. It was therefore very encouraging to see that half of the patients in the study, 10 patients, were alive and in remission

5 years after the start of their blinatumomab treatment. In fact, 5 of these 10 patients are still in remission without ever receiving a transplant.

The promising results of study 202 led to our development of study 203. Study 203 was a large multicounty, multicenter trial. Our goal was to confirm the 80 percent MRD response rate in exploratory study 202. We conducted the study in Europe where a centralized MRD assay was available at the time of the study development in 2009.

The investigators from three cooperative groups that were working with us were willing to randomize their extensively pretreated MRD-positive ALL patients to additional chemotherapy, particularly given the high rate of response in the early exploratory study. Therefore, in the end, the study design was a single-arm trial.

All patients enrolled had at least three prior blocks of intensive chemotherapy treatment. Patients had minimal residual disease, which was defined in the study as an MRD level at 10 to the

minus 3 or greater measured by an assay that had a minimum sensitivity of 10 to the minus 4, the best centralized MRD technology available in 2009 when the study was developed.

The baseline MRD level of 10 to the minus 3 allowed for demonstration of at least a 10-fold leukemic cell reduction from 10 to the minus 3 to 10 to the minus 4. The MRD cutoff of 10 to the minus 3 selected a population of patients at height of risk for relapse to allow for a feasible study to evaluate time-based endpoints. Patients were adults 18 years or greater with MRD-positive, B precursor ALL, who were either in their first or later complete remission. Key exclusion criteria are shown here, including a history of CNS pathology.

The primary endpoint is the proportion of patients who achieved a complete MRD response with the first cycle of blinatumomab treatment. Complete MRD response is defined as no detectable minimal residual disease. The value of this endpoint is an ability to measure conversion of

residual leukemia to MRD negativity as a key outcome measure. For this endpoint assessment, there was a null hypothesis of 44 percent based on historical data. Our goal was to show a response rate greater than that.

The key secondary endpoint was hematologic relapse-free survival amongst the Philadelphia chromosome negative patients at 18 months after the start of their blinatumomab treatment. Other secondary endpoints include overall survival and the incidence of adverse events. All endpoints were prespecified in the statistical analysis plan.

In study 203, all patients started 1 cycle of blinatumomab, which is defined as 28 days of continuous IV infusion followed by a 14-day treatment-free period. Therefore, 1 cycle is 6 weeks in duration, patients who've been assessed for the primary endpoint, achievement or not, of complete MRD response. Subsequently, patients could receive up to 3 additional cycles if clinical benefit had been demonstrated in the first cycle.

Based on individual and institutional

eligibility criteria, investigators determined which patients would go on to transplant. For patients who did go on to transplant, 100-day mortality was assessed. All study patients had clinical follow-up for efficacy over a two-year period and for survival.

In study 203, the median age of overall patients was 45 years with a range of 18 to 76 years of age. Thirteen percent of patients were actually 65 years or older. Patients entered this trial shortly after prior treatment, the median time period being 2 months. Of note, approximately two-thirds of all patients were in their first complete remission, one-third were in their second complete remission, and only 2 patients were in a later CR, CR3. The baseline MRD levels from central lab PCR testing are shown here in the bottom row with most patients at time of entry on study at levels of less than 10 to the minus 1 to 10 to the minus 3.

Now, let's turn to the primary results for the complete MRD response. Seventy-eight percent

of patients achieved a complete MRD response with an assay sensitivity of at least 10 to the minus 4 after just 1 cycle of blinatumomab; in other words, undetectable, minimal residual disease. Of note, the lower bound of the confidence interval for the result was above the prespecified threshold of 44 percent.

We looked closely to see if there were any distinguishing characteristics for the patients who were MRD responders, and here you see the analysis of complete MRD response rates by baseline patient characteristics. Across these variable characteristics, there are no predictive factors to distinguish those patients who responded to blinatumomab versus those who did not. Males and females, young and older ages, those with various baseline levels of MRD or remission status all achieved similar rates of complete MRD response.

The key secondary relapse-free survival at 18 months was met for Philadelphia chromosome negative patients. The prespecified analysis was censored for the events of transplant or

post-blinatumomab chemotherapy to assess the non-transplanted patients since an assessment of relapse-free survival was more meaningful without the factor of post-blinatumomab treatment.

The 18-month Kaplan-Meier estimate for relapse-free survival was 54 percent with the confidence intervals as noted. This exceeded the prespecified lower boundary of 28 percent. An analysis was also conducted for relapse-free survival without censoring. The 18-month estimate was 53 percent, which is similar to the primary censored result.

Note that in patients who are censored for the key events of transplant or post-blinatumomab treatment, the median has not yet been reached. We had expected that roughly half of patients on trial would go on to transplant. In fact, over two-thirds of patients were able to go to transplant and continuous remission after achieving a complete MRD response on blinatumomab treatment, a positive clinical outcome. Therefore, the number of non-transplanted patients in the analysis were

lower than anticipated.

Overall survival was another prespecified secondary endpoint. This overall survival analysis is uncensored for transplant or post-blinatumomab therapy. The median overall survival is 36.5 months with upper limits of the confidence interval not yet reached. Three years after the last patient enrolled, we conducted an additional longer term analysis. The median overall survival is 33.7 months with the upper limits of the confidence interval not yet reached, demonstrating a stable, long-term survival.

We conducted a landmark analysis to evaluate outcomes of MRD responders versus non-responders. For this analysis, we excluded patients who had relapsed or died prior to day 45, that by day 45 all other patients would have had their end of cycle 1 MRD assessments.

In the single-arm trial, the green curve represents complete MRD responders and the orange curve represents the non-responders. The median relapse-free survival for complete MRD responders

was 23.6 months in contrast to just 5.7 months for those who are non-responders. The hazard ratio was 0.38. A landmark analysis may have inherent limitations regarding confounding factors, however, we did not find a confounding factor that accounted for the large difference between the responders and the non-responders.

We also conducted a landmark analysis to look at the impact of MRD response on overall survival for complete MRD responders and non-responders. The median overall survival for complete MRD responders shown in green was 38.9 months with the upper limits not yet reached, and for non-responders, it was 10.5 months. The hazard ratio was 0.36.

Since 203 was a single-arm study, a historical comparator was provided to provide context for these results. Study 148, a historical study of MRD-positive ALL patients, had a key objective to estimate the outcomes of patients regarding relapse-free survival and overall survival. It is a retrospective cohort of patients

that had the Philadelphia chromosome negative B precursor ALL diagnosis.

The patient level data was obtained from eight study groups in Europe. A propensity score analysis was conducted to have a more direct comparator to patients enrolled in study 203. Primary endpoints were relapse-free survival and overall survival. The key inclusion criteria are listed noting that MRD detection was required by PCR at a level of greater than or equal to 10 to the minus 4 or by flow cytometry at a level of greater than or equal to 10 to the minus 3. Other criteria mirrored the study 203 inclusion criteria.

Alignment of inclusion criteria common to both studies permitted the propensity score analysis to be conducted according to the prespecified statistical analysis plan. In this analysis, we compared CR1 patients from each study with a common inclusion criteria, 73 patients in study 203 and 182 patients in study 148. Patients with MRD levels less than 10 to the minus 3 were excluded for this specific analysis.

A propensity score analysis is used to mimic the effect of randomization via its creation of balance between treated and untreated patients. Individual patients are weighted by the propensity to be treated by blinatumomab calculated on the basis of their characteristics at entry to study. This provides balance between the treatment groups with respect to the baseline covariates or baseline characteristics to give more valid comparisons between the two groups. Its use is most widely seen in observational studies and in device evaluation. More recently propensity score analysis has been used in regulatory settings for the evaluation of non-randomized studies.

Let's review the baseline covariate balance before and after making the propensity score adjustments. Here are the key characteristics or covariates common to both studies. The center column provides a profile of the common historical control and blinatumomab baseline patient characteristics.

These are the unadjusted scores with the

standardized differences noted. The higher the number, the less balance the patient characteristics are. On the right are the baseline characteristics after the propensity score weighting adjustments. There are several characteristics that became balanced after adjustment. An absolute standardized difference of less than 0.2 between study populations is considered to be balanced.

The Kaplan-Meier analysis compared blinatumomab treated patients in blue versus control patients in gray. We observed a statistically significant difference in relapse-free survival for the two MRD-positive ALL populations. For study 203, the median relapse-free survival is 35.2 months with the upper range not reached, and for study 148, the median relapse-free survival is 8.3 months. The hazard ratio is 0.5.

In summary, blinatumomab has an improved relapse-free survival when compared to historical data. To put this effect in perspective, we

performed sensitivity analyses to evaluate the impact of potential unmeasured or unknown baseline confounders. To change this result, these confounders would need to have an implausibly large effect size and to impact a high proportion of patients. When we looked again at the relapse-free survival three years after the last subject enrolled, the median is 28.8 months shown in red with the upper range not reached.

We also conducted a Kaplan-Meier analysis of overall survival. The median overall survival had a similar trend as the relapse-free survival, 36.5 months for study 203 and 27.2 months for study 148. When overall survival was reassessed three years after the last patient enrolled, the median overall survival was noted to be 44.6 months with the upper range not yet reached. We see a consistent separation of the curves.

It is difficult to isolate the contribution of transplant in any ALL clinical trial. There are a variety of statistical methods to address transplant although all have some limitations.

Transplant is a post-baseline, time-dependent variable instead of a baseline confounder. In the propensity score analysis, relapse-free survival was significantly longer for blinatumomab when compared to control as seen in the table, with and without adjustment for transplant, with a hazard ratio being 0.47 and 0.5, respectively.

A much higher percentage of blinatumomab-treated patients versus controls went to transplant. This was an unanticipated yet clinically positive outcome. Of note, almost twice as many blinatumomab treated patients greater than or equal to 35 years of age were able to go on to a transplant. The favorable relapse-free survival outcomes in study 203 were achieved despite more high-risk transplants, particularly in older patients.

In summary, across multiple published studies, MRD positivity reflects ongoing disease burden and identifies patients with poor outcomes. Blinatumomab has been demonstrated to induce a high, complete MRD response rate, and in fact,

78 percent of patients in study 203 achieved a complete MRD response rate after achieving only 1 cycle of blinatumomab.

The complete MRD response was associated with an improvement of both relapse-free survival and in overall survival. Our propensity score analysis demonstrated that blinatumomab treated patients had significantly prolonged relapse-free survival compared to historical patients. Nearly twice as many blinatumomab treated patients went on to transplant compared to the historical controls.

I will now provide an overview of the safety data that supports blinatumomab in the proposed indication for the treatment of patients with MRD-positive ALL. The safety profile of blinatumomab is established in relapsed/refractory ALL. Overall, the adverse events observed in the adult MRD-positive ALL population in studies were consistent with the experience of the replaced/refractory ALL setting.

Key safety risks for blinatumomab treatment are neurologic events, cytokine release syndrome,

and medication errors. These events are managed by additional warnings in the prescribing information as well as in the communication REMS to inform healthcare providers of these risks. There were no new safety risks identified for the MRD-positive ALL population.

The safety analysis set consists of a comprehensive data set of more than 800 patients with ALL who were treated with blinatumomab in clinical trials. I'll be describing safety data from the MRD-positive ALL clinical trial population seen on the left, which consists of 137 patients from studies 203 and studies 202. I will also present to you, as a reference, safety data from the total relapsed/refractory ALL clinical trial population seen on the right, which is comprised of 706 patients.

In the two MRD-positive ALL studies, patients were exposed to blinatumomab for a median of 55.5 days compared to a median of 39.9 days in the relapsed/refractory ALL studies. For both populations, the median number of started cycles

was 2. Overall rates of adverse events were similar between the MRD-positive ALL and the relapsed/refractory ALL populations. Nearly all patients experienced at least one adverse event. The subject incidence of serious adverse events was consistent between the two populations, while the incidence of grade 3 or higher events was lower in the MRD-positive ALL population.

Of particular note, it was a lower incidence of fatal adverse events occurring within 30 days of blinatumomab treatment in patients with MRD-positive ALL at a rate of less than 2 percent. The rates for events that resulted in a permanent discontinuation of treatment were also consistent between the two populations.

Next, I'll present the adverse events that were most common in the MRD-positive ALL population at a subject incidence of 25 percent or greater. On the left side, you see the subject incidence of any grade events in the MRD-positive ALL population, the blue bars, in contrast to the reference population of relapsed/refractory ALL

seen in the orange bars. The right side shows the incidence of these events that were grade 3 or higher.

Although the overall rates for these events were higher in the MRD-positive ALL population in general, the differences were driven by grade 1 or grade 2 events. These lower grade events did not have an impact on the patients' overall outcome or in ability to continue on treatment. Our review supports that the adverse events in this setting were consistent with those observed in the relapsed/refractory ALL setting.

Now I'll focused on the risk of neurologic events and cytokine release syndrome, which are included in the warnings section of the approved label as well as in the communication REMS. As shown on this slide for these two risks for both any grade events on the left side and grade 3 or higher events on the right side, the rate was comparable or lower in the MRD-positive ALL population.

I will discuss each of these risks in

further detail. The overall incidence of neurologic events in patients with MRD-positive ALL was 71.5 percent with the majority of events of lower grade in severity. The incidence of grade 3 or higher events was 16.1 percent, however, none of these events resulted in a fatal outcome. The neurologic events occurred early in treatment with an overall median time to onset of 2 days. Neurologic events resolved for the majority of patients, including for those who experienced the grade 3 or higher events. Overall, the neurologic events in this setting were consistent with the experience in the relapsed/refractory ALL setting.

As with other T-cell mediated immunotherapies, cytokine release syndrome is an identified risk of blinatumomab treatment. In the MRD-positive ALL population, cytokine release syndrome was observed in 4 patients translating to an overall incidence of 2.9 percent. There were no fatal cytokine release syndrome events in this setting.

Consistent with the experience of the

relapsed/refractory ALL population, cytokine release syndrome events occurred early in treatment with a median time to onset of 2 days from the start of the infusion. All 4 patients recovered quickly within 2 day of event onset. No patients discontinued treatment due to cytokine release syndrome.

In summary, the majority of adverse reactions were manageable with supportive measures with or without treatment interruption. In most cases, patients were able to resume or continue treatment without negatively affecting therapeutic benefit. The safety profile of blinatumomab in patients with MRD-positive ALL was consistent with that observed in the relapsed/refractory ALL setting as described in the approved prescribing information. No new safety risks were identified for patients with MRD-positive ALL.

Furthermore, physicians who would prescribe blinatumomab in this setting have prior experience with this use in relapsed/refractory ALL, and thus are familiar with the safety profile of the

product. The product labeling and the existing REMS are sufficient to manage the key risks in the postmarketing setting.

I'd like to introduce my colleague, Dr. Gregory Friberg, to discuss the benefit-risk profile of blinatumomab.

Applicant Presentation - Gregory Friberg

DR. FRIBERG: As you've heard today, the field has evolved. What was previously called the hematologic CR is no longer the best measure before remission in patients with ALL. MRD is now widely used in clinical practice as both a marker of disease persistence as well as incomplete response. MRD positivity predicts future disease recurrence and death in both the newly diagnosed and in those specifically going to transplant. A large meta-analysis recently demonstrated that achieving MRD negativity correlated with improved survival.

Blinatumomab was approved in 2014 for relapsed/refractory ALL based upon the ability to dramatically reduce leukemic burden. The phase 3 TOWER study later showed that it improves overall

survival in this same setting versus salvage chemotherapy. In study 203, patients had residual leukemia in their marrow after multiple cycles of cytotoxic induction and consolidation. These patients were selected for their especially poor prognosis and likelihood to relapse.

A single cycle of blinatumomab induced complete MRD negativity in 4 out of 5 patients, and more than half of these patients were relapse-free at 18 months. We recognize that interpreting survival results from single-arm studies could present specific challenges. To address immortality bias, we conducted landmark analyses and noted markedly improved survival for responders as compared to non-responders.

To address imbalances in baseline factors, we conducted a propensity-weighted analysis comparing study 203 to an historic MRD-positive control. Blinatumomab treated patients had significantly longer relapse-free survival, and after adjustment for transplant as a time-dependent covariate, it did not significantly affect this

benefit.

Another way to look at the clinical impact of blinatumomab is to look at the size of the leukemic productions that were observed on the 203 study. Picking a conservative approach and assuming no reduction is possible below the lower limits of detection of the assay, the median reduction for a responding patient was almost 3 logs or 750-fold. Individual reductions ranged between 100-fold and 30,000-fold for complete MRD responders. Non-responding patients had much smaller reductions or had increases in their leukemic burden.

Over 5,000 patients have received blinatumomab across studies in clinical practice, and its safety profile is well established. We did not identify any new risks in MRD-positive ALL patients. Adverse events are well described in the prescribing information and REMS communication plan, and they're manageable with the measures outlined in these materials.

In 2018, finding residual leukemia in the

marrow after initial chemotherapy presents physicians and patients with a dire situation. The only available options are to intensify so far ineffective chemotherapy or to proceed to a bone marrow transplant knowing that outcomes are poor. Blinatumomab has demonstrated that it can dramatically lower leukemic burden in these very patients with encouraging relapse-free survival. Together with the established efficacy and more advanced disease, it's biologically plausible and clinically reasonable to believe that MRD-positive patients are benefitting from blinatumomab.

In a complex and rare disease like ALL, definitive data sets are often unavailable. While the evidence presented today does not answer every question, it shows that blinatumomab is an active therapy versus MRD, and the degree of clinical efficacy outweighs the risks. In this setting where waiting for frank relapse can lead to higher morbidity and mortality, the use of such an agent to dramatically reduce leukemic burden is clinically justified.

I would like to introduce Dr. Aaron Logan to provide some concluding remarks.

Applicant Presentation - Aaron Logan

DR. LOGAN: My name is Aaron Logan. I'm a clinician and investigator with the adult hematology and blood and marrow transplant group at the University of California San Francisco. I am a paid consultant to Amgen, but I have no financial interest in the outcome of today's proceedings.

It's a very exciting time in the management of acute leukemias, ALL in particular, with several new therapies recently becoming available to treat relapse disease. Out of all of these developments, the one I'm most excited about is this proposed label modification to permit treatment of ALL MRD with blinatumomab. The positive impact of preventing relapse from an MRD state cannot be overstated. Measurable or minimal residual disease is not a biomarker. It is simply a more precise measurement of disease burden using modern technologies.

We know confidently from many studies that

MRD after the initiation of therapy represents the presence of leukemia cells that are resistant to traditional chemotherapy. It is those cells that cause relapse, and when patients relapse, they are in clinical distress commonly afflicted with infections and organ toxicities from things like tumor lysis syndrome. In many cases, patients are unfit to receive or to respond well to novel therapies at the time of relapse. It is thus essential that we move therapy of resistant leukemia to an earlier stage of disease; that is move treatment towards the targeting and eliminating of MRD.

Blinatumomab's manageable toxicity profile, which really is different from what we see with cytotoxic chemotherapy, enables us to help patients in this way. This label modification, if granted, is an important and I would say essential move forward for the field of leukemia management.

So I'm here today for my patients. I'm here today because the preponderance of data tell us that treating MRD is the right thing to do and will

improve patient survival and quality of life by avoiding treatment when in the throes of relapse. As a leukemia care provider, I'm glad we're having this conversation today, and I appreciate your thoughtful consideration of this proposal. Thank you.

DR. ROTH: Thank you to all the applicant speakers. We will now move to the presentations from the FDA.

FDA Presentation - Emily Jen

DR. JEN: Thank you, Dr. Roth, and good morning. My name is Emily Jen. I'm the clinical reviewer for this BLA efficacy supplement, and the members of the FDA review team are listed here. As mentioned previously, blinatumomab is currently approved for the treatment of patients with relapsed and refractory B-cell precursor ALL. The applicant is now seeking an indication for the treatment of patients with minimal residual disease positive B-cell precursor ALL based on a single-arm trial, study MT103-203, of patients in morphologic CR with MRD greater than or equal to 0.1 percent,

which the applicant has described in their presentation.

There are two key issues for consideration in the review of this application. The first is the patient population and whether the available data support a cutoff of MRD greater than or equal to 0.1 percent as describing a subpopulation of patients in morphologic complete remission who have a need for preemptive therapy. The second is regarding response. Specifically, is achieving undetectable MRD, as determined by an arbitrary assay sensitivity in this population, sufficiently meaningful to outweigh the risks of treatment with blinatumomab?

In the next 45 minutes, we will present to you FDA's perspective on these issues based on the information submitted in the BLA. I will first discuss the available data supporting MRD as a prognostic indicator of a high-risk population requiring further therapy. This will be followed by a discussion of the efficacy results from the pivotal trial and the data addressing undetectable

MRD as a prognostic indicator of long-term benefit. This includes a propensity score analysis, which will be presented by my statistics colleague, Dr. Xu. Finally, I will give a brief overview of the safety analysis.

Although some patients with ALL who achieve complete morphologic remission may survive long term, a large proportion of patients who achieve morphologic CR still experience relapse. The first question at hand is what level of MRD identifies this subgroup of patients in morphologic CR who are destined to relapse early and who might benefit from further therapy?

To address this issue, FDA assessed outcomes using patient-level data from study 20120148, which I will refer to as study 148. As you recall from the applicant's presentation, study 148 was a non-interventional retrospective analysis of data collected from European databases of ALL study groups that included MRD testing in their clinical trials. The prespecified primary objective of the study was to estimate the hematologic relapse-free

survival for adults with MRD at 0.01 percent or higher.

To confirm that 0.1 percent was an appropriate cut-point for selecting a subgroup with high risk for relapse, FDA performed an analysis of patient-level data in a cohort of patients in first morphologic CR or CRi from this study looking at hematologic RFS by baseline MRD level.

The characteristics of the patients in the FDA's analysis set are shown here. All patients in this cohort were 15 years of age or older, in first morphologic CR or CRi, and had MRD measured at greater than or equal to 0.1 percent after at least 3 blocks of intensive chemotherapy. Please also recall that the study excluded patients with MRD less than 0.01 percent or those with undetectable MRD. Also of note, 46 percent of patients in the cohort went on to allogeneic stem cell transplantation after their baseline MRD assessment.

This graph shows FDA's analysis of hematologic relapse-free survival for patients in

first morphologic CR or CRi by baseline MRD level. The top curve represents patients with the lowest level of MRD included in the study, while the bottom curve represents those patients with the highest MRD levels.

You can see that the three subgroups with MRD greater than or equal to 0.1 percent, represented by the green, orange, and blue curves, have a clearly poor prognosis with a median hematologic RFS of 10.6 months or less measured from the time of first MRD detection. However, whether the hematologic RFS for patients with MRD between 0.01 and 0.1 percent, seen here in the brown curve, is different from those with MRD less than 0.01 percent cannot be determined from these data since MRD-negative patients were not included in the cohort.

Therefore, we agree that the available data support an MRD of greater than or equal to 0.1 percent as a cutoff which describes a population of patients in morphologic CR with poor prognosis who might benefit from further treatment.

Having addressed the first issue, I will now turn to the efficacy results of the pivotal trial, study MT103-203, which I will refer to as study 203. Study 203 has been described in detail in the applicant's briefing document and presentation.

Briefly, 203 was a single-arm, open-label, multicenter trial in adults with B-cell precursor ALL who were in morphologic CR or CR without platelet recovery after 3 blocks of intensive chemotherapy and who had an MRD greater than or equal to 0.1 percent in an assay with a minimum sensitivity or lower limit of detection of 0.01 percent.

The primary endpoint was undetectable MRD after 1 cycle of blinatumomab. The secondary endpoint prespecified by the applicant was hematologic relapse-free survival at 18 months after treatment censored at the time of stem cell transplantation or when additional salvage therapy was given after protocol treatment with blinatumomab.

A total of 116 patients were treated with blinatumomab on study 203. The applicant excluded 3 patients for MRD assays of insufficient sensitivity or lack of screening bone marrow assessment resulting in a primary endpoint full analysis set of 113 patients. FDA's efficacy analysis set included only the subgroup applicable to the intended population.

Specifically, FDA excluded patients with a baseline MRD less than 0.1 percent, patients not in hematologic remission, those who had received other active therapies that could affect the primary endpoint of MRD response, and patients in morphologic CR with incomplete count recovery who were considered to have treatment failure. The remaining 87 patients comprised the FDA efficacy analysis set. The characteristics of the study populations are shown here. Patients in the FDA efficacy analysis set were mostly in first remission, and 79 percent went on to allogeneic stem cell transplantation after treatment with blinatumomab.

The primary endpoint of the trial was undetectable MRD in an assay with a sensitivity less than or equal to 0.01 percent after 1 cycle of blinatumomab. The study had a prespecified null hypothesis threshold of 44 percent. FDA's analysis showed that 79 percent of patients achieved undetectable MRD with a 95 percent confidence interval of 70 percent to 88 percent, which is comparable to the applicant's results in the larger population. We agree that the study met its primary objective. In addition, the response was consistent across demographic and baseline disease characteristic subgroups.

The key secondary endpoint was the hematological relapse-free survival rate at 18 months in all patients with Philadelphia negative ALL who were in morphologic CR at the start of treatment censored at either stem cell transplantation or post-blinatumomab salvage therapy. However, for assessment of outcomes of patients with acute leukemia, FDA does not recommend censoring at time of transplantation or

salvage therapy for the primary analysis. Using the FDA efficacy analysis set without censoring, the 18-month hematologic RFS estimate was 59 percent with an estimated median hematologic, relapse-free survival of 22.3 months.

Study 203 was a single-arm trial, and although it won on its primary endpoint with 79 percent of patients achieving undetectable MRD, it has not been established that achieving undetectable MRD under these circumstances is a valid surrogate for or is reasonably likely to predict long-term clinical benefit outcomes. Therefore, FDA sought to determine whether achieving undetectable MRD after post-consolidation blinatumomab predicts long-term benefit for these patients.

To address this issue, FDA reviewed two additional lines of evidence submitted by the applicant, a published meta-analysis by Berry et al. and a propensity score analysis assessing the effect of blinatumomab on hematologic RFS and OS in a cohort of patients from studies 148 and

203.

The meta-analysis by Berry et al. looked at the association of MRD with clinical outcome in ALL in 39 published studies. The characteristics of the 39 studies are summarized here. Overall, the studies had a mix of age groups, MRD measurement methodologies, timing of MRD measurements, and cutoffs used to designate MRD negativity. Eleven of the 39 studies were specifically identified as pertaining to B-cell ALL. These 11 studies, shown in the far-right column, included over 5,000 patients who were predominantly pediatric patients with MRD assessed at the end of induction. Seven studies used MRD less than 0.01 percent to define negativity and 4 studies used MRD less than 0.1 percent.

For the 11 studies of patients with B-cell ALL, the hazard ratio for event-free survival was 0.21 in pediatric studies and 0.28 in adult studies in favor of MRD negativity. These data provide support for the assertion that there is an association between MRD and outcome for patients

with B-cell ALL. However, the included studies used arbitrary binary cutoffs for defining MRD negativity, and therefore the analysis did not address quantitatively what level of MRD identifies treatment success.

Additionally, different studies in the Berry meta-analysis used different cutoffs for MRD negativity. None of the studies used an MRD cutoff level lower than 0.01 percent. Whether patients in the studies were in morphologic CR or CRi at the time of MRD assessment was not described, and the remission number, that is whether patients were in CR1, CR2, or later CR, was also not reported. Therefore, no conclusions can be drawn regarding what level of MRD is reasonably likely to predict long-term EFS or OS for patients with ALL by remission number.

To enable use of MRD response for regulatory purposes, FDA still seeks to review patient-level data by log group of MRD to identify those with consistently good long-term RFS and OS in a fashion similar to that used to identify the patients with

poor prognosis in study 148.

Since the meaningfulness of the MRD response endpoint in study 203 was not clear, FDA also reviewed the propensity score analysis submitted by the applicant. The objective of this analysis was to assess specifically whether there was a treatment effect of blinatumomab with respect to hematologic RFS or OS, more direct measures of clinical benefit, for patients with MRD-positive ALL.

The propensity score analysis included patients from study 148 and study 203 controlling for important baseline covariates. The patient population included adults with Philadelphia negative B-cell precursor ALL who were in first morphologic CR or CRi after at least 3 intensive chemotherapy blocks and who had MRD greater than or equal to 0.1 percent. Because 14 days was the median time from MRD assessment to start of blinatumomab for patients in study 203, patients from study 148 were excluded if they had a time to relapse of less than 14 days from the date of MRD

detection. The analysis endpoints included hematologic RFS and OS with RFS calculated as the time from first MRD detection in remission to hematologic relapse or death.

The characteristics of the two cohorts in the study population are shown here and have been described in detail by the applicant. Of note, a higher proportion of patients in the study 203 cohort, 78 percent, went on to hematopoietic stem cell transplantation compared with 44 percent in the direct comparison analysis cohort from study 148.

I will now turn the presentation over to Dr. Xu, the FDA statistical reviewer, for the discussion of the propensity score analysis.

FDA Presentation - Qing Xu

DR. XU: Thank you, Dr. Jen.

Good morning. My name is Qing Xu. I'm the primary statistical reviewer for this BLA. I will limit my presentation to a brief description of propensity score analysis, discuss some of the key elements of the propensity score analysis results,

and the limitations in their interpretation.

As you have heard, the propensity score approach attempts to mimic randomization by creating a balance between two groups with respect to important available baseline covariates. This is an accepted method using historical control. In this submission, the propensity score analysis was used to compare Blincyto patients from study 203 to those from study 148 with respect to RFS and OS after calculating the weight for each patient. Selected important baseline factors are expected to be balanced after adjusting the propensity score using a stabilized inverse probability of treatment weight.

This slide presents the FDA analysis and Kaplan-Meier plots comparing the Blincyto arm and the control arm using the propensity score and adjusted observations with respect to RFS on the left and OS on the right. The sponsor claims, based on these analyses, that the Blincyto arm is superior to the historical control. However, our evaluation has exposed confounding factors that

prevent us from concluding that Blincyto is superior to the historical control.

First, in both these analyses of RFS and OS, transplantation interaction by treatment was ignored. As noted earlier by Dr. Jen, differential rates of patients received stem cell transplant between the two arms and the effect of such differential rates cannot be ignored in this analysis. The hazard ratio of 0.5 in the RFS analysis and the hazard ratio of 0.76 in the OS analysis do not account for this imbalance in transplantation rates. This will be further explained in the next slide.

As seen in this plot, there was differential follow-up time between the two treatment groups. The median follow-up time in study 203 Blincyto arm, the blue curve in the plot was 8.2 months while the follow-up time was 18.4 months in study 148 control arm red curve. These could potentially introduce bias in estimating treatment effect based on time-to-event analysis such as RFS and OS.

Acknowledging the limitations of subgroup analysis, we looked at the difference between the treatment and the control in the subgroup of patients who did not receive stem cell transplant and those who received stem cell transplant. The top panel shows the RFS analysis on the left and the OS analysis on the right in patients who did not receive transplantation. The bottom panel shows the RFS and OS analysis in patients who received transplantation.

We observed that there is no difference among those who received stem cell transplant with respect to both RFS and OS suggesting a treatment by stem cell transplant interaction effect. Although the analysis is not presented here, we looked at stem cell transplant as time-dependent covariates in a Cox regression model, and the interaction effect was significant.

In addition, we noted that the data were not contemporaneous. The historical study 148 was started in 2000 and study 203 was started in 2010. The practice of medicine may have evolved with

respect to transplantation since 2000. Due to these issues inherent in historical control studies, some potential important covariates are not being included in the analysis and the confounding of the treatment effect due to transplantation, the interpretation of the comparative analysis results presented in the previous slide is not clear and the Blincyto effect cannot be concluded.

While the propensity score method is a useful method when comparing to historical control, there are inherent limitations due to the following reasons. First, the Blincyto study 203 includes patients that have achieved both CR1 or CR2 and historical control arm does not include CR2 patients. Thirty-five percent of patients in study 203 were removed so that this entry criteria matched the control arm.

In general, when using historical control data, the historical data are matched to the characteristics of the current trial and not the reverse by excluding patients. In study 203, the

treatment arm in the comparison is no longer representative of the original intended population.

Second, stem cell transplant is an effective treatment, which potentially pronounce RFS and OS. In other words, stem cell transplant may contribute to the estimate of RFS and OS -- confounding Blincyto effect, the rates of patients receiving stem cell transplant between the two arms, 78 percent of Blincyto patients received stem cell transplant; 44 percent of control patients received stem cell transplant. There may be many reasons for this difference. Third, different follow-up time between the two groups was observed. This could introduce bias in treatment effect estimate.

To summarize, in general, randomized trials are preferred, however, in selected cases, propensity score analysis may be a valid method for comparison to historical data. However, in this study, the interpretation of propensity score and adjusted analysis results is not clear due to the following limitations of the analysis: inappropriate data matching confounding from stem

cell transplant and a different follow-up time.

We cannot conclude from the propensity score analysis that Blincyto is superior to the historical control with respect to both RFS and OS. Thank you. I will return the podium to Dr. Jen for the clinical presentation.

FDA Presentation - Emily Jen

DR. JEN: Thank you.

Lastly, FDA looked also at hematologic RFS by the observed depth of MRD, in the response assessment in study 203. Although the response criteria required a minimum assay sensitivity of 0.01 percent, only 9 percent of the responding patients had a best assay sensitivity at this level. The remaining patients had MRD assessed in an assay with a sensitivity of at least 0.005 percent.

FDA looked specifically at those patients in morphologic CR1 with MRD assay sensitivity of less than or equal to 0.005 percent and a best cycle 1 response of 0.01 percent or lower. Note that this includes 5 patients with detectable MRD less than

0.01 percent represented here in the red curve. This analysis is limited by the very small number of patients on the red curve with MRD between 0.01 and 0.005 percent after treatment with blinatumomab, but it appears that those who achieved MRD less than 0.005 percent on the blue curve have a superior outcome. Overall, in study 203, 74 percent of patients achieved conversion from MRD greater than or equal to 0.1 percent to undetectable MRD less than 0.005 percent after treatment with blinatumomab.

In summary, in study 203, 79 percent of patients with B-cell precursor ALL in morphologic CR with MRD greater than or equal to 0.1 percent achieved an undetectable MRD with an assay sensitivity of at least 0.01 percent after treatment with 1 cycle of blinatumomab. Additionally, 74 percent had undetectable MRD with an assay sensitivity of at least 0.005 percent. Although this is encouraging, achievement of undetectable MRD by any definition has not been validated as a surrogate for clinical benefit, so

the meaningfulness of the MRD response results is not clear. The median hematologic RFS in study 203 was 22.3 months, but time-to-event endpoints are difficult to interpret in a single-arm trial.

The propensity score analysis was used as an approach to establish a treatment effect of blinatumomab on RFS, a more direct measure of clinical benefit, for patients in first remission. The applicant concluded that there was a difference in hematologic RFS favoring patients treated with blinatumomab. However, FDA found limitations to the propensity score analysis that affect the interpretability of the results, including exclusion of 35 percent of the trial patients; confounding due to an imbalance in subsequent transplantation; and a difference between the cohorts in follow-up time.

This concludes the efficacy discussion for this presentation. I will now focus on the analysis of safety. The analysis of the safety of blinatumomab in patients in morphologic CR or CRi with MRD utilized data from all 116 patients

treated on study 203 and data from study 202, an exploratory proof-of-concept, single-arm trial of 21 adult patients in morphologic CR or CRi with MRD greater than or equal to 0.01 percent who were treated with blinatumomab.

I will refer to this group collectively as the MRD-positive population. For context, I will also show key safety data from six studies of blinatumomab in patients with relapsed or refractory B-cell precursor ALL submitted by the applicant. I will refer to this group as the relapsed/refractory population.

In the analysis of on-study deaths, FDA found two fatal treatment-emergent adverse events in the MRD-positive population. One patient experienced a fatal atypical pneumonia within the first 30 days of treatment, and one patient had a subdural hemorrhage within 30 days of the last dose of blinatumomab. The incidence of treatment-related mortality is thus 2 percent for the MRD-positive population.

FDA also looked at early post-transplant

mortality in the patients going on to stem cell transplantation following study treatment with blinatumomab. In the follow-up of patients from the TOWER study, a randomized trial of blinatumomab versus standard of care chemotherapy in patients with relapsed and refractory ALL, patients from the blinatumomab arm who achieved remission and went on to allogeneic stem cell transplantation had a higher observed day 100 mortality than those from the standard of care arm.

Because of the question of whether blinatumomab affects post-transplant mortality, FDA also assessed this outcome in the MRD-positive population. In the MRD-positive in study 203, 90 patients ultimately went on to stem cell transplantation and 10 percent died within 100 days after transplant. Post-transplantation follow-up was not recorded for study 202.

From the limited data available, it appears that the post-transplant mortality rate in the MRD-positive population is similar to that observed in the relapsed and refractory population treated

with blinatumomab. Because the numbers of patients are small and the cohorts were not randomized, firm conclusions cannot be made, and FDA awaits additional results from a postmarketing requirement that was issued in July of 2017 to study the effect of blinatumomab on BMT-related mortality.

The most common treatment-emergent adverse events resulting in permanent discontinuation or interruption of treatment with blinatumomab are shown here in decreasing order of incidence in the MRD-positive population. The most common adverse events leading to discontinuation of treatment were neurologic toxicities. The most common adverse events leading to treatment interruption were cytokine release syndrome and related clinical manifestations as well as neurologic toxicities. The incidences of withdrawals and treatment interruptions in the MRD-positive population were similar to those observed for the relapsed and refractory population.

The applicant has provided a detailed listing of treatment related adverse events in

their briefing document. The safety profile of blinatumomab is well established, and overall, FDA identified no new safety signals in the MRD-positive population. Patients in both MRD-positive and relapsed/refractory populations received a median of 2 cycles of blinatumomab.

FDA's analysis of adverse events focused on adverse events of particular interest with exposure to blinatumomab, including cytokine release syndrome, neurotoxicities, fever, and sepsis.

Cytokine release syndrome, infusion reactions, and capillary leak syndrome are difficult to distinguish because the clinical manifestations and timing overlap. FDA incorporated reports of adverse events including these terms for the safety analysis. Using this grouped term, 7 percent of patients in the MRD-positive population developed any grade CRS, 3 percent developed grade 3 or higher CRS, and there were no fatal CRS events. The incidence of any grade CRS in the MRD-positive patients was slightly less than the incidence observed in the relapsed

and refractory population at 7 percent versus 15 percent, respectively.

Sixty-nine percent of the MRD-positive populations developed a neurologic toxicity after treatment with blinatumomab. The most common events were headache, tremor, dysphasia, and encephalopathy. Fifteen percent of patients experienced a grade 3 or higher neurotoxicity, the most common of which were headache, tremor, encephalopathy, and seizure. There were no fatal neurologic events in the MRD-positive population and all events were resolved with treatment discontinuation or interruption and supportive care. The incidence of neurologic events in the MRD-positive patients was similar to that observed in the relapsed and refractory population.

Despite the relatively low incidence of CRS, almost all patients in the MRD-positive population had fever, but relatively few, 7 percent, had grade 3 or higher fever. The incidence of sepsis was 2 percent in the MRD-positive population, which is substantially lower than that observed in the

relapsed and refractory population.

In summary, in response to the issue of whether patients in morphologic CR with MRD greater than or equal to 0.1 percent represent a population of patients that should be treated, the analysis of outcomes in study 148 showed that patients who did not receive blinatumomab had a median hematologic RFS of 10.6 months or less. In study 203, 79 percent of patients converted to MRD below the limit of detection of their assay and 74 percent had undetectable MRD in an assay with a sensitivity of less than or equal to 0.005 percent after treatment with 1 cycle of blinatumomab. But the meaningfulness of such an MRD response has not been established.

RFS is a measure of long-term benefit, and for the patients treated with blinatumomab in study 203, the median hematologic RFS was 22.3 months. For the MRD-positive patients in first remission, the applicant used the propensity score analysis to show that treatment with blinatumomab conferred a hematologic RFS benefit compared to historical

controls. However, FDA found that there were significant limitations that affected the interpretability of the propensity score analysis and that no conclusions could be drawn.

FDA does not usually use time-to-event endpoints in a single-arm trial for regulatory decision-making, but one has to acknowledge that the observed RFS in study 203 is strikingly better than expected, and the agency looks forward to hearing ODAC's perspective on this observation.

Lastly, with regard to safety, there were 2 percent fatal adverse events in the MRD-positive population treated with blinatumomab. The overall safety profile was similar to that established in patients with relapsed and refractory ALL, and the risks of neurotoxicity and CRS remain.

To close, here are the issues for discussion. First, do the data support the cutoff of MRD greater than or equal to 0.1 percent as describing a subpopulation of patients with ALL in morphologic complete remission who have a need for preemptive therapy? Second, the voting question is

whether the results of study 203 demonstrate that for patients with ALL in morphologic CR who have MRD greater than or equal to 0.1 percent, treatment with blinatumomab provides a potential benefit that outweighs the risks from the treatment.

Thank you for your attention. This concludes the FDA presentation. I will now turn the meeting back over to Dr. Roth.

Clarifying Questions

DR. ROTH: Thank you, Dr. Jen.

We will now take clarifying questions for the presenters, so if you have a question, please raise your hand. Dr. Tesh will write it down, and we'll try to take those in order. And also remember to please state your name for the record before you speak. If possible, please direct questions to a specific presenter. I will lead off.

I have a question about 203, so maybe for Dr. Franklin. The primary endpoint basically was MRD conversion following 1 cycle of therapy, but one could get up to 4 cycles of therapy. I wonder

if you could walk me through, was that an investigator discretion decision? How many people got 1 versus 2 versus 3 versus 4? If you could just take me through that process, what I'm trying to find out is if you have the information about how many people were treated with each of those, whether maybe only people that got 3 or 4 cycles got a hundred percent of the benefit.

I'm just trying to figure that out for myself.

DR. FRIBERG: Dr. Franklin?

DR. FRANKLIN: In terms of our 203 study design, patients who went on to get up to an additional 3 extra cycles, this was at the discretion of the physician but also with some evidence of clinical benefit in the first cycle. In terms of the numbers of cycles received, the median number was 2, and we'll go over the percentage of patients for each cycle. Slide up, please.

This shows you the data regarding cycles 1, 2, 3, and 4. As you can see, all patients received

1 cycle, possibly two-thirds 2 cycles, and the numbers drop off for cycles 3 and 4. So again, this was based on the issue of the concept in the ALL therapy of consolidation therapy.

For patients who are going on to a transplant, for example, there was in many cases a need to wait for the donor availability or the final criteria for the transplant to move forward. So that allowed patients to continue with therapy in that waiting period. And for those patients who did not go on to transplant, there was a decision made by the investigator in terms of whether there was continuing benefit for additional cycles. But again, the limitation was 4 cycles total maximum.

DR. ROTH: As just a follow-up, if someone decided that there was not any change with 1 cycle of therapy and stopped therapy, do we know that there aren't people who convert with a second, or a third, or a fourth to the primary endpoint, which has long since passed after the first course of therapy?

DR. FRANKLIN: Yes. Indeed, for our primary

endpoint, we did limit that to patient response after cycle number 1. There were some patients who had some reduction in their levels, and therefore the physician felt there was clinical benefit. They went on to receive 2 cycles. Slide up. We see that there are two additional patients who had achievement of a complete MRD response after two cycles, but there are no other benefits seen after cycles 3 and 4 for those who do not get into that status in the first 2 cycles.

DR. ROTH: Thank you. Dr. Nowakowski?

DR. NOWAKOWSKI: Thank you. Greg Nowakowski. Maybe I will start the questions with Dr. Radich. In your very nice overview of MRD and ALL, you showed us that some of the patients, which are MRD positive, still remain in CR. I'm just curious if you see spontaneous conversion. What happens to MRD in those patients? Are they constantly positive for MRD if they remain in CR or does it disappear over time? In other words, what's the rate of spontaneous conversion of MRD positive to negative over time in patients?

DR. RADICH: There's a little bit of both. There are some patients who have very low levels who in fact will become negative with time, and then there are rare patients who actually persist positive, and no one knows what that is. That's kind of a research issue that we're working on. But again, both categories can occur.

DR. NOWAKOWSKI: And your estimation of the rate of spontaneous conversion would be, just approximately in your experience?

DR. RADICH: Roughly 5, 10 percent maybe.

DR. NOWAKOWSKI: Okay. So it's roughly very low.

DR. RADICH: Yes.

DR. NOWAKOWSKI: Thank you.

DR. ROTH: Dr. Bollard?

DR. BOLLARD: I'm not sure who will be able to answer these questions, but I've got four questions if that's okay.

The first question is related to the MRD assays used in 203 and 148. I just want to confirm that these were the exact same assays, PCR-based

assays that we used for the historical control in your studies.

DR. FRIBERG: The assays that were used for the historic control were not always the exact same assays. There were local both flow cytometry and PCR. They were from the same institutions that we used, but the central assessment at Monika Bruggemann's lab was only done on the 203 study.

DR. BOLLARD: Thanks. I think we heard multiple times about BMT being an important confounding factor here. So I guess my question is what was the RFS in patients who achieved MRD negativity after blinatumomab but did not go on to BMT? Were there patients that were in that category?

DR. FRIBERG: I'm going to ask Dr. Franklin to come up. There certainly are, and we can show you that data.

DR. FRANKLIN: So we do have the data. We did do an assessment in terms of relapse-free survival in patients who did not go on to transplant and we stratified by their response

status of being complete responders or non-responders, and the landmark analysis, of course, start at day 45.

Slide up, please. Here we're able to see that for the responders -- and again, these are patients who did not go on to transplant -- 17.4 months is the median and the relapse-free survival for the non-responders is 1.6 months.

DR. BOLLARD: Do you know why these patients did not go on to transplant in the responding group?

DR. FRANKLIN: We don't have specific information on all the reasons why a patient did or did not go on to transplant. We know that certainly the availability of a suitable donor would be one factor. In some settings, because of institutional criteria, age may be the other factor, and then maybe other comorbidities or even the patient preference to not go on to a transplant. Those are some of the common reasons that may occur.

DR. BOLLARD: Another question I have is

related to safety. Do we have any data on B-cell aplasia and the need for IVIG in these patients and what percent of patients required in particular IVIG?

DR. FRIBERG: I'm going to ask Dr. Kormany to come up and comment on B-cell aplasia.

DR. KORMANY: Bill Kormany, global safety officer for Amgen. We evaluated the baseline IgG levels, and they were low for 55 percent of the patients in the MRD ALL population at baseline, and this did increase to about 72 percent after treatment. We did note that in patients who did receive IVIG replacement during treatment, they did not have a lower incidence of infections. This is a known risk of blinatumomab because it increased immunoglobulins due to mechanism of action, and currently we don't have any recommendations for IVIG prophylaxis or treatment with blinatumomab therapy.

DR. FRIBERG: One of the benefits of the short half-life of course is when the administration goes off so does the pharmacodynamic

activity.

DR. BOLLARD: Right. My last question is when you did your propensity analysis, I know you looked at white count, but at any time was the CD3 positive T-cell lymphocyte count looked at as a predictor?

DR. FRIBERG: We did not have that variable in the data set. Of course, that's one of the limitations of looking at the historic factors. We did look at the possibility for what the size of an unmeasured variable would need to be to change the large effect relapse-free survival that we saw, and it turned out it had to be quite large. The hazard ratio would have needed to be 0.25, and it would have needed to affect half the patients. We felt confident that the large result was not missing any of these unmeasured variables.

DR. BOLLARD: Thank you.

DR. ROTH: Dr. Harrington?

DR. HARRINGTON: Thank you. One of my questions just was answered. I wanted a bit more detail about the effect of a potential missing

confounder and its size, so thank you for that.

DR. FRIBERG: You're welcome.

DR. HARRINGTON: I had another question about the propensity score analysis for the FDA. You raised several issues about the non-comparability of the patients, and one of the major ones was that they were not contemporaneous. That in part leads to longer follow-up, but more likely might cause problems because of different ways of managing patients or managing their side effects over time.

Were you able to identify any specific changes in the patterns of care over the two epochs that you would think could cause problems here?

DR. XU: Thank you for your question. We don't have such information. Also, the other limitation for the status we also don't have the arrangement for the control study. This is hard to address.

DR. HARRINGTON: An important but hypothetical concern right now.

DR. FRIBERG: Yes.

DR. HARRINGTON: Another question for the FDA review team, there was an interesting statement made about the possibility of an interaction between stem cell transplant and the agent's treatment using a time-dependent covariate. These are relatively small groups; I'm a bit surprised. So the interaction effect must have been striking.

Can you give us a bit more detail about that?

DR. XU: As you see my presentation of the Kaplan-Meier plot from the subgroups, you see when patients received the stem cell transplant, there's no difference. This also prevented us to interpret the result of the Blincyto effect.

DR. HARRINGTON: Yes. The subgroups are very difficult to interpret there because they're likely not comparable groups.

DR. XU: And time-dependent covariate analysis also shows significant interaction effect. We have backup slides.

Can we go to our backup slide number 10, slide 10? As you can see, when you include

interaction with stem cell transplant, the hazard ratio increased to .90 [indiscernible] for RFS, and the confidence interval included 1. That demonstrated there's no difference. This is from the interaction time-dependent covariate model.

DR. HARRINGTON: I don't want to make this sound too inside baseball for statisticians, but it's a difficult analysis to interpret there because they're likely unmeasured factors leading to transplant that may or may not have been picked up, or do you feel in your adjustment where you use a time-dependent covariate that you also captured all the other important predictors?

DR. XU: No.

DR. HARRINGTON: One last question to either the sponsor or the FDA or both. There is the option, of course, to either censor or not censor cases at time of transplant, but those are the extreme options. And in fact, there are other newer methods that look at the possibility of adjusting for informative censoring here that would try to pick up the differences in patients who are

leading to transplant and what causes them to be removed from standard therapy.

Did either of the two groups look at those and whether or not the analyses were sensitive to that?

DR. FRIBERG: Mr. Holland?

MR. HOLLAND: Chris Holland, biostatistics, Amgen. It sounds like you're suggesting possibly a propensity score approach of transplanted-only patients.

DR. HARRINGTON: No, not necessarily. There are ways to try to model the dependent censoring that may be happening there. There are papers, some, by Pernon [ph] and others that are similar to the ones that you've cited for propensity scores and matching.

MR. HOLLAND: Well, maybe just to clarify, the censoring was only done in the 203 study for the evaluation of RFS at 18 months, the censoring for transplant post-blin chemo. In all other RFS analyses, we didn't censor for the time of transplant. And then to address your specific

question, there wasn't much done beyond that to identify potential informative censoring reasons. Rather, we just looked at RFS without censoring for transplant.

DR. HARRINGTON: FDA, did you do that? Did you look at other ways of modeling the censoring here? It's clearly a very important confounder, potential confounder.

DR. XU: We did an analysis for the time from stem cell transplant to RFS. And it shows also there is no difference for such analysis for the RFS and OS between two groups.

DR. HARRINGTON: One last question.

DR. FRIBERG: If I could just add, we did do one sensitivity analysis on the 203 study, on the RFS at 18 months.

Mr. Holland, do you mind, just for others to see as well?

MR. HOLLAND: Our primary analysis, as you saw, regarding the 18-month RFS estimate, that was the key secondary endpoint in the 203 study and resulted in a estimate of 54 percent. Without

censoring, it's 53 percent, so the numbers there were very similar.

Again, your other question regarding differences in the transplanted populations, we have evaluated baseline characteristics between those two populations. We know, for example, the transplant patients who received blinatumomab were quite a bit older, on average 10 years older than those in the historical data. Also there was a high degree of mismatch donors in that case, up to 30 percent. We don't have that information from the controls, but from our clinicians, they consider that a somewhat high rate of mismatched donors.

DR. HARRINGTON: Do I continue or am I done?

DR. ROTH: If you have one, go ahead.

DR. HARRINGTON: A clarification from the FDA on the discussion question. There clearly is some uncertainty in the level of minimal residual disease here, which is the one that would determine treatment. But I just want some clarity on whether you believe it's still questionable about whether

to use MRD as a guide for further therapy or you were simply questioning the optimal cutoff, which is very hard to get at here because the data don't support a refined analysis of that.

DR. PRZEPIORKA: Thank you for the question. We are looking specifically at the cut-point that would define the population. And we know that assays have various sensitivities, and in the field, negativity is defined as just negative for the assay without specifying exactly what the sensitivity should be. So we wanted to be clear that moving forward, there would be homogeneity in how we select patients independent of the assay.

DR. HARRINGTON: Although that's likely to be a moving target I would guess as the technology increases over time.

One last question about the side effects. I need clinical guidance here. The side effect profile to a statistician looks reasonably similar to the historical data, but in the historical data, those are patients who were typically relapsed/refractory ALL. They were sicker. So one

might evaluate the side effect profile different in populations who are in CR and who do not necessarily yet need the agent.

I wonder, either from Amgen or the FDA, or clinical colleagues at the table, when they come around, whether someone could say whether this is a reasonable side effect profile to anticipate for patients who are clinically doing well.

DR. FRIBERG: Dr. Logan?

DR. LOGAN: Again, I'm an adult leukemia provider, and in our experience we find the toxicity profile of blinatumomab to be quite manageable, and one should not forget that patients continuing on multi-agent chemotherapy when they're MRD positive and not receiving blinatumomab are subjected to a lot of toxicity, including infections. And I think that's borne out by the adverse event profile seen in the TOWER study where 1 out of 6 patients actually had a sepsis event when receiving standard of care chemotherapy.

So this is a very vulnerable patient population, so the opportunity to avoid those

toxicities, including infections by using a well tolerated agent like blinatumomab is actually a major clinical advantage.

DR. ROTH: Thank you. Please remember to turn your mics off when you're done. Dr. Flatau?

DR. FLATAU: I had a follow-up to Dr. Roth's question for Dr. Franklin. The patients who got additional therapy after becoming MRD negative, was that just as a bridge to transplant or are there other patients for other reasons who got additional therapy?

DR. FRIBERG: I believe the question is about the idea of consolidation versus bridge to transplant.

DR. FRANKLIN: For patients who did get the additional cycles, they were both patients who went on to transplant and those who did not. So it would have been used in the setting of those expecting the transplant to be available shortly as a bridge to transplant to continue them in their MRD-negative status while waiting for the transplant. Then there were other patients who

were not going on to transplant, and they used the additional cycles as consolidation therapy as commonly is done with ALL patients, a means to continue that effective therapy for a little longer for disease control.

DR. FLATAU: One more question. Is there any relationship or has anyone looked at the relationship between how many doses they got and the transplant-related mortality?

DR. FRIBERG: The numbers of course are very small. The transplant related mortality was a handful of patients. There was no apparent relationship between number of doses and transplant related mortality. That 10 percent that was seen on the study and that 14 percent on the TOWER study do compare to the published literature for 100-day mortality. We're looking at this quite closely, but again, the signal looks consistent with what's in the literature.

DR. ROTH: I have a couple of clinical questions. I suppose Dr. Radich and Dr. Logan if he wants to chime in as well. Could you call up

Dr. Radich's fifth slide, CM-5? My question, it's philosophic.

When you're giving this therapy, do you think you're taking a patient from blue to gray? Do you think that you are either -- are you giving with the intent of rendering the patient disease-free, leukemia cell-free, or increasing the likelihood of cure with subsequent therapy with or without transplant?

DR. RADICH: I would say probably the latter. I think most of us think that patients who have become MRD negative are probably going to need a transplant for consolidation. Leukemia free, there's a lot of gray area there.

DR. ROTH: You're not giving it with the intent of delaying the time until relapse. You're giving it with the intent of cure.

DR. RADICH: I think any therapy we treat for MRD positivity, the first step is getting a prolonged remission, and then if that's prolonged enough, you actually may be able to be cured with that. But for those people who go to transplant,

you would never know. So I think as a transplanter, I see it as the first step to get someone to debulk and then get through an ultimate definitive therapy. There are some patients who are not going to be able to get a transplant, and then for that, this therapy in itself may do the trick. We'll find out.

DR. ROTH: I would think that if this is a valid biomarker of outcome and it happens 80 percent of the time, that we should see a pretty dramatic impact on survival, not just relapse-free survival. Is that a reasonable -- I mean, I'm not a leukemia doctor. I'm asking is that a reasonable expectation to see a maybe dramatic difference in survival if this is a valid biomarker of subsequent outcome.

DR. RADICH: Well first, I think that here we're talking about this as a measure of disease, not as a biomarker of long-term outcome. We're looking at it -- at least I'm looking at it as an actual quantitative measure of disease, so I would suspect that when you get into that gray area, if

you had better tests, in many cases you will still find disease. We know that from next-generation sequencing.

So I think it's not going to be surprising that some patients who get in the negative state end up going to relapse because there's still lots of leukemia there.

DR. ROTH: Thank you. Dr. Papadimitrakopoulou? How was that?

DR. PAPADIMITRAKOPOULOU: That's good. Thank you.

(Laughter.)

DR. PAPADIMITRAKOPOULOU: My question is actually very complementary to yours. I was wondering all this time while we're presenting the data and debating the transplant question, if conversion of a minimal residual disease leads to a higher number of patients that become candidates for transplant, can that benefit be measured? And I have another one.

DR. FRIBERG: It's a very tricky question. Of course, the transplant's not a baseline

variable. There's a variety of factors that go into the choice of transplant. What we do know is that patients need to be in the best shape that they can going into transplant to get the most benefit. Two-thirds of the patients on the study were able to go to transplant in an MRD-negative state. We know that these tended to be older patients. They had a higher degree of unrelated donors, mismatches in some cases, than we would typically expect, and still we saw what appeared to be an impressive relapse-free survival that compared favorably to the propensity score analysis result.

With that regard, it's difficult to dissect a transplant out. This is a problem, a challenge that's been facing all ALL studies, but it's reasonable to believe that these patients, a higher degree of them went to transplant in a better state, and we think that's a good outcome, and it looks like in the single-arm fashion that the results were favorable.

DR. PAPADIMITRAKOPOULOU: My second question

relates to my lack of good statistical background, so I cannot explain the difference between your analysis of the propensity score for transplant that demonstrates that there is benefit in terms of RFS regardless of transplant and the FDA analysis actually doesn't show the same thing. Maybe that's a question for a statistician.

DR. FRIBERG: Could I have Dr. Simon actually comment on that?

DR. PAPADIMITRAKOPOULOU: Yes.

DR. FRIBERG: Thank you.

DR. SIMON: Thank you. I'm Richard Simon. I'm here in the capacity of a paid consultant for Amgen, but I have no financial interest in the outcome of your deliberation. Usually we don't like to do analyses adjusted for things that are not confounders in a traditional sense, things that are after the fact variable because they can be affected by the treatment and given distorted results. After the fact, patients are no longer comparable when you stratify them by who got a transplant and who didn't get a transplant.

So statisticians generally don't like to do that particularly when you have a treatment that's trying to prevent or delay recurrence and get more patients to transplant. Here if you're going to do an analysis somehow adjusted for an after-the-fact variable like transplant, I think the best way to try to do it is with a time-dependent covariate analysis, which was done and had really no effect on the significance of blinatumomab. I think doing the analysis where you separate patients by who got a transplant and who didn't get a transplant is a very biased look at the data.

DR. ROTH: Thank you. We're going to have several additional clarifying questions. Maybe we should go ahead and take a break now, and then come back, finish those off, and then move to the open public session. It's 10:17. Why don't we reconvene at 10:30?

(Whereupon, at 10:17 a.m., a recess was taken.)

DR. ROTH: Let's go ahead and start back up. Dr. Halabi has some questions.

DR. HALABI: Thank you, Dr. Roth.

I have some questions for the sponsor and the FDA. The first question has to do with, again, MRD level predicting RFS. The sponsor presented different levels of MRD, and they showed a very nice relationship between MRD levels and RFS. Was a similar analysis made for overall survival?

DR. FRIBERG: With regard to the historic analysis from the Berry paper or are you asking with regard to the 203 study?

DR. HALABI: Through your trial.

DR. FRIBERG: We looked of course at complete MRD response totally extinguishing the signal that was measurable, and that describes that 78 percent of patients. We did repeat the FDA's analysis to look if you took small cuts with assay sensitivity that didn't reach quite as low, and what was apparent was, again, deeper is better.

DR. HALABI: Basically, I'm looking at slide number 6 from the FDA, and the specific question was if you looked at that with OS, but I think you've answered that you did not do that. I guess

the key thing that I'm struggling with is was there any attempt from the sponsor to validate also that cut-point.

DR. FRIBERG: It's important to remember that we didn't choose the cut-point of 10 to the minus 4. That was what the technology at the time was able to have as a minimum competency. The study wasn't designed to determine the optimal threshold the patient should go below. Instead we used the international recommendation of this complete MRD response extinguishing the signal. The preponderance of the data would tell us that deeper is better, though the tools that we used to get there weren't sufficient enough at the time the study was performed to be able to answer the question you're asking. We didn't have enough range.

DR. HALABI: I'm really perplexed. You have the data and you can still look at it. Even though the study may not have been designed to do this, you can still do an exploratory analysis and see if you have the same trend, and this is what I'm

getting at.

DR. FRIBERG: So there were only 10 percent of patients who had an assay sensitivity that was at that minimum threshold of 10 to the minus 4. Most of the patients had individual probes that were deeper. And again, the complete MRD response is the extinguishing of that signal getting below.

Is your question did we look at it as a continuous variable?

DR. HALABI: Right. Again, I'm trying to address the first question that the FDA is trying to get our vote on.

DR. FRIBERG: Sure.

DR. HALABI: And really, it's not clear, based on today's presentation, whether that cut-point is established or not. And it seems to me the MRD greater than or equal to 0.1 -- sorry -- greater than 1 percent is not -- based on what's presented today, greater than or equal to 0.1 percent has not been validated; neither has an attempt been made.

DR. FRIBERG: So from a patient selection

standpoint -- I'm sorry. I misinterpreted your question. From a patient selection standpoint, there's a wealth of data suggesting that 10 to the minus 3 and above is indeed a high-risk population. The question of whether patients below a starting threshold of leukemia could benefit from therapy is a risk-benefit discussion.

We have a handful of patients who we did treat it that were in that range on the 202 and 203 study. We did see that there was a similar complete molecular response rate in those patients, but proportionately the less leukemia you have starting, the better you will do. You don't do all better, though, compared to someone who is MRD negative.

Am I answering your question?

DR. HALABI: I think you are, yes. Thank you. The other question also related to the analysis presented by the FDA slide 18. When you look at the propensity score analysis, I think we all understand the motivation for doing this analysis, is because we want both groups to be

comfortable; I mean, not only comfortable in terms of covariate history but in terms of eligibility, in terms of the patients from 148 versus 203.

One question that comes to mind is in terms of the transplant after MRD, did you look at those patients in 203 versus those in 148 in terms of differences? You may have information in terms of age and other prognostic factors. Again, I don't study ALL, so I don't know what other prognostic factors may determine who may or may not get a transplant. So I'm wondering if either the sponsor or the FDA have looked at that information.

DR. FRIBERG: Mr. Holland, you can come up and comment.

MR. HOLLAND: Yes, we did try to do a similar analysis, propensity score analysis, looking at only the only transplanted patients. However, one initial diagnostic one can do in order to determine whether a propensity score analysis is appropriate is to look at the box plots of the propensity scores. We saw something similar in the FDA's presentation for the entire MRD population.

If those box plots are so disproportionate, such an analysis can't be done. We did look at individual covariates that were possibly responsible for that. We've mentioned age earlier.

Slide up, please. This is looking at the same set of baseline covariates that were evaluated for the overall propensity score analysis and an attempt to adjust for those with propensity score adjustments. You can see two factors in particular, which are severely imbalanced and age as a continuous endpoint, borderline imbalance. If you dichotomize that by certain thresholds such as 35 years of age and over, it was above that 0.2 threshold suggesting an imbalance.

So ultimately, the determination was you couldn't really compare these two sets of patients due to the number of imbalances between them.

DR. HALABI: Thank you.

DR. ROTH: Ms. Preusse?

MS. PREUSSE: I'm not sure who this question is directed to, but per Dr. Radich's slides, I understand that the presence of any MRD is still

associated with a worse outcome. Looking outside CM5 however, MRD detected by 10 to the negative 4 through 10 to the negative 6 is CR without MRD.

So I would, from a consumer perspective, consider that a cure, but per Dr. Roth's question prior to the break, my understanding was that was not considered a cure. It was just considered a more difficult level of detection via NGS. So I guess I'm confused as to what level of MRD is -- I guess I'm confused as to the level of MRD positivity that is benefitting from Blincyto.

DR. FRIBERG: If I understand your question correct, you're asking if you can't detect the MRD with the assay, is it still there or not. We know that there are long-term survivors from our original 202 study, almost five years out, who had an MRD response. Five out of the 20 of them did not receive transplant and they're still alive and relapse free today, but there are some patients who are not so fortunate who we just can't see it.

Dr. Radich, can you come up and comment on your perspective of this gray area on your chart?

DR. RADICH: The blue is basically taking a cutoff of the technology that was used in the blinatumomab assays. There are current technologies with next-generation sequencing that will go down to 10 minus 5 to 10 to the minus 6. Basically, we haven't found the level yet where MRD is okay. Even when you go down to 1 in a million, actually the curves begin to widen and widen as you take people and reclassify them.

So there may well be a level of MRD if you get down to 1 in 10 to the 9th or something that you can live with, but so far we have not found that at that level. So I think one confusion is, is that cartoon is static. So if we could pull that line down and gray a couple of notches, you'd see the same effect with the newer technology. But I think the main point is, as was commented on, these cutoffs are sort of artificial and fluid. And as the technology increases, when we get down to 1 in 10 to the 5th or 1 in 10 to the 6th, MRD is still greatly associated with relapse.

MS. PREUSSE: A quick follow-up. That

completely answers my question; thank you. So just to confirm then, it's possible that 10 to the negative 5, 10 to the negative 6, et cetera, you're simply pushing the survival curve outward in terms of time to event or time to mortality.

DR. FRIBERG: Yes.

DR. ROTH: If there are no other questions, I think we'll move on to the -- I'm sorry. Dr. Sung?

DR. SUNG: Hello. I have two questions. The first is for Dr. Franklin. In the 203 study for patients who did receive transplant, what were the outcomes for those who were MRD positive versus those who were MRD negative?

DR. FRIBERG: Dr. Franklin?

DR. FRANKLIN: So we did look at this factor in terms of patients who did go on to transplant even though they were not complete MRD responders, and we do have an assessment for relapse-free survival. Slide up, please. We are looking at green for the responders and orange for the non-responders, and then looking how the

pre-transplant MRD status impacted relapse-free survival. Responders, median is 25.7 months in comparison to non-responders, 11.4 months.

DR. SUNG: And in terms of overall survival?

DR. FRANKLIN: Slide up. This is the same analysis, but again with the endpoint of overall survival. Again, we see that the MRD responders, those who go into transplant at an MRD negative state. MRD complete responders by our study criteria, the median has not yet been reached. With those who are non-responders, 16.1 months median.

DR. SUNG: So it appears this is not a statistically significant difference?

DR. FRANKLIN: For overall survival, it's a trend. As you see, the p-value is 0.069, but for relapse-free survival, it was statistically significant.

DR. FRIBERG: The numbers are quite small in the MRD non-responders gone to transplant.

DR. SUNG: I guess the question that I'm trying to get at, I think everyone will agree that

if you go to transplant with MRD-positive disease, you have worse outcomes. But the question in my mind is will getting blinatumomab prior to transplant, if you can shift from one curve to another, will that improve outcomes, or is it simply if you are MRD positive at baseline, if you have MRD positivity, that just puts you in a bad group regardless of whether or not you get blinatumomab.

DR. FRIBERG: That is the question. Of course, blinatumomab is a fully approved drug that has shown that it improves survival in the relapsed/refractory setting against active chemotherapy. It would be reasonable to believe that that reduction that's achieved with blinatumomab in the MRD-positive setting would also be a clinically meaningful effect, though the study is not designed to definitively answer your question.

DR. SUNG: The second question I have, as a bone marrow transplant physician, I'm obviously in favor of drugs that can serve as a bridge to

transplant or get more patients to transplant, but we have seen with some drugs like gemtuzumab that receiving that drug prior to transplant will significantly increase transplant-associated toxicities. And I've seen safety data presented today related to blinatumomab, specifically as far as I understand.

Have we looked at the safety of transplant or toxicities after transplant for patients who received blinatumomab prior to transplant?

DR. FRIBERG: Yes, we have data on 100-day mortality as well as the adverse event terms. I'm going to ask Dr. Kormany to come up and walk you through the safety data in the patients who went to transplant.

DR. KORMANY: Yes, we looked at the 100-day mortality for patients who went to transplant in study 203 after receiving blin. Slide up, please. Looking at 100-day mortality, the rate was 7.9 percent, which is again below what has been reported in the published literature. Looking at long-term mortality in these patients, the rate was

27.6 percent, which again was also lower than the published two-year treatment related mortality following transplant.

DR. SUNG: But in terms of other adverse events, grade 2, grade 3, grade 4 adverse events?

DR. KORMANY: The safety profile is very similar. Slide up. In terms of the treatment related mortality, in terms of cause of death for these patients, slide up please, we had 21 patients who died following stem cell transplant without documented relapse, and you can see that the types of events that led to death were primarily infectious events.

DR. SUNG: But again, my question was more about grade 2, 3, 4 adverse events after transplant, and if those are increased after blinatumomab and then transplant versus someone who just receives transplant without blinatumomab.

DR. KORMANY: We don't have a slide to present for that data.

DR. ROTH: Let's do three more questions. Drs. Hoffman, Chen, and Nowakowski, and then we'll

have to move on.

Dr. Hoffman?

DR. HOFFMAN: Again, like Dr. Roth, I'm not a leukemia doctor. I just want to question either Dr. Radich or Dr. Logan. We keep hearing about consolidation to move toward -- or using bone marrow transplant as the consolidation if we've accomplished some reduction in the MRD. Can I assume that the holy grail here is eventually to not need a transplant? This may not be the drug, and it may be 10 years down the line, but ultimately, we're probably hoping to not need a transplant.

Am I correct about that in the big picture?

DR. FRIBERG: Could I grab Dr. Logan?

DR. RADICH: Aaron, you can come up. But I think Aaron and I agree, even as a transplanter, as much as it pains me to say, yes, that the ultimate event is to be cured without a transplant.

DR. LOGAN: Currently the field feels that the only gold standard in MRD-positive or relapsed/refractory ALL is that patient needs an

allogeneic transplant if it's medically feasible, and that's because we only have proof of long-term cures without allogeneic transplantation.

With single-antigen targeted amino therapy such as blinatumomab or other technologies such as CAR T cells that are targeting single agents, we still actually plan to use those therapies as a bridge to transplant whenever medically feasible. I think immunology has taught us that when we target single agents, biology will circumvent that one single bottleneck, and there will be antigen-escape variance.

So currently I believe that should this be approved for MRD-positive patients, the most common usage will be as a bridge to transplant. There are, however, patients that are not medically fit or not socially fit to undergo an allogeneic transplant, and they may simply receive blinatumomab with additional consolidation chemotherapy or consolidation blinatumomab at the discretion of the provider. And we may see outcomes more frequently such as those that were

seen in 202 in long-term follow-up, where some patients not receiving an allogeneic transplant after blinatumomab for MRD positivity can actually maintain a long-term remission, and I think that's something that the field will need to explore further in the future.

DR. ROTH: Thank you. Dr. Chen?

DR. CHEN: One of the first questions I have is for Dr. Radich. You had made a comment that any degree of minimal residual disease you would not be comfortable with. This study used a cutoff of 0.1 percent. Do you think this is an appropriate regulatory benchmark for future studies or not?

DR. FRIBERG: Dr. Radich?

DR. RADICH: If you're just evaluating this study per se, this is what the data is based on with a study at that cut-point. If you are saying historically, I think there's a fair amount of data across many studies that if you can do the assay down to 10 to the minus 4, that's probably appropriate. I think that is going to be a moving target, and it may well be -- I guess one question

is do we actually need thresholds? Should it be MRD positivity detected at all? And just assume this is a quantitative variable.

Certainly the 10 to the minus 4 has the advantage of being recommended by experts at EON and NCCN, and it's a level that labs here and in Europe can obtain.

DR. CHEN: The reason I ask this question, as others have mentioned, there are other antibody drug conjugates and immunotherapy as CAR T coming forward, do you think that the threshold should be set similar to this study, at 0.1 percent, or should we try, as you're suggesting, 10 to the minus 4 or minimal residual disease at any level?

DR. RADICH: If you're just saying my personal opinion, I would personally not really try to attach specific levels on anything. I would rather have things be a continuous variable than a categorical variable and say an assay that can detect at least 10 to the minus 4, which is basically not the level of disease per se but gives you a measure of confidence in the ability of that

group to do that assay. So that's basically how I put the level, as more as a confidence in the assay and the people doing it.

DR. CHEN: My next question is directed to the FDA. The presenter had given their response to the difference in the BMT, whether or not it was an effect or not in the confounding variable. And I was wondering if you would like to give a response of the difference of what you found as the effect of BMT or not.

In particular, your slide showing the exploratory subgroup analysis by transplant and you showing that there was not -- in your analysis, finding that there was not a benefit, while in their analysis, they did say that there was a benefit. It was done by two different statistical methods. They gave their response of why they chose yours, and I would like your response of why you chose yours. And I would also appreciate if Dr. Harrington had any comments about it.

DR. XU: Our analysis includes interaction of the time-dependent covariate. That's why it

shows a larger hazard ratio and a wider confidence interval, that I showed on the backup slides.

DR. CHEN: No. I'm sorry. I guess you're misunderstanding my question. So in your exploratory subgroup analysis slide, you show that in the product limit survival estimates, there is no difference between Blincyto and the historical control in the patients who got transplant.

DR. XU: That's the subgroup.

DR. ROTH: What slide is that? Let's just put it up.

DR. XU: That's slide -- subgroup.

DR. ROTH: In backup?

DR. XU: My presentation slides of subgroup analysis by transplant or not transplant. Yes, that is subgroup exploratory analysis. We see there's no difference. This is just a subgroup analysis. So maybe it could be due to smaller sample size or could be due to some unknown reasons, but we saw these results.

DR. CHEN: But in comparison, the company in their slide CE-27 shows that for transplant, there

is in their hands a statistical difference of a hazard ratio of 0.5.

DR. XU: The hazard ratio from sponsor I think is just a main effect without including interaction, stem cell transplant interaction. Remember, another limitation of these studies is imbalanced transplantation. So we think it's appropriate to adjust this as a time covariate. Time-dependent covariate is the best way that we can do for such an analysis.

DR. HARRINGTON: I think that Dr. Simon has made a compelling case that the subgroups shown on slide -- I can't see the number -- with the subgroups is probably very difficult to interpret here because this is post-baseline variables that are at least a much a marker of the patient as they are of the effect of transplant here.

I think the analysis that we don't see, that we don't have the actual numbers for, that includes a time-dependent covariate and an interaction for that time-dependent covariate by the treatment, it's important information. It's model based. It

probably would need to be explored in a larger data set. These things can be quite sensitive to things that happen in small data sets, so I wouldn't regard it -- I'll let the FDA speak for this -- as definitive in showing that the sponsor is wrong. I think it does show that the survival data here is highly confounded by the presence of transplant post baseline, and it's going to be very hard to sort out the effect of Blino in transplanted patients.

DR. ROTH: Raje, did you want to comment?

DR. SRIDHARA: Dr. Raje Sridhara from FDA. Yes, I agree with Dave. That's why I had the disclaimer that this was an exploratory analysis. We were looking at what were the things that were confounding the survival and whether we can actually come to a conclusion that definitely there is an effect. So at the moment, with the data that we have, we cannot definitely conclude that there is an improvement in Blincyto compared to the historical control.

Given the retrospective nature of it, the

historical control always has issues. Not only was the transplant itself an issue, but also the issue of imbalance in time of follow-up and number of transplanted as well.

DR. CHEN: Thank you.

DR. ROTH: Rick?

DR. PAZDUR: If memory serves me right, there are several randomized trials that are going on with this drug in looking at MRD, too. Can you present those and also tell us what the accrual is and what the expected readout on these are?

DR. FRIBERG: Dr. Franklin can come up and review the E1910 study, the adult study going on currently.

DR. PAZDUR: Also a pediatric study.

DR. FRIBERG: Yes. She can cover the COG study as well.

DR. FRANKLIN: There are two ongoing cooperative group studies that we're aware of being run in the U.S. One is the ECOG 1910 study, and this is enrolling a population of newly diagnosed ALL patients. The enrollment as of the end of

February, February 28th, was 301 patients, and the total patient number is 509, so a little more than 50 percent enrolled. We do know that this study is to be completed with readout in 2023. Quarter 1 of 2023 is the most recent information we have from the cooperative group on that study.

I'm sorry?

DR. PAZDUR: Could you tell us about the design of the trial?

DR. FRANKLIN: Yes, I can. I just want to give you the primary objective, and I'll show the schema in just a moment. The primary objective is overall survival by MRD status after induction.

Slide up, please. The schema is shown here. It's a study that, again, enrolls patients who are newly diagnosed, B precursor ALL patients, Philadelphia chromosome negative. The patients come on in overt disease and receive 2 cycles of induction, 1 cycle of intensification. This is quite common in an ALL treatment strategy, and then the randomization occurs after there is information regarding the MRD status, MRD positive or negative.

There are a series of stratification factors and MRD status is one of them. At this point, patients were randomized, received 2 cycles of blinatumomab versus no blinatumomab. And then the issues of going to transplant if a donor is suitable and otherwise determined to be in the best interest of the patient's treatment choice or for the patients who cannot go to transplant for whatever reason, consolidation continues with 4 cycles of chemo plus 2 cycles of blinatumomab for those who have received blinatumomab by the randomization assignment.

Of course, those who are in the no blinatumomab group do not receive blinatumomab, and then of course there's also maintenance treatment for those not going to transplant, which is a common feature of ALL protocols. They get 2 to 3 years of therapy. This is the adult newly diagnosed ALL trial that's ongoing.

There is another cooperative group study that's ongoing, and that is the children's oncology group study. Their population is also somewhat

different from the 203 study we presented. They're presenting a population of patients who are in their first relapse. It is a pediatric cooperative group, but the patients enrolled can be from age 1 to 30 years, as is common for many of the young adults.

You can put the slide up, please, for the schema. This particular study has as its primary objective disease-free survival, and looking at two groups of patients, one group being consolidated as the high-risk and intermediate-risk group, and then the low-risk relapse group. That's to stratify by differences in terms of how these patients are believed best treated. The MRD question as part of this trial is the MRD level incorporated by the stratified risk groups and can be therefore looked at in terms of the survival endpoint that they have.

So it's a complicated slide. It's a complicated study, so it therefore takes all first relapse B precursor ALL patients, and then there's an evaluation regarding their risk classification,

and they get assigned by that group. So high- risk and intermediate-risk patients are treated commonly and lower-risk patients are treated differently.

For the randomization, if you're a high risk or intermediate risk, you are assigned to blinatumomab or to a block 2 of chemotherapy. Again, I should have highlighted that all patients on the far left get block 1 of standard chemotherapy while there's a further evaluation about the next assignment. Then patients can go on to additional blinatumomab second cycle and then block 3 of chemo if that was their assignment. Because the pediatric cooperative group was able to come to a commonality about how they would transplant their patients, they actually were able then to have a common pathway to transplant for either of these two arms.

For the lower-risk group, their strategies are different, so the blinatumomab question is postponed until later. They receive 2 blocks of chemotherapy, and then they go on for evaluation. Patients are then randomized regarding blinatumomab

as part of their continuation and maintenance treatment versus those who receive standard of care continuation and maintenance treatment. So that's the two profiles.

This study has 415 patients enrolled as of the end of February, February 28th, with a total of 598 patients required to complete the study. This study also, just by chance, has their study completion in Q1 of 2023.

Open Public Hearing

DR. ROTH: I would like to move on to the open public hearing, and then after that, when we have some additional internal discussion after the question is proposed, maybe we can address a final couple of questions from Dr. Nowakowski and Dr. Hourigan, if that's all right.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the

context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

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

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of

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

Will speaker number 1 step up to the podium and introduce yourself, and then please state your name and any organization that you are representing for the record?

MR. ZACHARY: Good morning, everyone. My name is Matthew Zachary. I'm the founder and CEO of a nonprofit called Stupid Cancer. I'm here of my own financial volition. I will disclose that sponsor is one of many supporters of my organization as an unrestricted educational grant process. And thank you for letting me read off my iPad because my brain is a bit of tapioca today thanks to chemo brain.

I'd like to speak about patients' rights and human dignity in medicine, and that clock is not

judging me. When I was 11 years old, my purpose truly began when I started taking piano lessons, and 10 years later at the age of 21, I was an accomplished concert pianist and composer who was 6 months shy of not only completing his undergraduate in music but 9 months away from starting his masters in film at USC under the tutelage of Jerry Goldsmith.

Out of the blue, a diagnosis of terminal pediatric brain cancer cost me my career and nearly my life. They not only said that I had 6 months to live and I had no options, I was told that if I did live, my life would be horrible and I'd never play piano again, and that was 22 years ago this month.

Doctors may have saved my life, but they didn't give me choice and they didn't help me live. There was no what's now or what's next for a 21 year old; no ideas about risk of recurrence, side effects, adverse events from treatment, and latent, long-term stuff. I was 21 and had no idea what to do with the rest of my life and how to fear death. But I got to rebuild it on my terms even though

they said I wouldn't. However, there was no dignity. I never got to go to grad school and pursue my dreams.

Ten years later in 2006, I created new dreams to pursue by founding Stupid Cancer, which is now the largest patient advocate group in the world supporting adolescents and young adults. I did this to ensure that the next 21-year-old kid who was cast asunder by unabated apathy by their HCPs has the lifeline to the community of peers and support resources that I only wish that I had.

Stupid Cancer is again the leader in young adult cancer advocacy, research, support, and we're the largest advocacy group of our kind in the world. We impact the lives of over 3 million Americans annually offering dignity and supporting rehabilitation from cancer. I address the committee both as a proud 22-year-old cancer survivor and perhaps more importantly as a patient advocate leader speaking to the freedoms, rights, and civil liberties of every cancer patient survivor and caregiver in the United States.

There is no higher aspiration than to ensure that Americans are guaranteed their constitutional right to freedom of choice, and we must ensure that Americans facing cancer, specifically ALL and specifically peds and teenagers, are made objectively aware of all treatment options and treatment risks so their decisions are made on their terms. This is the dignity of choice that we all deserve, and I will remind everyone in this room that we're all patients.

ALL patients face indignity every time they are not made aware of MRD testing and risk of relapse. The understanding of risk in MRD testing can literally be the difference between life and death. This happens all too frequently and is a scenario that can be entirely avoided. MRD testing is the strongest predictor of relapse, and relapse is the strongest predictor of outcomes. And I would also challenge that we think about what the definition of the word "outcome" means. From my perspective, it means something very different. I wanted to play piano again. That was my outcome.

In an age where quality of life is now tantamount to quality of care, do not all ALL cancer patients deserve the dignity and awareness of choice? Patients who test MRD negative may not even need a transplant, and for patients whose outcome is MRD positive, transplant risks are much more palatable with -- I don't know the generic name, it's too many syllables -- Blincyto. I've literally personally seen this medicine with my work in pediatrics come to life and the difference it makes for so many parents who have children with cancer.

We are literally, as we like to say at Stupid Cancer, making cancer suck a little less, and who doesn't want to make cancer suck a little less? This may be the one issue we all agree on, that dignity of choice equates to promise of hope, and who wouldn't want a little more hope these days?

My name is Matthew Zachary. I somehow survived terminal brain cancer at 21 and suffered through the most ignominious indignities one could

imagine. My choices were taken away from me, and that's not okay that this still happens. We're all better than this, so let's ensure the most important thing that I wished that I had 20 years ago exist today. Dignity. Thank you.

Clarifying Questions (continued)

DR. ROTH: Thank you, Mr. Zachary.

We have only one speaker this morning, so the open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. Let's go back to mop up a couple of the questions before we have a discussion about the questions at hand.

Dr. Nowakowski?

DR. NOWAKOWSKI: Thank you; just a clarifying question to sponsor. What are the differences in clinical characteristics between MRD responders and non-responders? The numbers here are small, but I would be curious to know. And the other thing, are there any predictors of lack of response to therapy?

DR. FRIBERG: I can ask Mr. Holland to come

up and comment on what we've looked at in that regard.

MR. HOLLAND: So you asked about differences between responders and non-responders with respect to their baseline characteristics?

DR. NOWAKOWSKI: Baseline characteristics, yes.

MR. HOLLAND: Well, we have forest plots showing the various subgroup analyses, various subgroups. Slide up, please. This shows across a number of different subgroups based on gender, age, MRD level, remission status. Nothing really stood out as a predictor as to whether or not one would achieve a response, but essentially, all subgroups had a high probability of achieving an MRD response.

Your second question again?

DR. NOWAKOWSKI: That's the same, predictors of response. It doesn't sound like there were any predictors of response or lack of response. Did you look at CD19 expression, or it's thought to be universal expressed in this setting?

DR. FRIBERG: All the patients on the study were CD19 positive malignancy by history. We did look at flow cytometry data in that regard. We captured it on the eCRF. There were some patients who were noted as negative who did respond to therapy, probably reflecting the limitations of the assays that were used at the time.

DR. NOWAKOWSKI: Thank you.

DR. ROTH: Dr. Hourigan?

DR. HOURIGAN: So I'm a leukemia doc but not a transplant doc. I just wanted to refresh your memory. If we can see the long-term follow-up data, which is new, on the 202 and the 203 study?

DR. FRIBERG: Which of the graphs? The survival?

DR. HOURIGAN: RFS.

DR. FRIBERG: RFS.

DR. HOURIGAN: Either, because I'm confused by the issue of transplant, and I think one clean bit of data we now have is long-term follow-up data.

DR. FRIBERG: Can we pull that up from the

core? Slide up. This is from the propensity score analysis, so this of course is a weighted comparison. But it's looking at the relapse-free survival in blue from that primary propensity score. And the red, as you can see by the numbers at risk at the bottom, have increased as we move over to the right, trying to account for some of this ascertainment bias in terms of time.

DR. HOURIGAN: Can you show that for the subset who didn't get a transplant? I think you've shown it already today.

DR. FRIBERG: It was not the propensity score. It was earlier in the analysis. I don't believe we've generated the same long-term follow-up for the patients who -- Dr. Franklin, actually, why don't you walk through this figure? This is the long-term follow-up you presented in your core. It's not exactly what you're asking for.

DR. FRANKLIN: We have the overall survival, which is an uncensored analysis, and that was one of the secondary endpoints. Slide up, please. I

believe this is maybe the curve that will help answer your question. This is what we do have with uncensoring, of course, in this analysis, as I mentioned previously.

The blue line is the secondary endpoint by the original analysis, 36.5 months, and then for the long-term follow-up, which was a minimum of 3 years of follow-up, that's the red line. And you can see that the median is very similar, so a steady expression of the curves.

DR. HOURIGAN: And for the cohort, you didn't receive -- not all your patients received a transplant, and there was 22 percent or so who did not receive a transplant?

DR. FRANKLIN: Correct.

DR. HOURIGAN: Do you have that data?

DR. FRIBERG: We have the responder versus non-responder version of that, though it doesn't have the additional follow-up.

DR. FRANKLIN: Right. We don't have that exact slide that you're asking form.

DR. HOURIGAN: Can we see what you do have?

DR. FRANKLIN: We can show you the other one, yes.

This slide that I'll put up is, again, overall survival in the non-transplant patients, and it's a different type of analysis. This is a landmark analysis. Slide up. This is where the green is the MRD responders, and the orange, non-responders. Then you'll able to see with the stratification and the landmark analysis, the distinctions.

DR. HOURIGAN: So the questions for Dr. Radich and Logan, how does this compare to the experience? We know in the historical cohort of 148, 60 percent of people couldn't or didn't want to have a transplant. We know the group with MRD positive has an RFS of less than 1 year. For those who can't get a transplant, does this match with the experience of the Hutch?

DR. LOGAN: I think these data recapitulate what Dr. Radich showed in the study from the Hutch as well as other studies that look at the outcomes of patients who go to an allogeneic transplant with

MRD detectable at that time with roughly 20 percent long-term, disease-free survival if the MRD is in CR1 with improvement of overall survival if they go into transplant MRD negative.

I'm not sure that there are data from these studies that can yet help us decide whether to avoid transplant in certain patient populations. Again, that remains a question for the future I believe for our field to determine. And I'll just add that there is no drug that's ever been approved for ALL that specified whether a transplant should subsequently be performed or not.

The way I view this, this is a decision that needs to be individualized, and that individualized decision actually makes the assessment of the role of transplantation as is trying to be performed today very complicated because transplantation is not two buckets. It's not no transplant or transplant. It's no transplant or which of these 12 different kinds of transplants did the patient undergo? Was it myeloablative? Was it reduced intensity? What kind of donor did you use? How

did you manage the immune suppression after the transplant? And were your decisions about any of those things informed by your knowledge of MRD?

In the current era, all of those things are influenced for every patient on an individual basis by knowledge of their MRD. Our field has already accepted 10 to the minus 4 as a threshold for specifying patients as being high risk for relapse unless they need a transplant. If they remain MRD positive at the time of transplant, we're less likely to do a reduced intensity transplant. If they remain MRD positive at 10 to the minus 4 or higher after transplant, we're more likely to rapidly taper their immune suppression.

These are things that cannot be captured in the type of analyses that are presented today, and that's why I don't really think that that should be the focus of the discussion. The discussion should be did this drug take a high-risk population, MRD-positive patients, and enable them to go on to potentially curative therapy? And I think that's been demonstrated, that a very high percentage of

patients were able to go on to a potentially curative allogeneic transplantation. And in this high-risk population, which was older likely because there were other types of transplants that were enabled by the conversion MRD negativity such as reduced intensity, even with that, this patient population did very well. And I think that speaks well for this indication.

DR. ROTH: Thank you. Dr. Bollard?

DR. BOLLARD: Sorry. Last question. I just want to ask, in the patients who did not respond, do we know what percent of them, if any, relapsed or did not respond because they had CD19 negative disease? There are other alternatives out there for CD19 directed therapy, and if you are now pushing the leukemia into a CD19 negative state, it could potentially deprive those patients from additional therapies.

DR. FRIBERG: We've looked across our studies. On the original 202 study, there were 21 patients exposed; 2 ultimately relapsed. They relapsed later, but they relapsed with

CD19-negative disease, about a 10 percent rate. A similar rate has been observed in the TOWER study as well. Of the patients exposed to blinatumomab, about 10 to 15 percent of them who ultimately relapsed will relapse with CD19-negative disease. So it's a fairly rare event, but it's measurable.

DR. BOLLARD: But what about in those non-responders in the MRD study? Because you're treating earlier disease there.

DR. FRIBERG: We don't know the answer to that question explicitly, but we have looked in the larger data sets in the relapsed/refractory.

Questions to the Committee and Discussion

DR. ROTH: Thank you. The committee will turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments. We'll proceed with the questions to the committee and panel discussion. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the

panel.

Question number 1, study MT103-203 included patients with MRD greater than 0.1 percent. Do the available data support the cutoff of MRD greater than 0.1 percent as describing a subpopulation of patients with ALL in CR who have a need for preemptive therapy?

Are there any questions about the phrasing of this question posed to the committee?

(No response.)

DR. ROTH: If not, we'll open it to discussion, and I'll have our leukemia colleagues help lead us in this discussion --

DR. HOURIGAN: So I'm one.

DR. ROTH: -- or we'll have a GU physician lead us in this discussion.

(Laughter.)

DR. HOURIGAN: I can. I'm a leukemia physician. I think as a disease, I think we talked about a couple of different uses for MRD today, and I think one thing is just defining a patient population that could benefit. I think it's been

clearly shown by the data presented by Jerry Radich, by Berry meta-analysis, that this represents patients who when completing standard of care therapy are at a high risk of relapse and reduced overall survival. Where that exact cut-point is, I think Dr. Harrington mentioned inside baseball.

MRD has its inside baseball, too, and I think one of the issues is we test what's given to us in a sample; we don't test the patient. So these tests and these thresholds are going to change over time as technology evolves and the way we sample evolve, but it's clear, at least to me, that this 0.1 percent threshold represents a population of patients who are at risk.

Just to state, what we use now as a response criteria was picked in 1956 for cytomorphology, and it was based on the best available tools available in 1956. If they had Jerry Radich and his NGS or PCR specific parameters, they would have incorporated those into response criteria. So we're really just looking just below the surface

here of 0.1 percent MRD as essentially refractory disease that can be detected molecularly rather than with a microscope. So I would argue that this a high-risk population that gets this treatment.

DR. CHEN: Speaking a little bit further along those lines, I think that the minimal residual disease we know is bad. I think it does define a high-risk population. But as others have stated and as the representatives of the sponsor have stated, we don't know the best cutoff for MRD. I think if we do move forward in the regulatory framework, that we would not want to enshrine this 0.1 percent as the appropriate cutoff.

There are commercial next-generation sequencing assays now available that can detect 1 in a million cells, a significantly much lower threshold than what is here now. Currently, the NCCN consensus is not even 0.1 percent. As others have said, it's log minus 4, so I think we need to keep that in mind moving forward. Yes, MRD is bad and MRD does define a high-risk population, but we do not know the appropriate cutoff, and I would

argue that part. Thank you.

DR. ROTH: Other comments?

DR. SUNG: I think I would agree. I think the more interesting question is -- I think clearly patients that have greater than 0.1 percent probably need therapy and likely are benefitting from this. But I think the more interesting question is if there's a lower cutoff with better technology and better assays, do patients at 0.1 percent benefit or even lower? I think that's more interesting. And obviously we're not going to decide that here because we don't have the data, but it would be nice to get the data in the future to know that.

DR. ROTH: Other comments? Go ahead.

DR. HOURIGAN: Just one thing I'd point out from the 148 data set, the majority of patients with detectable MRD were above this cutoff of 0.1. It's actually a small proportion of patients who would need high sensitivity testing. Only 28 percent of patients were beneath this point of 0.1 percent cutoff. So I agree it's important that

we keep refining these thresholds over time, but the majority of patients who are MRD positive were recaptured by this group.

DR. CHEN: I would like to make one last comment. Even though we know that MRD is bad and defines a poor-risk group, we don't really have randomized data yet to say that eradication of MRD improves outcome. And that leads to the second part of this question. I think that's the more difficult question for us, as Dr. Pazdur brought up and the company presented. Hopefully, we will have randomized data for that in the future, but we do not have that at this time. And I think the difficult question for us is whether or not this presentation here is strong enough in the absence of that.

DR. ROTH: So to summarize, it's clear that any residual leukemia is bad, that this is not an unreasonable place to start for this particular trial, but not predictive of where we'll be years from now. So much like the disclaimer past performance is not a predictor of future results, I

wouldn't want to make a comment about this being the standard for all subsequent trials. That will depend on technology and additional information, so this is a reasonable place to start.

(No response.)

DR. ROTH: Any other comments? Don't make me summarize again.

(Laughter.)

DR. ROTH: Question number 2, as we now know, this will be the more difficult question. Do the results of MT103-203 demonstrate that for patients with ALL in CR who have MRD greater than 0.1 percent, that treatment with blinatumomab provides a potential benefit that outweighs the risks from the treatment? When you're discussing here, please don't discuss what your pending vote will be, but just talk in general terms about the issue, if you will.

DR. HOURIGAN: So as a leukemia doc who doesn't transplant, the reason I wanted that slide pulled up last was because this is a big population of patients who -- not able and can go to a

transplant. I think it's important we don't get caught in the weeds about the confounding factor of transplants in this. I think there are a group of patients who have disease that we can detect, and the standard of care is not to do anything beyond that, and I think that's the immediate question.

The question of what comes next in terms of a randomized study, I'd be worried if I was a transplanter. I think the randomized study I'd like to see is blin versus transplant versus blin, transplant or both. But I think the idea that we wouldn't do anything in these patients given the terrible risk profile they have is not an option.

DR. ROTH: Other comments?

DR. CHEN: I think with this indication it's where would it be used in treatment? I think the inclusion of the CR2 and beyond patients who are in MRD positive is a little bit confounding because those patients would go to transplant regardless. So it's really where would you use this as a clinician. It's in the patients in CR1 after intensive induction who are still MRD positive, and

then would you give them blinatumomab, and then would you transplant or not.

Well, for the patients that you would give blinatumomab alone to use this study for clinical benefit, the patients who got blinatumomab alone is very small in number. I think it would be very difficult to reach any conclusions about how patients would do without transplant. So the greater proportion of patients, nearly 80 percent, went on to transplant, so we're really talking about the blinatumomab plus transplant. And as the FDA reviewers, and as their statistician has said, and as the sponsor's statistician has said, it is confounded by the whole issue of transplant, and it's very difficult to tease out the clinical benefit in that setting with the available data.

It is promising, but is it actually strong enough to merit an FDA label? The NCCN guidelines do say to consider blinatumomab therapy in this setting, but as we all know, the NCCN guidelines are a little bit looser than an actual FDA imprimatur effect.

DR. ROTH: I was actually having a little deja vu with this discussion. I think that it harkens back to several decades of solid tumor questions. And yes, responders always live longer than non-responders. Patients who get debulking for ovarian cancer, are they better because their biology got them to a point where they could be debulked or is it the actual debulking that impacts here?

To summarize, I'd say that clearly there are a number of patients who will never get to what's considered the standard of care in this situation, which would be transplant. It's almost a question of are you willing to take the leap of faith in those individuals who will never become candidates for the definitive therapy, that lowering their MRD a couple orders of magnitude you would hope would have some benefit, even if not eradication of the leukemic clones.

Any other comments?

(No response.)

DR. ROTH: If there's no further discussion

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

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will then read the vote from the screen into the record, and then next we'll go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to, and we'll also have Dr. Gordon make comments at that time if he wishes to.

Please press the button on your microphone that corresponds to your vote. You'll have approximately 20 seconds to vote. Please press the

button firmly. After you've made your selection, the light may continue to flash. If you're unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. TESH: For the record, the voting result is 8 yeses, 4 nos, zero abstentions, and zero nonvoting.

DR. ROTH: Now that the vote is complete, we'll go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record, and we'll start at this end.

Dr. Gordon, if you'd like to make some comments even though you're a nonvoting member.

DR. GORDON: As a nonvoting member, I would just like to congratulate and thank FDA and the sponsor for really bringing forward and advancing the consideration of minimal residual disease and how we really begin to integrate this into assessing patients, considering how we use it to

make decisions around therapy, and ultimately how it will potentially become an outcome measure for clinical care.

I think clearly the field is moving from the days of laying on of hands, radiographic evaluation, microscopic evaluation, to now molecular determinations of disease and disease response, and that's going to become incredibly and increasingly important over the next decade.

DR. HOURIGAN: Christ Hourigan. I voted yes. I share the desire to have randomized study and better quality evidence about the confounding impact of transplant, but I believe MRD-positive patients need treatment now, and we want to have options for them while we're working out the confounding influence of transplant.

DR. CHEN: I'm Andy Chen. I voted no. I do believe that MRD is an important marker, and it should be used in studies going forward. I thought that the results from this phase 2 study was too confounded by transplant to say for certain that there's a significant clinical benefit. And I

thought that patients, the numbers for those who did not get transplant, were too small to make any conclusion there.

DR. SUNG: Anthony Sung. I voted yes. I do think that there was significant data that was presented that showed that use of this drug in this setting is able to convert patients from an MRD-positive status to an MRD-negative status. I think that there was data presented that is suggestive that having an MRD-negative status is beneficial regardless of whether or not you're going to transplant after receiving blinatumomab.

I do note that the reason I voted yes, however, was because the question was worded as a potential benefit. I do not think, as Dr. Chen mentioned, that there's significant evidence suggesting that this is for sure definitively the way that we should go in terms of treatment.

I also think that it's important to look at the data from the randomized trials that are upcoming that were discussed because I don't think that -- for example, if this was a question of

whether or not it should be approved for this indication, I probably would have voted no in that setting, but I do think there's enough data to suggest a potential benefit.

The other thing that I would like to comment is I would like to see more data about the potential adverse effects in patients who receive blinatumomab and then go on to transplant because I feel that was not adequately presented. As one person early in the conversation noted, a lot of the historical data was from 2000, where transplant in 2000 is very different from transplant in 2009, which is very different from transplant now. So I think a more granular look at that detail and data is needed.

DR. FLATAU: Arthur Flatau. I voted yes. I think, as Dr. Sung commented, patients probably benefit from being MRD negative going to transplant. I don't think that patients who are MRD positive after the chemotherapy and then get Blincyto and become MRD negative are quite the same, but it still looks like there's some benefit

over being MRD positive at the time of transplant. So that's why I voted yes. Oh, and I wanted to add, I'd like to see more randomized trials. I agree with that.

MS. PREUSSE: Courtney Preusse. I also voted yes. I felt that the survival benefit in MRD-positive patients was there. Although we can't exactly quantify it, and we don't know what the exact MRD cutoff is, and we don't know how much MRD you can live with and not relapse, I felt that the data was sufficient in the 10 to the negative 1 to 10 to the negative 4 population to provide this additional treatment option to patients and their providers.

DR. HALABI: Susan Halabi. I voted no contrary to my previous peers. And the reason why I voted no was mostly because I wasn't totally convinced that you can interpret the data as clean because the outcomes are being confounded due to HSCT, which limits, obviously, the interpretations of the results. And even though the study met its primary endpoint, I believe that additional follow-

up is needed for the 203 study, and additional analysis may help to adjust for confounding.

DR. PAPADIMITRAKOPOULOU: I also voted no, and it was mostly a question of interpretation of the intent of the question here. My interpretation of the intent was that we were asked to vote on these, and the question was indicative of our intent to approve the drug in this indication, therefore, that tainted my vote.

Although I think there is potential benefit and I think there is plenty of data and a clear need for these patients to have some therapy in the setting of MRD, I do not feel that we have the exact definition of the population that benefits. For example, it was adequately phrased CR1 versus later CR, and also the confounding factor of transplant, as everybody else mentioned, was not clarified by the analysis. It was not feasible to clarify it I think.

DR. ROTH: Bruce Roth. I ended up voting yes. I actually wanted yes and no, and then I wanted to abstain.

(Laughter.)

DR. ROTH: I voted yes because I think it met the primary endpoint, and I think fairly impressive. Mostly 80 percent of the people MRD converted. I also voted yes, kind of in the back of my mind for the patients who do not have transplant as an option, as another option to reduce MRD and hopefully have something else available down the road.

The no part of my brain said that I am not convinced of clinical benefit from what was presented. And I think it was an impossible task to take this heterogeneous group of historical controls and try to get anything out, and that's in fact I believe what happened. I'd be very interested to see the results of the upcoming randomized trials to confirm that MRD conversion actually does end up resulting in improved clinical benefit.

DR. HOFFMAN: I'm Philip Hoffman. I voted yes. I think perhaps in the most simplistic way, after hearing the data and reviewing this, that the

drug is currently approved for treating refractory ALL, and the way I see it, MRD positive is a form of refractory ALL. It's a different mechanism of measurement, as we've heard, and it will probably get, as it has been discussed, even more sensitive over time. But I think that that is an indicator of persistent and refractory disease, and I was swayed by the predominance of clinical evidence that even with using it as a bridge to transplant that it was still valuable since patients who get transplanted and are MRD positive going in have a less good outcome than those who go in MRD negative.

DR. NOWAKOWSKI: Greg Nowakowski. I voted yes really on the three pillars. One is that MRD appears to be clearly predicting or identifying the patients at risk of relapse. We can argue about the cutoff, but multiple publications and data show that MRD is important in ALL.

Secondly, the 203 study demonstrated that blinatumomab can actually convert patients from being MRD positive to negative, and does it in a

significant proportion of the patients.

Thirdly was the clinical benefit, and here, just like others, I struggled a lot if the conversion from MRD positive to negative truly corresponds to a clinical benefit. But I think overall, looking at the evidence, there's a reasonable probability that, indeed, it does help.

Finally, biologically I think about being MRD positive like almost being tied to the railroad tracks and you see this train coming, and you see the lights far away. And you can think about that I'm going to wait until the train comes closer and use my ammunition then or maybe I'll try do something early to stop this train. And biologically, I cannot help thinking that early intervention could be of help here.

DR. HARRINGTON: Dave Harrington. So apparently Dr. Roth and I agree on everything except the vote.

(Laughter.)

DR. HARRINGTON: I voted no, and I voted no primarily because for me there is still uncertain

benefit in the patients who are eligible for transplant after their CR. I don't think of the subgroup necessarily as the ones who got transplant, but the ones who you know after that CR could get transplant. I think what's difficult to sort out here is that different analyses show a different level of benefit for blinatumomab before the transplant.

So for me it doesn't quite reach the level of labeling evidence. I think in most trials or studies, most of us are willing to approve an indication when a subset that you're particularly worried about is small, but this is a large subset, and it leaves open the question of whether they should be treated or go right to transplant. There was a claim that one hopes that the deeper the response, that inducing less residual disease prior to transplant will lead to a longer and better outcome for transplant, but I think that remains to be shown.

DR. BOLLARD: Catherine Bollard. I voted yes. Again, like Dr. Sung, the key word for me in

this question was "potential" benefit that outweighs the risks from the treatment. I think we all agree that MRD-positive patients need treatment. The sponsor gave a very good risk-benefit ratio. I think the study met its primary endpoint. For me, the data they showed in response to my question about the patients who did not go on to BMTs, in those 22 percent responding patients who did not go on to BMT, they clearly had an excellent RFS, especially compared to the absolutely dismal prognosis or outcome for the patients who did not respond and did not go on to transplant.

Obviously, we all weight the data of the COG and ECOG randomized trials, and my one caveat would be, if we do move forward in this MRD setting, that we do need to look at the incidence of CD19 negative disease in the non-responders, understanding that there are other CD19 directed therapies these patients might not be eligible for after this therapy.

DR. ROTH: Thank you. Any comments from the

agency? Dr. Pazdur?

DR. PAZDUR: I have one. I believe this is your last meeting.

DR. ROTH: After that performance, yes.

(Laughter.)

DR. PAZDUR: So on behalf of the FDA, we'd really like to thank Dr. Roth for his tenure on the ODAC as well as his leadership during his tenure here as chair. So we really think you did a really excellent job, and we really appreciate your thoughtfulness in these deliberations. Many times, they're difficult deliberations. We don't bring slam-dunks here, so there are the issues that we're facing in the agency and that we're debating internally about, and we'll take the information and the discussion today under consideration.

Again, Bruce, I really wish you -- a sincere thank you, rather I should say, for your tenure here on the committee and leadership.

So can we have a round of applause for Dr. Roth?

(Applause.)

Adjournment

DR. ROTH: Thank you, Rick.

We'll now adjourn the meeting. Panel members, please leave your name badge here on the table so that they may be recycled. Please also take all your personal belongings with you as the room is cleaned at the end of this meeting day. Meeting materials left on the table will be disposed of. Thank you.

(Whereupon, at 11:44 a.m., the meeting was adjourned.)