FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

(ODAC)

Friday, April 12, 2024

9:00 a.m. to 3:19 p.m.

Meeting Roster

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(*Industry Representative*)

Senior Vice President, Head of Oncology Development

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(9:00 a.m.)

Call to Order

Introduction of Committee

DR. NOWAKOWSKI: Good morning, and welcome. I would like, first, to remind everyone to please mute your line when you're not speaking. Also, a reminder to everyone, please silence your cell phones, smartphones, and any other devices if you have not already done so. For media and press, the FDA press contact is Lauren-Jei McCarthy. Her email address is currently displayed.

My name is Dr. Greg Nowakowski, and I'll be chairing this meeting. I will now call the April 12, 2024 Oncologic Drugs Advisory Committee meeting to order. We'll start by going around the table and introduce ourselves by stating our names and affiliations. We'll start from the FDA on my left to go around the table.

DR. PAZDUR: Richard Pazdur, Director, Oncology Center of Excellence, FDA.

DR. THEORET: Good morning. Mark Theoret,

Deputy Director, Oncology Center of Excellence, FDA.

DR. GORMLEY: Nicole Gormley, Division Director, Division of Heme Malignancies II at the FDA. I'm also the Associate Director for Endpoint Development within the Oncology Center of Excellence. Thank you.

DR. KANAPURU: Good morning. Bindu Kanapuru. I'm the Associate Director of Therapeutic Review at Division of Hematologic Malignancies II. Thank you.

DR. ERSHLER: Good morning. I'm Rachel Ershler. I'm a clinical reviewer in the Division of Hematologic Malignancies II. Thank you.

DR. VALLEJO: Jonathon Vallejo, Supervisory Statistician, Division of Biometrics IX, FDA.

DR. ZHANG: Good morning. My name is Jing Zhang. I'm a statistical reviewer of the Division of Biometrics IX, FDA.

DR. ADVANI: Ranjana Advani, heme malignancies, Stanford.

DR. CONAWAY: Mark Conaway, biostatistics,

University of Virginia.

DR. STEVENSON: Good morning. Takyiah Stevenson, Designated Federal Officer, FDA.

DR. NOWAKOWSKI: Greg Nowakowski, Medical Oncologist at Mayo Clinic, Rochester.

DR. LIEU: Chris Lieu, GI Medical Oncologist, University of Colorado.

DR. MADAN: Ravi Madan, Medical Oncology, National Cancer Institute.

MR. MITCHELL: I'm David Mitchell. I'm the consumer representative to the ODAC, and I am President of Patients for Affordable Drugs.

MR. RIOTTO: Good morning, everybody. My name is Michael Riotto. I'm a 12-year myeloma survivor, and I'm the patient representative.

DR. NIEVA: Good morning. My name is Jorge Nieva. I'm the Section Head of Solid Tumors at the University of Southern California, Norris Comprehensive Cancer Center.

DR. VASAN: Good morning. Neil Vasan. I'm a breast oncologist at Columbia University.

DR. HOURIGAN: Good morning. Christopher

Hourigan, Virginia Tech, FBRI, Cancer Research Center in Washington, DC.

DR. MARTIN: Good morning. Tom Martin, Associate Chief Hematology/Oncology, UCSF in San Francisco.

DR. MAURER: Good morning. Matthew Maurer, Biostatistics at Mayo Clinic.

DR. FRENKL: Good morning. Tara Frenkl. I'm the industry rep. I am the Head of Oncology Development at Bayer Pharmaceuticals.

DR. NOWAKOWSKI: For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of those issues and that individuals can express their views without interruption. Thus, 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 advisory committee members take care that their conversations about the topics at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with FDA about those proceedings; however, FDA will refrain from discussing the details of this meeting with media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topics during the breaks or lunch. Thank you.

Dr. Stevenson will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

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

interest laws and regulations.

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

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

Related to the discussion of today's

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

Today's agenda involves discussion on the use of minimal residual disease, MRD, as an endpoint in multiple myeloma clinical trials, including considerations regarding timing of assessment, patient populations, and trial design for future studies that intend to use MRD to support accelerated approval of a new product or a new indication. This is a particular matters meeting during which general issues will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee

members and temporary voting numbers, 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 topic at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Tara Frenkl is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Frenkl's role at this meeting is to represent industry in general and not any particular company. Dr. Frenkl is employed by Bayer Pharmaceuticals.

We would like to remind members and temporary voting members that if the discussions involve any other topics 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 participants to advise the committees of any financial relationships that they may have regarding the topic that could be affected by the committee's discussion. Thank you, and I'll hand it back to the chair.

DR. NOWAKOWSKI: Thank you.

We will now proceed with FDA introductory remarks starting with Dr. Nicole Gormley.

FDA Introductory Remarks - Nicole Gormley

DR. GORMLEY: Good morning. My name is Nicole Gormley. I'm a hematologist and Director of the Division of Hematologic Malignancies II and the Associate Director for Oncology Endpoint Development within the Oncology Center of Excellence. Thank you for joining us at today's ODAC meeting to discuss the use of minimal residual disease as an intermediate clinical endpoint to support accelerated approval in multiple myeloma clinical trials.

You will hear from the FDA review division and two sponsors that have conducted patient-level meta-analyses to evaluate the acceptability of MRD

to be used as an intermediate clinical endpoint. Prior to hearing from the FDA review division and the sponsors, I will share a few considerations regarding endpoint development within oncology. Specifically, I will begin by discussing how endpoints are used in regulatory decision making at the FDA; considerations for how novel endpoints can be developed; and lastly, some Oncology Center of Excellence initiatives related to endpoint development.

The FDA Guidance International Conference on Harmonization E9 document states that there should be sufficient evidence that the primary variable, or primary endpoint, can provide a valid and reliable measure of some clinically relevant and important treatment benefit. While this is a simple statement, there are several key components of this criterion. There should be a valid and reliable method of measurement for the endpoint. Additionally, the endpoint should assess a clinically relevant and important treatment benefit. These fundamental considerations should

be kept in mind when thinking about the adequacy of a clinical trial endpoint.

There are two pathways for approval in the U.S., regular approval and accelerated approval. For either approval pathway, there must be substantial evidence of effectiveness based on adequate and well-controlled investigations. For regular approval, approval is based on demonstration of clinical benefit or an effect on an established surrogate. Accelerated approval is intended for products that treat serious or life-threatening illnesses. Taking into account the condition and availability of alternative treatment options, it should provide a meaningful benefit.

In this instance, approval is based on a surrogate endpoint that is reasonably likely to predict clinical benefit or a clinical endpoint that can be measured earlier than survival or irreversible morbidity, what is sometimes referred to as an intermediate clinical endpoint. There is often the requirement to conduct post-approval

trials to verify and describe the anticipated clinical benefit.

There are four terms that I would like to elaborate on a little bit more. The first is clinical benefit, which could be summarized as a measure of how a patient feels, functions, or survives, but really captures what we mentioned earlier, a clinically relevant and important treatment benefit. A surrogate endpoint predicts clinical benefit but is not a direct measure of clinical benefit. In this instance, the endpoint has been fully clinically validated to predict clinical benefit.

Next, is a surrogate endpoint reasonably likely to predict clinical benefit. In this scenario, the existing data suggest that this may be a predictor of clinical benefit but we lack robust validation data to confirm that it is a surrogate. Lastly, there are intermediate clinical endpoints, which are measurements of therapeutic effect that can be measured earlier than morbidity or mortality and are deemed reasonably likely to

predict clinical benefit. The first two endpoints are used to support regular approval, while the last two are used to support accelerated approval.

Most accelerated approvals in oncology are based on intermediate clinical endpoints. We have used overall response rate, progression-free survival, and EFS in several diseases and have deemed them as intermediate clinical endpoints, as robust data are not available to support that these are surrogates, and there may even be data to suggest that they are not surrogates. It is rare that there are true surrogates in oncology.

In order for a biomarker to be a true surrogate for a long-term outcome of interest, it should be in the causal pathway between treatment of the disease and the true clinical endpoint of interest. In this figure, the biomarker of interest is within the causal pathway of the disease and directly impacts the clinical endpoint of interest. The classic example is CD4 count in HIV. One could argue that BCR/ABL in CML also has a similar fundamental relationship between the

disease, biomarker, treatment, and clinical endpoint of interest.

More typical in oncology, there may be multiple pathways through which the disease can have an impact on survival, and not all may be measured by the biomarker. Additionally, the intervention may not have the same degree of impact on pathways measured by the biomarker or other pathways. Lastly, the intervention may affect the true clinical endpoint by mechanisms that are independent of the disease process. In oncology, there are very few true surrogates, and most of the endpoints we use to support accelerated approval are intermediate clinical endpoints. I'd like to share some considerations for how novel endpoints can be developed in oncology in light of this.

Historically, the Prentice criteria have been put forth as statistical operational criteria to validate potential surrogates. The Prentice criteria could be summarized as, one, a requirement that the surrogate must be a correlate of the true clinical endpoint; and, two, the treatment effect

on the surrogate should capture the full effect of treatment on the true clinical endpoint.

It is generally thought that the Prentice criteria are too stringent and not attainable. As such, other statistical methods have been developed to validate a proposed candidate surrogate. One approach relies on meta-analysis data. When considering using a meta-analysis for validation of a surrogate, there should be patient-level data from multiple clinical trials. This allows for assessment of both individual-level and trial-level surrogacy.

Individual surrogacy is the correlation between the candidate surrogate and the true clinical endpoint on an individual patient level; trial-level surrogacy is the correlation between effective treatment on the candidate surrogate and the effective treatment on the true clinical endpoint; and the surrogate threshold effect is the minimum treatment effect on the surrogate necessary to predict a non-zero effect on the true clinical endpoint.

Other meta-analysis considerations are that inclusion of more trials increases the statistical rigor of the analysis and may allow for more interrogation of the data to address any remaining uncertainties. Inclusion of both positive and negative trials increases the accuracy and precision of the trial-level surrogacy assessment. When designing a meta-analysis, consideration of the biomarker timing and amount of missing data is important. Lastly, the trial populations and treatments included in the meta-analysis inform the future applicability of the surrogate biomarker.

There are caveats regarding the use of a surrogate endpoint, even those that are fully clinically validated. First, the use of the surrogate may not be appropriate for subpopulations or future trial populations if there are significant differences between the meta-analysis population and the new trial population. Additionally, the use of the surrogate may not be appropriate for therapeutic modalities that have a substantially different mechanism of action than

those of the therapeutics included in the meta-analysis.

I'd like to share an example that underscores the importance of understanding the relationship between the potential surrogate endpoint and the true clinical endpoint of interest and potential risks associated with the use of early endpoints. The Cardiac Arrhythmia Suppression Trial, or the CAST trial, was designed to evaluate the hypothesis that suppression of asymptomatic, post-ventricular contractions post-myocardial infarction would reduce the incidence of arrhythmic death and was not a test of a particular drug.

In the late '80s and '90s when this trial was conducted, there were multivariate analyses which demonstrated that arrhythmias after MI were associated with worse overall survival. It was recognized as a prognostic biomarker. So this trial was designed to test if suppression of post-MI PVCs correlated with long-term clinical outcomes of overall survival.

Subjects were patients with a history of MI in the preceding 6 days to 2 weeks, and all subjects were treated with class 1C antiarrhythmics in the open-label titration phase. If patients tolerated the drug and had suppression of their PVCs, they were then randomized to one of the drugs or placebo. Again, the main focus of this trial was evaluation of the surrogate endpoint and the hypothesis that suppression of PVCs post-MI would reduce the incidence of arrhythmic death.

The surprising results demonstrated that in patients receiving class 1C antiarrhythmic agents, there was a 3.6-fold increase in arrhythmic death and cardiac arrest despite all patients tolerating the drugs and demonstrating PVC suppression during the open-label dose titration phase of the trial. If suppression of PVCs post-MI had been relied upon as a surrogate endpoint, disastrous consequences could have occurred.

The finding of divergent early endpoints in overall survival has been observed in several other settings as well, notably, the PI3 kinase

inhibitors in follicular lymphoma. There were six trials of various PI3 kinase inhibitors, which demonstrated potential detriments in overall survival, and in all but one trial, the potential overall survival detriments were in the setting of favorable overall response rates and progression-free survival hazard ratios. These trials were conducted in indolent lymphomas where patients have the potential for long survival outcomes.

Progression-free survival is often used in these settings, but overall survival information is still captured and evaluated. In these trials, there was limited and early overall survival information, but the overall survival findings were accompanied by higher rates of death in several of these trials compared to the control arm.

I'd like to conclude by sharing some Oncology Center of Excellence initiatives related to endpoint development that were initiated, in part, due to some of these observations. Project Endpoint is an OCE initiative to enhance

development of endpoints in oncology drug development. It aims to explore uses for early novel endpoints, foster engagement with the broader community on development of these novel endpoints, and aims to advance the use of late endpoints as well, recognizing the complementary nature of early and late endpoints.

In July 2023, the FDA in OCE's Project Endpoint co-sponsored a public workshop with the American Association for Cancer Research and the American Statistical Association on overall survival in oncology clinical trials. The objectives of this workshop were to discuss best practices of trial design, analyses, and interpretation of overall survival in oncology clinical trials; explore approaches to address the uncertainty of overall survival analyses based on early or limited data; and advance methods to incorporate overall survival when it's not the primary endpoint or a secondary endpoint, with particular attention on the assessment of overall survival as a safety endpoint that can be measured

to evaluate for potential harm.

So there are risks associated with the use of any early endpoint. The risks associated with use of early endpoints can be mitigated by assessment of late endpoints as well, which was the objective of the overall survival workshop, overall survival as a safety endpoint. If an early endpoint is used to support accelerated approval, there is a requirement for the conduct of a confirmatory trial.

Recently, new regulatory authorities were enacted with the Consolidated Appropriations Act of 2023. This provides FDA with the authority to require a confirmatory trial be underway prior to granting accelerated approval. This also created a formal expedited withdrawal procedure for drugs approved through the accelerated approval pathway in which the confirmatory study failed to verify the anticipated clinical benefit.

So in conclusion, novel endpoints have the potential to expedite drug development. Endpoints used to support regulatory decisions should provide

a valid and reliable measure of a clinically meaningful and important treatment benefit. Most endpoints that support accelerated approval in oncology are not surrogate endpoints but rather intermediate clinical endpoints. To minimize the risks associated with use of intermediate clinical endpoints, or any early endpoint, later endpoints such as overall survival should also be evaluated.

Thank you very much for your attention. Next, Dr. Bindu Kanapuru will introduce the topics for today's discussion.

FDA Introductory Remarks - Bindu Kanapuru

DR. KANAPURU: Thank you, Dr. Gormley.

Good morning. I'm Bindu Kanapuru, a hematologist/oncologist physician and the Associate Director of the Division of Hematologic Malignancies II at the FDA. I will introduce the topics for today's discussion and provide a brief overview of multiple myeloma and minimal residual disease, henceforth referred to as MRD.

Today's discussion will not focus on specific products; rather, we would like the

committee to discuss the adequacy of the available data to support the use of MRD as an accelerated approval endpoint in multiple myeloma. Additionally, we request the committee's input on the adequacy of the data to support the use of MRD as an endpoint in different multiple myeloma disease settings, the acceptability of the time points for MRD assessment, and whether an assessment of durability is required. We look forward to a robust discussion on these topics.

We would like the committee to consider the following voting question. Does the evidence support the use of MRD as an accelerated approval endpoint in multiple myeloma clinical trials? With these topics and voting questions in mind, I'll begin my overview of multiple myeloma disease and the treatment landscape.

Multiple myeloma is a plasma cell disorder that is characterized by clonal proliferation of malignant plasma cells in the bone marrow and an overproduction of monoclonal immunoglobulins, with monoclonal protein in the blood or urine leading to

characteristic end-organ damage. Multiple myeloma is characterized by frequent relapses --

DR. STEVENSON: Excuse me, Bindu.

DR. KANAPURU: -- shortening periods of remission, and --

DR. STEVENSON: I'm sorry. Excuse me, Bindu; apologies for the interruption. Could you please shift over to the right?

DR. KANAPURU: Multiple myeloma is characterized by frequent relapses, shortening periods of remission, and ultimately development of refractory disease in many cases. The diagnosis and staging of multiple myeloma are based on well-established criteria. The International Myeloma Working Group established criteria to assess response to treatment in multiple myeloma. The standard response criteria are based on the depth of reduction in monoclonal protein, or free light chains, and bone marrow assessment of plasma cells.

The treatment of multiple myeloma is distinctly divided into options for patients who

are newly diagnosed and those with relapsed or refractory disease. In the newly diagnosed setting, treatment is generally based on whether the patient is eligible for an autologous stem cell transplant. In the relapsed or refractory setting, treatments are considered based on the types of prior therapies and response to the previous therapies.

There has been tremendous progress in drug development in multiple myeloma over the years. Multiple therapies and combination regimens are currently approved. These include therapies with different mechanisms of action, including immunomodulatory drugs, proteasome inhibitors, CD38 monoclonal antibodies, and more recently, chimeric antigen receptor T cell therapies and T cell directed by specific antibodies.

These treatment advances have resulted in substantial improvements in the outcomes for patients with multiple myeloma across disease settings; however, despite the availability of multiple therapies, multiple myeloma remains an

incurable disease with a 5-year relative survival rate of less than 60 percent, and there remains a need for safe and effective therapies.

With that disease background, I would like to briefly review the approval pathways and endpoints used for approval of new therapies or indications in multiple myeloma. Both regular and accelerated approval pathways, as described previously, have supported approval of therapies for the treatment of patients with multiple myeloma. While overall survival is the ultimate clinical benefit endpoint, in diseases with long natural history such as multiple myeloma, progression-free survival has supported regular approval; however, overall survival is always assessed. Recent clinical trials have demonstrated substantially improved progression-free survival and overall survival results.

In multiple myeloma, accelerated approvals, based on an endpoint of overall response rate supported by duration of response, has expedited the approval of new therapies. Approval in overall

response rate can be assessed earlier than progression-free survival and overall survival and reduction in tumor burden, as measured by overall response, is considered clinically relevant.

This figure shows the response rates observed with selected recent therapies approved for the treatment of multiple myeloma. As shown here, current approved therapies have demonstrated high overall response rates both in the newly diagnosed and relapsed or refractory setting. Specifically, we are now seeing response rates with single agents in a very relapsed patient population that are as high as those observed with combination regimens evaluated in earlier line settings.

Developing new drugs or therapies in multiple myeloma has become challenging, with the availability of highly effective regimens, and demonstrating statistically significant difference in overall response rates may require infeasibly large clinical trials, so there is an interest in having response assessments that can better discriminate the treatment effect of new therapies

and that could potentially serve as an endpoint to expedite drug development in multiple myeloma.

This brings us to the focus of our discussion today. In multiple myeloma, advances in technologies have enabled an assessment of clearance of residual tumor cells at orders of magnitude or threshold below the limit of conventional response categories in the bone marrow or MRD. MRD allows for a more sensitive and a deeper level of response.

Specifically regarding the methods, cellular flow-based methods are widely available and utilize specific markers to distinguish tumor plasma cells in the bone marrow from normal plasma cells. Sequencing-based methods identify specific clonal rearrangements of the immunoglobulin gene in the tumor cells from the bone marrow. The dominant sequence identified in the baseline sample can be monitored over time and assessed at the time of relapse for residual multiple myeloma disease.

Considering the emerging data on MRD, the International Myeloma Working Group in 2016 updated

the standard response criteria for multiple myeloma to include the definition of MRD negativity. The criteria recommended evaluation of MRD negativity in patients who have achieved complete response or better. MRD can be assessed by either flow or sequencing methods, with a minimum sensitivity to detect one tumor cell in 100,000 normal cells, thereby allowing assessment of a deeper level of response. The criteria also include a definition for sustained MRD negativity, allowing an assessment of durability.

These advances have increased interest in evaluating the use of MRD to support regulatory decisions. Clinical trials designed to support approval of multiple myeloma therapies have evaluated MRD response in addition to traditional response endpoints, and several studies and literature-based meta-analysis have evaluated the impact of MRD with long-term clinical outcomes of progression-free survival and overall survival.

This slide depicts two previous meta-analyses of published data in patients with

multiple myeloma. These meta-analyses show that patients who achieved MRD negativity versus those who remained MRD positive had better progression-free survival. In studies that had information on MRD and overall survival, patients who achieved MRD negativity also had better overall survival. Although a more recent analysis included relapsed/refractory multiple myeloma trials, the majority of these studies and the meta-analysis included patients with newly diagnosed multiple myeloma and there were differences in assessment time points in these studies.

Recently, patient-level meta-analyses of multiple clinical trials in both the newly diagnosed in relapsed or refractory settings, and with consistent time points of MRD assessments, have been conducted to evaluate the strength of evidence of MRD with long-term clinical outcomes of progression-free survival and overall survival. You will hear the results of these patient-level meta-analyses following my presentation.

I will now highlight some key aspects to

consider when thinking about the use of MRD to support regulatory decisions for approval. For any endpoint, an accurate measure of the endpoint is important. For an MRD endpoint, the assays used for measurement of MRD is an important consideration. As stated previously, assays for MRD measurements in multiple myeloma generally use flow-based or sequencing-based platforms. While FDA is generally agnostic to the assay used, the assay should have adequate performance. The assay should be appropriately validated for the context of use. The MRD threshold should be within the limit of detection of the assay, and they should be standardized procedures for sample collection and processing.

The importance of the assay performance on the utility of the MRD data for regulatory purpose is highlighted by a recent FDA analysis. In this analysis, only 42 percent of the trials in multiple myeloma that evaluated MRD response were deemed adequate for inclusion in the prescribing information. The leading reasons for excluding MRD

data from the prescribing information were analytical and test validation deficiencies followed by performance issues; for example, inability to identify a clone and issues with trial conduct or design such as inadequate data collection. If MRD is to support approval of multiple myeloma therapies, the assay used for MRD measurement should be appropriately validated and the data should be robust.

Another consideration is the risk that may be associated with approvals based on intermediate clinical endpoints, as has been previously described; that is, the treatment effect on the early endpoint may not translate to long-term outcomes of clinical benefit. In this context, I would like to briefly mention the BELLINI trial.

This trial was a randomized trial that evaluated the addition of venetoclax to bortezomib and dexamethasone. The trial met its primary endpoint to demonstrate superior progression-free survival in the venetoclax or investigational arm compared to the standard of care arm. The overall

response rates and the MRD negativity rates were also higher in the treatment arm compared to the standard of care arm.

As you can see here, despite an improvement in progression-free survival, overall response rates and MRD negativity rates in the venetoclax arm compared to the placebo arm, the trial results demonstrated an increased risk of death for patients receiving venetoclax as compared to the standard of care arm. The BELLINI trial results serve as a caution that deeper responses may not always translate to improved long-term outcomes and highlights the need for an assessment of early endpoints and late clinical benefit endpoints in multiple myeloma.

If MRD is used as an accelerated approval endpoint in multiple myeloma, there is a risk that improvement in MRD may not predict clinical benefit with long-term follow-up; however, this is a risk with the use of any intermediate clinical endpoint. Certain provisions in the accelerated approval regulations, as mentioned previously, can

potentially mitigate this risk. I will reiterate a few of these.

For therapies granted accelerated approval, subsequent verification of clinical benefit will be required. In December 2022, the Congress passed the Food and Drug Omnibus Reform Act that provided FDA with the authority to require a confirmatory trial to be underway prior to accelerated approval. Additionally, these regulations also create a formal expedited withdrawal procedure for removal of approvals of drugs that do not verify clinical benefit from the market. These authorities minimize the risk for granting an accelerated approval based on an intermediate clinical endpoint such as MRD.

In summary, in multiple myeloma, MRD has the potential to expedite drug development. MRD is the most sensitive measure of tumor burden, and achieving a deeper level of response with MRD may be associated with improvement in long-term outcomes. Specific regulatory considerations exist in the evaluation of potential new endpoints to

support approval.

Today, you will hear the results of patient-level meta-analysis conducted by two independent applicants, the University of Miami and the I2TEAMM, and the FDA evaluating the association of MRD with long-term clinical outcomes of progression-free survival and overall survival. We request the committee to consider the data presented and look forward to a robust discussion. Thank you.

DR. NOWAKOWSKI: Thank you, Dr. Kanapuru.

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, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the industry and non-employee presenters, to advise the committee of any financial relationships that they may have with

industry, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based on the outcome of the meeting.

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

We will now proceed with the first industry presentation from Sylvester Comprehensive Cancer Center, University of Miami. Thank you.

Industry Presentation - C. Ola Landgren

DR. LANDGREN: Good morning. I'm Dr. Ola Landgren. I have no financial interest in the outcome of this meeting. I'm a myeloma expert with more than 30 years of scientific leadership and clinical experience in translational cancer medicine, focusing on multiple myeloma. Over the past two decades, I have served as the leader for

large myeloma programs at the National Cancer Institute at the NIH, Memorial Sloan Kettering Cancer Center in New York City, and Sylvester Comprehensive Cancer Center at the University of Miami.

I am delighted to present the EVIDENCE meta-analysis. The aim of the study is to evaluate minimal residual disease, MRD, as an early clinical endpoint for multiple myeloma. I serve as the lead principal investigator for the EVIDENCE meta-analysis, and I work closely with our lead statistician, Dr. Sean Devlin, and all our pharma and academic partners.

Dr. Devlin and I have complementary expertise, and we are both academic full-time faculty members. Over the years, we have published extensively on MRD in multiple myeloma. For example, in 2015, we published a comprehensive review article in Nature Reviews Clinical Oncology, and in 2016, we published the first meta-analysis on MRD in multiple myeloma. We have published several original studies using MRD testing in

multiple myeloma clinical trials.

The EVIDENCE meta-analysis is a worldwide collaborative effort with pharmaceutical companies and academic institutions. It was initiated in 2009. It has evolved gradually over time. Currently, we have data on over 8,000 patients. The data come from 16 high-quality data sets with MRD data from assays, which were validated to a sensitivity level of at least 10 to minus 5, or 1 cell in 100,000, and that is the established cutoff for MRD negativity as defined by the International Myeloma Working Group criteria, the NCCN guidelines, and the FDA. Our mission is driven by the unmet need of patients diagnosed with multiple myeloma.

For multiple myeloma, we do not yet have an established curative treatment. The most effective treatments are in the first line. With our current endpoint, progression-free survival and overall survival, studies for patients with newly diagnosed multiple myeloma were taking a long time to mature. New effective therapies are unavailable to patients

for more than 10 years while waiting for studies to mature. We're here today to answer the question, can MRD serve as an objective and reliable early endpoint for accelerated approval in multiple myeloma to facilitate patients access to new drugs?

As I mentioned before, the EVIDENCE meta-analysis started in 2009, and we started as an interagency initiative between investigators of the Intramural National Cancer Institute, the National Heart Lung and Blood Institute, and the FDA. Eventually, in 2012, we organized a round table on MRD in myeloma here in this building at the FDA in Silver Spring. Several of today's participants were there, Dr. Gormley, Dr. Paiva, Dr. Durie, me, and others.

In 2014, we published a conference paper. In 2014, I also initiated an MRD in myeloma meeting, where we invited all the key leaders in the field, myeloma patient organizations and the FDA. And since the inception, we have had well-attended annual meetings and the FDA has participated every year.

In less than a month, on May 9th, we have the 11th Annual MRD myeloma meeting hosted by the Myeloma Institute at the University of Miami in collaboration with the International Myeloma Foundation, the Multiple Myeloma Research Foundation, the HealthTree Foundation for Multiple Myeloma, and the FDA will participate in the meeting as well.

In 2015, I filed an IND as the principal investigator for this academic study, which is a partnership with former companies in academia. The same year, we started developing a statistical analysis plan in collaboration with the FDA. Transfer of data sets from pharma and academic partners started in 2016 and continue to this day. Also, we had many meetings with the FDA, including in-person meetings here in Silver Spring, as well as virtual meetings.

In the end of 2021, the statistical analysis plan was approved by the FDA. In 2023, we completed the preplanned analysis and submitted all the results to the FDA mid 2023, and during

follow-up discussions with the FDA in late 2023, we were told that we will be invited to present at an ODAC meeting in the coming months. Today, we are here together at this April 12, 2024 ODAC meeting, and as you can see, we have worked relentlessly on this study for 15 years, and we have continued FDA feedback throughout the entire process.

I will now give you a brief background on multiple myeloma's unmet medical need and the role of MRD. Multiple myeloma is a plasma cell malignancy that can manifest in many different ways. Commonly, patients have lytic bone lesions, anemia, and sometimes patients present with hypercalcemia and renal failure, and the disease can also cause immunosuppression leading to infections. Other symptoms and abnormalities are sometimes present.

In the United States, more than 35,700 new multiple myeloma cases are diagnosed annually and over 170,000 people are living with this disease here in the United States. Blacks have a two-fold higher incidence of multiple myeloma and about a

10-year earlier age of onset compared to Caucasians. New therapeutic approaches have resulted in substantial improvements in progression-free survival for patients with newly diagnosed myeloma and relapsed myeloma. Despite numerous new drugs in recent years, there is no established curative treatment, and this is reflected in 12,500 deaths in the United States in 2023 due to multiple myeloma.

Although several new drugs have been developed in the past years, there remains a significant and a critical unmet need for new therapeutic options to better control the disease, to provide deep and sustained responses, to safely deliver long-term clinical benefits, and to seek a cure for this disease.

An important clinical piece of information is that large numbers of patients are lost at every line of therapy. Data show that up to 35 percent of patients will not make it to the next line, and as expected, the most effective treatment happens in the first line of therapy. If MRD is approved

as an early clinical endpoint for multiple myeloma, new therapies could be made available to patients more quickly than today.

Currently, clinical trials in newly diagnosed multiple myeloma use progression-free survival as the endpoint to demonstrate clinical benefit of a new treatment regimen for full approval. The FDA's decision to endorse progression-free survival as the regulatory endpoint has facilitated the development of several new effects to multiple myeloma drugs over the past 15 years, and the success is reflected in the improvement of progression-free survival rates and quality of lives for many patients overtime.

Clearly, demonstrating a treatment effect on PFS entails waiting for enough PFS events to occur, and based on PFS results in recent multiple myeloma clinical trials, after all patients have been enrolled, comparative studies may now require over 8 years to show a statistically significant effect of a new therapy. Current clinical trials for patients with newly diagnosed myeloma take at least

two years to recruit and enroll due to the large sample size needed to ensure sufficient statistical power, and as mentioned before, it takes over 8 years to show a statistically significant effect for a new therapy on PFS.

So as we can see today, it takes over 10 years for a new therapy to be developed for the patient with newly diagnosed multiple myeloma, and this is something that can be significantly shortened with MRD approved as an early endpoint.

As we all know, the FDA has launched important initiatives to help multiple myeloma drug development. The accelerated approval pathway has been implemented to grant approval based on intermediate endpoints reasonably likely to predict clinical benefit and can be measured earlier than disease progression or death. Project FrontRunner has been launched to encourage development of treatments that may benefit patients in an earlier stage of the disease rather than the usual sequential approach.

For multiple myeloma, overall response rate

has been identified as an intermediate endpoint reasonably likely to predict clinical benefit on the basis of accelerated approval; however, in newly diagnosed multiple myeloma, overall response rate is challenging to use as an endpoint.

This slide is very important, and it illustrates the dilemma with overall response rate as an intermediate endpoint for accelerated approval. Using RVd or D-RVd therapy as a control group, the overall response rate in the control group will be over 92 percent, close to 99 percent. One may argue that we don't need any further treatment in newly diagnosed multiple myeloma because ORR is so high; however, ORR only requires 50 percent reduction of the disease, and patients with residual disease will inevitably suffer from relapse and refractoriness.

In newly diagnosed multiple myeloma, there is an unmet need until we have curative therapies. It is no longer possible to develop new therapies for patients with newly diagnosed multiple myeloma with ORR in the accelerated approval pathway. To

accelerate the availability of new and effective treatments for patients with multiple myeloma, an objective and reliably measured early endpoint that is reasonably likely to predict long-term outcomes and clinical benefit is urgently needed.

Several studies by us and other groups have demonstrated that minimal residual disease negativity is associated with improved progression-free survival and suggests the depth of response, as demonstrated by MRD negativity, may potentially be used to reliably predict both PFS and OS in patients with multiple myeloma. MRD is a measure of the number of multiple myeloma cells in the patient's bone marrow, and it's often used in patients with complete response to further quantify the depth of response of treatment beyond CR.

In 2020, the FDA published Industry Guidance on Regulatory Considerations for the use of MRD in development for drug and biologic products for treatments, and the final FDA guidance described two potential uses of MRD: a validated surrogate endpoint for traditional approval and a surrogate

endpoint reasonably likely to predict clinical benefit for accelerated approval. In both these cases, the guidance explained that the strength of evidence required for surrogate endpoint is based on the biological plausibility of the relationship; demonstration of the prognostic value of the surrogate endpoint for clinical outcome; and evidence from clinical trials shows that the treatment effects on the surrogate endpoint correspond to the effect of the long-term clinical outcome. MRD fulfills all these criteria in multiple myeloma.

We were motivated to design and conduct an analysis based on FDA guidance for a meta-analysis of MRD as a clinical endpoint and potential basis for accelerated approval, with the aim to assess the prognostic value of bone marrow MRD negativity and prediction of the treatment effects for PFS and OS in clinical trials of patients with newly diagnosed multiple myeloma. And our results, as you will see shortly, support the consideration of MRD as an early clinical endpoint reasonably likely

to predict clinical benefit in multiple myeloma that may be used to support accelerated approval, and thereby expedite approval and adoption of novel therapeutic agents for treatment of patients with newly diagnosed multiple myeloma.

I will now introduce to you the EVIDENCE meta-analysis. Based on guidance from the FDA, our statistical analysis plan, the main analysis, focuses on patients with newly diagnosed multiple myeloma. A prespecified time point to evaluate MRD status was jointly agreed upon by our lead statistician, the FDA collaborators, and me, and we used 12 months with a window of 3 months as the time points.

Based on guidance from the FDA, patients in complete remission of CR but without MRD evaluation were annotated as MRD positive, and we used the intention-to-treat approach. We only included studies which used MRD assays with a sensitivity level of 10 to minus 5, 1 cell in 100,000, which is the established cutoff for MRD negativity by the International Myeloma Working Group, the NCCN

guidelines, and the FDA.

We have included patient-level data from randomized-controlled trials that meet the following criteria. Phase 2 or phase 3 randomized-controlled trials enrolled patients with newly diagnosed multiple myeloma independent of transplant status; performed validated MRD assays; and MRD negativity was specified as a primary, secondary, or exploratory endpoint on the protocol, and the trial had a median follow-up of at least 6 months beyond the time point of 12 months, I mentioned earlier.

The primary objectives of our study are to evaluate whether MRD negativity, while in a CR at an a priori defined time point, is a reasonably likely endpoint for clinical benefit as measured by PFS in newly diagnosed myeloma and for patients that are transplant eligible; and secondly, to evaluate MRD negativity the same way in patients that are transplant ineligible.

The key secondary objectives of our study are to evaluate whether MRD negativity, while in

the CR at an a priori defined time point, is a reasonably likely endpoint for clinical benefit as measured by PFS in newly diagnosed myeloma independent of transplant status; and lastly, to evaluate whether MRD negativity is a reasonably likely endpoint to predict clinical benefit as measured by overall survival.

I will now hand over to my colleague, Dr. Sean Devlin, who will present data, methodology, and results from the EVIDENCE meta-analysis.

Industry Presentation - Sean Devlin

DR. DEVLIN: Thank you, Dr. Landgren.

My name is Sean Devlin. I'm a statistician at Memorial Sloan Kettering. Before I begin, I would like to state I have no financial interest in the outcome of this study.

We started with 16 randomized studies that included MRD evaluations using an assay that was validated to a sensitivity of 10 to minus 5. Among those 16 trials, a few had to be excluded because either too many patients were missing the 12-month

MRD evaluation or too few patients achieved MRD negativity during the 12-month window. That left us with seven newly diagnosed trials. One of those trials had multiple randomized arms that we could separate to provide two separate treatment contrasts; therefore, in the newly diagnosed population, we had eight two-arm comparisons. In this, we had 4,907 patients included.

In the transplant-eligible population, we had three two-arm comparisons and included 1,686 subjects and five two-arm comparisons in the transplant-ineligible population, totaling 3,221. We additionally had four trials in the relapsed/refractory setting with 1835 subjects; however, we focused our analysis where we had the most data, and that was in newly diagnosed multiple myeloma.

Our methodology, the analytic framework for evaluating MRD as a reasonably likely endpoint for clinical benefit, followed the FDA's guidance on evaluating MRD using a meta-analysis. There are two different associations that we examine. We

first look at the trial-level association; is the treatment effect on the MRD endpoint correlated with the treatment effect on the long-term endpoint? In addition, we look at the individual-level association; is the attainment of MRD negativity prognostic for your long-term endpoint?

For trial-level association, there are two general approaches that are used. For this, we look at the coefficient determination R-squared, which can be estimated using weighted least squares or copula. For weighted least squares, we have two separate models. We have the treatment effect on our MRD endpoint using logistic regression and our treatment effect on our long-term endpoint using Cox regression. Then across our different trials, we look at the correlation between the treatment effects across the trials. Using weighted least squares, we can weigh either by the total sample size or the standard error from our logistic regression model.

Another approach is to use the copula model to estimate R-squared. This model accounts for the

fact that we have the same patients included in those two models, and it's accounting for the patient-level correlation. This methodology has been developed and widely used in oncology to look at intermediate endpoints or validated surrogates. This methodology, in general, is the same methodology that's used by our colleagues in the I2TEAMM.

In addition, we look at the individual-level association. From that Plackett copula, there is an odds ratio that's our parameter of interest, and it's interpreted that the ratio of the odds of the long-term endpoint being greater than a fixed time point such as 4 years for MRD negative patients compared to MRD positive patients. An example of that calculation, if the probability that an MRD negative patient has a PFS greater than 4 years, it's 75 percent, and the probability that a MRD positive patient has a PFS greater than 4 percent [sic - years] being 33 percent, we see that gives you an odds ratio of 6, indicating a very strong association between MRD and your long-term

endpoint.

In addition to that analysis, we looked at a landmark analysis. In this analysis, we take all patients alive and progression free at 12 months, and we look at the impact of MRD on subsequent survival, and we quantify this using a hazard ratio using logistic regression.

The analysis followed the intent-to-treat principle. All randomized patients were included. Patients with missing MRD evaluations were considered as not achieving an MRD negative response. The primary analysis included only studies with less than 20 percent missingness for that 12-month endpoint, aligning with other studies in this setting.

As an example, we have from the time from randomization, a patient first achieves a complete response, then within our window of 12 months or plus or minus 3, they have an MRD evaluation which is negative, and that patient is classified as MRD negative. Another example is a patient who has achieved a complete response but their MRD

evaluation is after the time window; because it's after the time window, that patient is considered as MRD positive. Another example is a patient who has no MRD testing. That patient will again be classified as MRD positive.

Lastly, if a patient first achieves a very good partial response, and then within our time window, it achieves MRD negativity and subsequently after that achieves a complete response, per our statistical analysis plan, that patient is also considered as MRD positive. Lastly, if a patient has early progression of disease, that patient will also be considered as MRD positive.

Now to get to the results, this is the individual-level association from our copula model. This is looking at MRD in progression-free survival. In the combined population with 4,907 patients, we had a global odds ratio of 4.72, indicating a strong association between MRD and progression-free survival. We look in our two subpopulations, and in transplant eligible, we had an odds ratio of 2.45, and in transplant

ineligible, where we have a majority of the data, about two-thirds of our patients, we have an odds ratio of 6.15, again indicating a strong association. For overall survival, the odds ratio was 4, again indicating a strong association between MRD negativity and overall survival.

Here is the alternative way we can look at it. The first is looking at progression-free survival outcome, where we're taking all patients who are alive and progression free at 12 months and we're looking at the impact of MRD negativity. So we have the transplant eligible and the transplant ineligible population, and across these studies, we see a fairly consistent association.

The MRD negativity is associated with a reduced risk of progression or death. We can combine these different point estimates using a random effects meta-analysis, and overall, we have a hazard ratio of 0.4. For overall survival, where we're looking at all patients who are alive at 12 months, we see, again, a fairly consistent association with using the meta-analysis approach

and has a hazard ratio of 0.4 as well.

Now for the trial-level association, here we have two plots. One is the weighted least squares where we're weighting by the inverse variance and the other one we are weighting by the sample size. Each of those circles correspond to a trial the size of the circle. The larger the size, the larger weight it carried in that analysis. We have the yellow circles which correspond to the transplant eligible population and we have the green circles which correspond to the transplant ineligible population.

So combining all those different studies, we see that the R-squared is moderate to high, ranging from 0.67 to 0.84, depending on the analysis. Just a note, there's an additional trial in there, Trial 2.1, which wasn't included in our primary analysis but was included as a sensitivity analysis, and including that additional trial had little impact in our estimates.

Here, we are now looking at the transplant-ineligible population. We have the same

figures, but now we're focusing on the green dots in those plots; those are the transplant ineligible. Here, we have a strong correlation, trial-level correlation, across the different methods, ranging from 0.83 to 0.85.

Here is another way we can view those results. This is the treatment association first on the MRD negativity endpoint using logistic regression, and then we have the treatment effect on progression-free survival. As expected, we have heterogeneity in those treatment effects across the different randomized studies, but we can see there are four trials that have a strong effect on our MRD negativity endpoint, with an odds ratio of 2 to 4 or greater. If you look at those same studies over in progression-free survival, Study 1.3, 1.5, 1.6, and 1.7, we again see a strong association for those treatment effects on progression-free survival.

Now, looking at overall survival, we see when we combine all patients, we have a moderate to weak correlation, ranging from 0.21 to 0.33. There

are challenges looking at treatment effect on overall survival in this setting, as patients may either cross over after progression or disease, or receive other effective lines of therapy post-progressing -- after progressing -- on the study in the newly diagnosed setting. When we look at the transplant-ineligible population, we see a moderate to high correlation in that setting, ranging from 0.63 to 0.83.

Lastly, a few slides ago, we were looking at the treatment effect on MRD and the treatment effect on progression-free survival. We saw for four studies, there was treatment effect on MRD that was ranging from an odds ratio of 2 to 4 or greater; when we looked at the treatment effect on PFS, those hazard ratios range from 0.35 to 0.55.

Here, we're just now looking at the test of association. The first column is the treatment effect on MRD, the second is the treatment effect on progression-free survival, and lastly is the treatment effect on overall survival. We see the four studies had a significant effect on MRD and

also had a very significant effect on progression-free survival.

At this point, I will turn it back over to Dr. Landgren.

Industry Presentation - C. Ola Landgren

DR. LANDGREN: Thank you very much.

I will now provide a summary and a clinical conclusion. The most effective treatment in multiple myeloma occurs in the first line. With current endpoints, it takes over 10 years to show statistically significant effect of a new therapy on PFS in the newly diagnosed multiple myeloma patient population. This delays timely drug approval and availability of new highly efficacious treatments for patients diagnosed with multiple myeloma. And as you have seen today, our results support the consideration of MRD as an early clinical endpoint reasonably likely to predict clinical benefit in multiple myeloma that may be used to support accelerated approval.

Today, the ODAC committee will review two independent studies investigating the role of MRD

as an early clinical endpoint in multiple myeloma. There are many similarities. There are a few differences between the two studies. In the interest of time, I'm not going to review the differences, but importantly, the results from these two independent studies are consistent and they are supportive of each other.

I've been a physician for 29 years, and the majority of my career has been dedicated to multiple myeloma. When I was in fellowship, chemotherapy was widely used. We are now in the immunotherapy era from a drug development perspective, with opportunities to develop modern chemotherapy free regimens with the potential to offer patients the same lifespan as the general population. However, clinical development of new therapies in newly diagnosed multiple myeloma is moving very slowly, 10 years on average, due to challenges brought up here today. In newly diagnosed multiple myeloma, there is an unmet need until we have curative therapists.

Today, you have seen that MRD is an

objective and reliably measured early endpoint that is reasonably likely to predict long-term outcomes and clinical benefit in multiple myeloma. Approval of this endpoint will accelerate the availability of new and effective treatments for our patients. Thank you very much for your attention.

DR. NOWAKOWSKI: Thank you, Drs. Landgren and Devlin.

We'll now proceed with the second industry presentation from International Independent Team for Endpoint Approval of Multiple Myeloma Minimal Residual Disease.

Industry Presentation - Brian Durie

DR. DURIE: Good morning. I'm Brian Durie, Chief Scientific Officer at the International Myeloma Foundation. I have no financial interest in the outcome of this meeting. I'm a myeloma clinician and researcher with a long-standing focus on diagnostics, staging, standard of care therapies, and response assessment. I created the International Myeloma Working Group, led that group's response criteria publication in 2006, and

co-led the MRD enhanced version in 2016. I am especially interested in the precise documentation of deep response and brought together the I2TEAMM to seek FDA approval for MRD as an early endpoint. I will introduce the work of our team today.

The I2TEAMM is a collaboration between academic sites, shown here, to test the utility of MRD as an endpoint in myeloma trials. In combination with our industry partners, we have a global reach for the gathering of data from clinical trials, encompassing over 12,000 individual patient files.

This is, as you've heard, really a unique time in the progress of myeloma therapy. Nineteen drugs have been approved in the last 20 years, and there have been significant prolongations in survival outcomes. Fortunately, these new drugs and combinations continue to prolong patient survival; however, this means that patients have to wait longer and longer for access to new drugs to be approved based upon PFS benefit. Thus, as you've heard, there is an unmet need for an early

endpoint, which can reliably predict progression-free and overall survival. Minimal residual disease testing addresses this unmet need.

As illustrated on this slide, depth of response really does matter. The deeper the response, the longer the PFS. Response is indicated by ORR and complete response at the top of this blue arrow. With deeper response to the MRD level, more myeloma cells are eliminated. At the 10 to the minus 5 level, only one myeloma cell in 100,000 thousand can be detected.

This 10 to the minus 5 level is clearly superior to the ORR and CRR levels and is the key target for the early MRD endpoints we're describing today, which reliably predict longer PFS. You will hear more about this 10 to the minus 5 level target as we describe our statistical analysis. There are many advantages of MRD as an early endpoint. Faster readouts using a 9 to 12 month endpoint versus an endpoint requiring more than 5 years is an obvious advantage. These faster readouts can lead to timely approval of life-saving therapies

and combinations, bringing a major positive impact to patients with myeloma.

Our initial discussions on pursuing an MRD endpoint began back in 2015 and have included key FDA interactions and agreement shown on this timeline, which lead up to March 2023, when data were submitted to the FDA.

Our intent for today's ODAC meeting is to present and discuss our findings that support the use of MRD testing as an early endpoint for accelerated approval. First, we will present more detail about the need for minimal residual disease assessment; next, we will present meta-analysis and key results that support the use of MRD assessment as an early clinical trial endpoint; and finally, we'll end with a conclusion.

First of all, I'd like to invite Dr. Bruno Paiva to provide an overview of MRD assessment.

Industry Presentation - Bruno Paiva

DR. PAIVA: I am Bruno Paiva, Director of Flow Cytometry, together with Professor Jesús San Miguel of Myeloma Research at the University of

Navarra, Spain. We have worked in the field of MRD assessment in myeloma for more than 15 years and made seminal contributions in its methodology and clinical application. I will present background on the need for MRD assessment in multiple myeloma. I have no financial interest in the outcome of this meeting.

While overall response rate has generally supported accelerated approval of new treatments, most patients respond to new standards of care. It is very likely that ongoing and future trials will show overall response rates of 100 percent, which makes overall response rate impractical as an endpoint.

In addition, among all response categories, only the achievement of MRD negativity, here represented in the blue line, truly identifies patients displaying high rates of PFS, on the left, and OS, on the right. In fact, patients achieving complete remission but having persistent MRD, here identified in the green line as survival outcomes, are clearly inferior to MRD negative patients and

virtually identical to those in a partial response. In other words, in myeloma, MRD negativity is recognized as the new complete remission, and achieving MRD negativity is a new endpoint of therapy.

Because of this recognition, the International Myeloma Working Group established new response criteria in 2016 in which for patients achieving CR, there will be a more sensitive category of MRD negative CR, requiring a minimum sensitivity of 10 to the minus 5, defined by two next-generation methods that have been analytically validated, and whenever used in the same patient population, display high concordance and similar prognostic value. These methods have been used in virtually all trials since 2016, and the feasibility of having MRD endpoints in future clinical trials is reassured.

Here is one clinical trial example of our global experience across groups participating in the I2TEAMM, which is a fact that technical failures are very rare, and medium limited

detection is very high, and that the minimum sensitivity of 10 to the minus 5 is achieved in virtually all samples.

Why did the International Myeloma Working Group, the EVIDENCE study, and the I2TEAMM propose a 10 to the minus 5 sensitivity threshold? Now, based on the large meta-analysis reported by Dr. Munshi and colleagues, we now know that the more sensitive the MRD assessment, the better the prediction of clinical benefit and that the sensitivity level of 10 to the minus 4 is suboptimal to define MRD negativity. Because the minimum sensitivity of 10 to the minus 5 can be achieved in virtually all samples, which is not the case of 10 to the minus 6, the optimal threshold today to define MRD negativity is indeed 10 to the minus 5.

Again, according to a large meta-analysis of more than 90 studies, including more than 8,000 patients, it was observed that MRD is a key, if not the most, relevant prognostic factor in all disease settings; that is, newly diagnosed

transplant-eligible and ineligible patients, as well as those with relapsed/refractory disease. Once patients are classified into MRD negative, shown in blue traces, versus positive, shown in purple traces, there are few differences in PFS across the three disease settings, and this observation is very important to keep in mind for some of the analyses that will be presented by Dr. Shi.

This meta-analysis reflects the global prognostic value of MRD in patients treated with proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies. In fact, MRD assessment in phase 3 trials that led to approval of new treatments based on anti-C38 monoclonal antibodies is paradigmatic. In all these trials, regardless of the disease setting or regimens, the significantly higher MRD negative rates in the investigational versus the control arm preceded significant differences in survival, which led to the approval of new treatments for patients with multiple myeloma.

The most recent example is the PERSEUS trial that investigated the addition of an anti-C38 monoclonal antibody to the standard of care -- that is the D-VRd and Vrd acronyms in this slide -- and MRD negative rates at 10 to the minus 5 after intensification were significantly higher with a 4-drug regimen, shown in navy blue, compared to the triplet, shown in green, and these differences in MRD negative rates measured in between 9 and 12 months after treatment initiation, anticipated years in advance, was finally confirmed as a significant improvement in PFS. The prognostic value of MRD assessment has also been demonstrated with CAR T cells and T cell engagers shown here. In fact, some ongoing randomized clinical trials investigating CAR T cells or T cell engagers are using MRD as co-primary endpoint.

In summary, overall response rates are needing 100 percent in myeloma and treatment efficacy must be measured with higher sensitivity. Since 2016, MRD is evaluated with state-of-the-art and uniform technology, which provide results and

achieves 10 to the minus 5 sensitivity in virtually all samples, and is more sensitive than the CR criterion. MRD assessment has shown to be prognostic in all disease settings and treatment scenarios, and virtually all phase 3 trials leading to drug approvals have shown superior MRD negative rates in the investigational arm.

Both observations have been confirmed in meta-analysis of published data; however, both observations were yet to be confirmed in a large meta-analysis based on individual patient data. This was exactly what we aimed in the I2TEAMM, and Dr. Chi will now present the detailed results of this effort.

Industry Presentation - Qian Shi

DR. SHI: I am Qian Shi, Professor of Biostatistics and Oncology at Mayo Clinic. I have been the lead statistician for international surrogate endpoint research across solid tumor and hematology for more than 15 years, including formal qualification of CR-30 as surrogate endpoint in follicular lymphoma. I have no financial interest

in the outcome of this meeting. I will present some meta-analysis and key results on behalf of independent data and statistical team.

The initial objective of this research was to formally validate MRD as a surrogate endpoint of progression-free or overall survival in multiple myeloma clinical trials. With available data, we revised our objective to evaluate if current evidence can support MRD as early endpoint that is reasonably likely to predict clinical benefit in future multiple myeloma clinical trials. Therefore, within the two-level meta-analytic framework, a strong individual patient-level correlation between MRD endpoint and progression-free or overall survival is considered as the primary evidence. On the other hand, the trial-level correlation could provide supplemental evidence if it is promising.

Multicenter, randomized clinical trials with more than 100 multiple myeloma patients and published after 2006 were eligible for inclusion in this analysis. Trials with uncertain or

insufficient MRD data were not considered. Twenty-nine randomized clinical studies were identified through formal literature search. Of these, individual patient data from 12,316 patients were received from 20 studies covering three multiple myeloma populations: newly diagnosed, transplant eligible, newly diagnosed transplant ineligible, and relapsed/refractory. This was an unprecedented, data-sharing effort from a broad community in multiple myeloma research worldwide.

Across the 20 studies, MRD and activity status were classified at different thresholds shown here. At the individual patient level, the correlation between MRD endpoint and progression-free or overall survival is measured by global odds ratio estimated from bivariate Plackett copula model. Global odds ratio quantifies the ratio of the odds of a patient remaining progression free and alive beyond any time point for patients who achieve MRD negativity compared to those who did not. The higher the value is above 1.0, the stronger the correlation.

The common landmark log rank test comparing progression-free or overall survival between patients with versus without MRD negativity was also performed. Trial-level correlation measures how precisely the treatment effect on progression-free or overall survival may be predicted based on the observed treatment effect on MRD endpoint. Strong trial-level correlation is required for formal surrogate endpoint validation; however, to be considered as early endpoint that is reasonably likely to predict clinical benefit, strong individual patient-level correlation can be considered to be sufficient. Promising trial-level correlation can provide further supplemental evidence.

Two commonly used R-squared quantify the strength of the trial-level correlation. To estimate trial-level correlation, two-arm comparisons were formed within each trial. The pair, the data points, are log odds ratio on MRD endpoint and log hazard ratio for progression-free or overall survival endpoints. The figure on the

left is an example of a regression line to show strong trial-level correlation. Additional data requirements were prespecified for two-arm comparisons to be eligible for trial-level analysis, shown in the gray box on the right. Among eligible two-arm comparisons, two analyses were performed. Either patients with missing MRD status were excluded or missing MRD endpoint was imputed as MRD positive.

Very similar definition and derivations were used for MRD negative CR endpoints as those in the EVIDENCE meta-analysis. In our research, 9 months MRD negative CR was the primary early endpoint candidate and 12 months MRD negative CR was the secondary candidate. Note, for both MRD endpoints, at least one confirmed CR or stringent CR during the evaluation time period was required.

First, I will present the results for the 9-month MRD negative CR rate endpoint. Based on MRD classification threshold, different number of two-arm comparisons can be formed in each of the three multiple myeloma populations. Analysis at

each classification threshold and pooling two-arm comparisons with different thresholds were performed. In this presentation, we will focus on 10 to a negative 5 threshold analysis since the majority of the trials included MRD assessment at 10 to a negative 5 threshold after the International Myeloma Working Group MRD response criteria was established in 2016.

First, progression-free survival, here you see the estimated global odds ratio for each of three multiple myeloma populations regarding 9-month MRD negative CR rate. As a reminder, the global odds ratio measures individual patient-level correlation between MRD and long-term clinical endpoints. Here, we've restricted the analysis to two-arm comparisons, which are eligible for trial-level correlation.

Consistent high global odds ratio values were observed across three populations. Remember, the higher the value is above 1.0, the stronger the correlation. Furthermore, 95 percent confidence intervals are excluding 1.0, indicating statistical

significance. This means the patients who achieved 9-months MRD negative CR at 10 to a negative 5 threshold had substantially higher odds of remaining progression free and alive beyond any time point compared to those who did not with strong statistical significance.

In a sensitivity analysis, missing MRD endpoint was imputed as MRD positive. Global odds ratio values remained consistently high despite minor attenuations. For overall survival, again, high individual patient-level correlations were observed between 9-months MRD negative CR and longer survival for each of three multiple myeloma populations. All of the numbers are higher than 1.0.

Here, we see landmark progression-free survival Kaplan-Meier curves for patients who achieved a 9-month MRD negative CR, shown in blue, and those who did not, shown in purple for each of three multiple myeloma populations separately. Large separation of Kaplan-Meier curves with a hazard ratio range from 0.24 to 0.31 show very

strong prognostic value of 9-month MRD negative CR at 10 to a negative 5 threshold in each multiple myeloma population. Landmark overall survival Kaplan-Meier curves also showed a strong prognostic value of 9-month MRD endpoint in each population.

As a reminder, trial-level correlation measures the correlation between treatment effect on MRD endpoint and treatment effect on long-term clinical endpoints. Only the two-arm comparisons with more than 80 percent of patients have sufficient data to derive MRD endpoint are eligible. For the initial objective, we had planned to evaluate trial-level correlation within each multiple myeloma population; however, the number of eligible two-arm comparisons is limited in each population.

Given that trial-level correlation provides supplemental evidence for early endpoint that is reasonably likely to predict clinical benefit, we evaluated trial-level correlation by pooling three populations to see if there were any promising trends. The R-squared values ranged from 0.66 to

0.73 across estimation and missing data handling methods. These values indicate moderate trial-level correlation between 9-month MRD negative CR at 10 to a negative 5 threshold and progression-free survival, pooling three populations. Similar results are obtained looking at overall survival, moderate trial-level correlation between 9-month MRD endpoint and overall survival, again pooling three populations.

Here, we see results of an analysis which excludes the relapsed/refractory population, which corresponds to the EVIDENCE meta-analysis that you heard about earlier. R-squared values range from 0.67 to 0.79, again, moderate trial-level correlation between 9-month MRD endpoint and long-term clinical endpoints for combined newly diagnosed multiple myeloma population.

Now, following the same outline, I will present the results for the 12-month MRD negative CR rate endpoint. Compared to a 9-month MRD endpoint, slightly fewer patients had available MRD data at 12 months. Again, we were focused on 10 to

a negative 5 threshold. Here, we see individual patient-level correlation between 12-month MRD negative CR status at 10 to a negative threshold and progression-free survival. As we saw with the 9-month MRD endpoint, consistent high global odds ratio values were observed across three multiple myeloma populations with 95 percent confidence intervals excluding 1.0, indicating statistical significance.

For overall survival, consistent results were obtained in newly diagnosed transplant-eligible and newly diagnosed transplant-ineligible population. The estimates were not available in relapsed/refractory population due to low MRD negative rate and high survival rate among patients with MRD negative CR. For progression-free survival, we see strong prognostic value of 12-month MRD negative CR consistently across three multiple myeloma populations, and the same is seen for overall survival.

For progression-free survival, pooling three

multiple myeloma populations, the R-squared values range from 0.61 to 0.72 and, again, indicate moderate trial-level correlation between 12-month MRD endpoint and progression-free survival. Pooling three populations for overall survival, the R-squared values reduced slightly but still indicate moderate trial-level correlation.

Excluding relapsed/refractory population as was done in EVIDENCE meta-analysis, R-squared values range from 0.69 to 0.85, indicating moderate to strong trial-level correlation between 12 months MRD endpoint and long term clinical endpoints for the combined newly diagnosed multiple myeloma population.

In summary, consistent high individual patient-level correlation provides strong evidence that 9-month MRD negative CR rate at 10 to a negative 5 threshold reasonably likely predicts clinical benefit of progression-free survival in newly diagnosed transplant-eligible, newly diagnosed transplant-ineligible, and relapsed/refractory multiple myeloma populations.

The promising trial-level correlation provides supportive evidence. Furthermore, similar results were seen for 12-month MRD endpoint and for overall survival.

The MRD endpoints evaluated here were prespecified and uniformly derived regarding time points and sensitivity threshold across all trials. In conclusion, we recommend the consideration of the MRD negative CR rate classified at 10 to a negative 5 threshold at 9 and 12 months as early endpoint for accelerated approval in each of the three multiple myeloma populations.

Now, Dr. Anderson will conclude our presentation.

Industry Presentation - Kenneth Anderson

DR. ANDERSON: I'm Ken Anderson from Harvard Medical School and Dana-Farber, and I've carried out bench-to-bedside research for over 40 years in myeloma, including most of the FDA-approved drugs to treat this disease. I have no financial interest in the outcome of this meeting.

We've made a case that there's a clear

rationale to seek endpoints measuring early responses in myeloma. We're fortunate that great progress has been made in the myeloma therapeutic landscape, leading to overall response rates near 100 percent and complete response rates over 70 percent. The median progression-free survival has been prolonged over six years and overall survival to over 10 years.

As you have heard, however, there's an urgent need to develop alternative endpoints that may provide both a sensitive and an earlier readout so that we can allow patients access to newer treatment options sooner. MRD determination provides such a reproducible assessment for residual disease and predicts outcome. Technological advances allow for reproducible assessment for the presence of even very small numbers of myeloma cells, minimal residual disease, and studies over the last 15 years confirm a significant impact of MRD on both PFS and OS.

We reviewed the very encouraging trial-level analyses correlating MRD sensitivity of 10 to the

minus 5th or better with PFS and overall survival. We have presented the results from our initial trial-level meta-analysis of 20 large robust, randomized-controlled, phase 3 trials with mature PFS data. These trials enrolled patients from around the world. The trials varied in their design; line of therapies; treatment strategies; MRD testing methods; timing and/or number of MRD assessments; and MRD sensitivity levels. Importantly, this heterogeneity is a major strength, as these results are largely representative of a wide spectrum of treatment options and clinical practice.

We recognize that the treatment types represented are small molecules and monoclonal antibodies and that the results from trials evaluating chimeric antigen receptor and T cell engager therapies, although not included in this analysis, do suggest that MRD negativity, shown in the blue line, is correlated with PFS after treatment.

Two independent analyses, one from the

I2TEAMM and one from the University of Miami, with some differences in methodologies, showed a similar strong association between MRD negative CR and PFS, and in fact, a reanalysis by the I2TEAMM using similar inclusion criterion regarding missingness of data shows consistent results.

The trial-level association between MRD negative complete response and PFS is promising, using the proposed 10 to the minus 5th MRD sensitivity level. At the individual patient level, two analyses showed very strong associations between MRD negative, measured at both 9 and 12 months, after achieving conventional complete response and PFS.

We strongly believe that MRD assessment is an early endpoint reasonably likely to predict clinical benefit. We found very encouraging trial-level surrogacy estimates that are aligned with a strong and consistent patient-level association between MRD negative CR and PFS. The combined conclusions of the individual patient-level and the trial-level surrogacy provide

confidence in the role of MRD negative CR as an early endpoint reasonably likely to predict clinical benefit, supporting its use for accelerated drug approval in multiple myeloma. Thank you for your attention.

DR. NOWAKOWSKI: Thank you, Dr. Anderson and I2TEAMM.

We'll now proceed with the FDA presentation, starting with Dr. Rachel Ershler.

FDA Presentation - Rachel Ershler

DR. ERSHLER: Good morning. My name is Rachel Ershler, and I'm a hematologist/oncologist and a clinical reviewer on the Multiple Myeloma Team in the Division of Hematologic Malignancies II at the FDA. Today, we would like to further discuss MRD as a potential endpoint to support accelerated approval. I will begin our presentation with some background information, and then we'll turn it over to my colleague, Dr. Jing Zhang, the statistical reviewer, to discuss the results of FDA's meta-analysis. And finally, I will present FDA's considerations and the topics

for discussion today.

The members of the FDA review team are listed here. My presentation represents their collective input. As mentioned previously, the purpose of today's meeting is to discuss the adequacy of the available data to support the use of MRD as an accelerated approval endpoint in multiple myeloma. We will ask the committee to discuss additional considerations around the use of MRD, including the use of MRD as an endpoint in different myeloma disease settings and the proposed time points for MRD assessment.

This slide shows the therapies approved for multiple myeloma since 2003. Over the past 20 years, there have been 17 drugs approved for myeloma, which has resulted in substantial improvement in the survival of patients with both newly diagnosed and relapsed/refractory disease; however, despite this, myeloma remains incurable and patients ultimately relapse.

There are two approval pathways that have been used for approval of new therapies and

treatment combinations in multiple myeloma, regular approval and accelerated approval. For regular approval, demonstration of clinical benefit is required, which could be described as a measure of how a patient feels, functions, or survives. In multiple myeloma, traditionally, progression-free survival and overall survival have supported regular approval. However, because therapies have become more effective and survival has increased substantially, demonstrating a statistically significant improvement in these endpoints can take quite some time; therefore, there has been increased interest in ways to expedite drug development in this disease space.

One such way is the accelerated approval pathway. To meet the requirements for accelerated approval, the new treatment must be for a serious or life-threatening disease; generally demonstrate substantial evidence of efficacy based on an intermediate clinical endpoint or a surrogate endpoint reasonably likely to predict clinical benefit; and provide meaningful benefit in the

context of other available therapy.

In multiple myeloma, the accepted intermediate endpoint to support accelerated approval has traditionally been overall response rate, defined as partial response or better, supported by duration of response; however, similar to the improvements in PFS and OS, recent clinical trials in multiple myeloma have demonstrated very high response rates, particularly in the newly diagnosed setting; therefore, ORR is becoming more challenging to use as an early endpoint.

One example that illustrates the challenges with the currently accepted endpoints in multiple myeloma is the MAIA trial. This was a randomized study of daratumumab in combination with lenalidomide and dexamethasone compared to lenalidomide and dexamethasone alone, in patients with newly diagnosed multiple myeloma who were not eligible for transplant.

As you can see here, the response rates in this study were quite high in both arms, with an ORR of almost 93 percent in the DRd arm and

81 percent in the control arm. Thus, even in this trial that compared a doublet with a triplet regimen, the difference in response rates was only about 11 percent. As the field of myeloma continues to advance with the use of triplets, and now quadruplet regimens, the response rates will continue to be even higher, and demonstrating a meaningful improvement in this endpoint will become even more challenging. Of note, ORR was not used as the regulatory endpoint to support regular approval.

The primary endpoint of the MAIA trial was PFS, and this study was used to support regular approval of the DRd regimen in this patient population. As seen in the Kaplan-Meier curve on the left, this study demonstrated an improvement in PFS in the DRd arm. At the time of approval, the median PFS was not reached in the DRd arm and was 31.9 months in the Rd arm. As seen on the right, with a median follow-up of 56 months, this study demonstrated an improvement in overall survival in the DRd arm as compared to the Rd arm. The median

OS was still not reached for either arm.

DRd is now an approved regimen for this patient population. This example illustrates how achieving a meaningful or statistically significant improvement in these endpoints has become quite challenging in this disease space. Not only will new therapies have to have very high response rates, but clinical studies will also have to have very large sample sizes and long durations of follow-up to demonstrate an improvement in PFS and OS; therefore, there is a need for novel endpoints to expedite drug development in this field.

As noted earlier, the ORR was high in both treatment arms, and therefore demonstrating an improvement in ORR will continue to become quite challenging. MRD was also evaluated in this study. The MRD rate in the triplet regimen was 24 percent, and the difference in MRD negativity between the two arms was greater than the difference in ORR, at almost 17 percent. Assessment of MRD allows for better differentiation of the treatment effect of new therapy, and thus could potentially serve to

expedite drug development.

So as you've heard, and as we are discussing today, one of the potential early endpoints in multiple myeloma is MRD. MRD is a measure of tumor burden assessed in the bone marrow and detects the presence of malignant cells at orders of magnitude below the limit of conventional ORR. Several studies have reported the prognostic value of MRD status, as shown here, with achievement of MRD negativity being associated with depth of clinical response and prolongation of PFS.

MRD negativity has been demonstrated to provide prognostic value beyond CR; therefore, as we're discussing today, there has been great interest in evaluating MRD as a potential endpoint to expedite drug development in multiple myeloma. To this end, as we just heard, several efforts were undertaken using meta-analyses to potentially validate MRD as a surrogate endpoint or to provide sufficient data to support the use of MRD as an intermediate clinical endpoint in this disease space, and therefore could potentially be used to

support accelerated approval.

In thinking about the development of new endpoints for regulatory purposes, it is important, again, to consider the regulatory pathways. Regular approval is based on an effect on clinical benefit or a validated surrogate endpoint. Accelerated approval may be based on an intermediate clinical endpoint or a surrogate endpoint that is reasonably likely to predict clinical benefit.

Overall response rate is the most commonly used endpoint for accelerated approval in multiple myeloma. ORR is not a validated surrogate endpoint; however, it is of clinical relevance for monitoring and treating patients, and as such, it is an intermediate clinical endpoint that is used to support accelerated approval.

I would like to briefly mention some of the considerations regarding the methodology for assessing potential endpoints for surrogacy, which typically involves conducting a meta-analysis that includes patient-level data from multiple clinical

trials. The goal of the meta-analysis is to assess the strength of the association at the individual level and at the trial level.

For individual-level association, the objective is to evaluate the strength of the association between the candidate surrogate endpoint, in this case MRD, and the true clinical endpoints of PFS and OS at the patient level. In other words, is MRD negative CR prognostic for PFS and OS? Are individual patients after treatment likely to have favorable PFS or OS outcomes based on their MRD negative status?

For trial-level association, the objective is to evaluate the strength of the association between the treatment effect on the surrogate and the treatment effect on the true endpoint. In other words, if a treatment improves MRD negative CR over the control arm, will a similar improvement be observed in PFS and OS?

I would like to highlight that if a strong trial-level association is achieved, or if trial-level surrogacy is met, the endpoint may be

deemed as a validated surrogate endpoint, and depending on the totality of the data available, this endpoint may be used to support regular approval. However, very few oncology endpoints have met this standard and most endpoints that support accelerated approval have either not been assessed for trial-level surrogacy, or if they have been assessed, they have weak trial-level associations.

At this time, I would like to turn it over to my statistical colleague, Dr. Jing Zhang, to discuss the FDA's meta-analysis.

FDA Presentation - Jing Zhang

DR. ZHANG: Thank you, Dr. Ershler.

Good morning. My name is Jing Zhang. I'm a statistical reviewer of the myeloma team of the Division of Biometrics IX. I would like to discuss the FDA's meta-analysis. This slide reviews the statistical methods used in the applicants' meta-analyses. The association between the MRD negative CR and PFS and OS were evaluated at individual level and trial level. The same

methodology was used for FDA's meta-analysis.

The global odds ratio was used for quantifying individual-level association. An estimated odds ratio value greater than 1 with the lower bound of the 95 percent confidence interval excluding 1 indicates individual-level association. For the trial-level association, R-squared quantifies the association. For these analyses, R-squared was calculating using two different methods. R-squared ranges from 0 to 1.

In addition to the above assessments, surrogate threshold effect was also evaluated. The surrogate threshold effect is defined as the minimum treatment effect on the proposed surrogate necessary to predict a non-zero effect on the true endpoint. The surrogate threshold effect provides additional information about the usefulness of the surrogate in future trials.

These results from the two sponsors have the following overall conclusions. There is strong overall individual-level association. Trial-level associations were weak to moderate in the disease

subpopulations. These associations were higher for the ineligible subpopulation. In general, the pooled populations had moderate to strong associations. FDA agrees with the overall results and interpretations.

These analyses should be interpreted within the context of their strengths and the limitations. We note a few high-level considerations here. Overall, the trials included in these analyses varied in design, conduct, and patient populations, with various MRD assays utilized. For this reason, it is unclear whether the pooling is appropriate in some analyses; however, these data provide a broad experience of randomized trials across multiple settings, potentially allowing for broader conclusions.

In general, the number of trials is low and the data do not allow for robust inspection of key subgroups such as disease subpopulations and assay types. The impact of the disease setting on the results is an open question. The overall process and data validity should be considered strengths.

Both applicants prespecified analysis in an SAP and discussed these with the FDA prior to executing the analyses. In addition, both applicants collected and provided the patient-level data, which allows for inspection of data accuracy, as well as the individual-level associations presented today.

FDA conducted additional meta-analyses based on the data submitted by either applicant. A total number of 18 trials were included, which resulted in 25 two-arm comparisons. The purpose of these pooled analyses was to determine whether utilization of all available data would impact the results or conclusions. In addition, surrogacy of MRD negative CR at any time in the relapsed/refractory setting was also explored using data submitted to the FDA. The reason for exploration of this additional endpoint is because in the relapsed/refractory setting, MRD is typically measured to follow any achievement of CR rather than at prespecified time points. In these analyses, the analysis population included all randomized patients whose data were available.

This study flowchart summarizes the number of comparisons and patients included in the meta-analysis based on 18 trials. There are 25 two-arm comparisons in total, including 11,019 patients overall. The analysis population for FDA's meta-analyses includes 14 comparisons of the newly diagnosed transplant-eligible population, 7 comparisons for the newly diagnosed transplant-ineligible population, and 4 comparisons for the relapsed and refractory population. The association between the MRD negative CR and clinical endpoints were evaluated separately for each population.

This slide summarizes the scope of the results for the MRD negative CR meta-analyses. These results broadly apply to both MRD negative CR at 9 months and MRD negative CR at 12 months. At the individual level, strong positive association for PFS and OS is observed across all populations, which suggests MRD negative CR is a strong prognostic factor for PFS and OS at the individual patient level. As for the trial level, moderate to

strong association between MRD negative CR and PFS was only observed in the newly diagnosed transplant-ineligible population. For the other two subpopulations, weak or no association was observed with PFS. At the trial level, weak to moderate association between MRD negative CR and OS was observed in all three populations.

This table summarizes the individual-level association results for MRD negative CR versus PFS and OS. The associations were evaluated separately for 9-month and 12-month MRD across the three subpopulations. The last column of this table presents the global odds ratio with 95 percent confidence interval. A higher global odds ratio indicates a higher prognostic value of MRD. This value can be interpreted as odds of surviving beyond a particular time point for a patient who achieves MRD negative CR versus a patient who does not. The odds ratio ranges from 2.77 to 7.67, and all 95 percent confidence intervals exclude 1, indicating strong individual-level association for all endpoints and settings.

This slide presents the trial-level association results for the MRD negative CR versus PFS for each disease setting. For brevity, results are given only for MRD negative CR at 12 months. For the newly diagnosed transplant-ineligible population in the middle, the R-squared value met the threshold prespecified by the I2TEAMM. For the other two populations, R-squared values were lower and did not meet the I2TEAMM criteria. Similar results were observed for MRD negative CR at 9 months.

In summary, numerically higher correlations have been observed for both 9-month and 12-month MRD assessments in newly diagnosed transplant-ineligible population. This result is limited by the fact that only seven two-arm comparisons are included in this analysis. In addition, this result was not replicated in other settings.

This slide summarizes the trial-level association for OS. The associations are generally weaker for OS than for PFS. None of the R-squared

values met the I2TEAMM criteria. Similar results were observed for the 9-month MRD negative CR. In summary, weak or moderate association was found between the MRD negative CR and OS in the trial-level analysis for all three populations.

This slide summarizes the sensitivity analysis of trial-level association between the 12-month MRD negative CR versus PFS by pooling populations. This sensitivity analysis was performed to further quantify the overall evidence provided across three subpopulations. The plot of pooled newly diagnosed populations is on the left and the plot of all three subpopulations pooled is on the right. Both R-squared values are above 0.5, suggesting a moderate association between MRD negative CR and the PFS in the pooled populations.

This slide summarizes the sensitivity analysis of trial-level association between 12-month MRD negative CR versus OS by pooling populations. Weak associations were found for OS in pooled populations with both R-squared values below 0.5.

This slide summarizes the surrogate threshold effect for PFS and OS. As mentioned before, the surrogate threshold effect is defined as the minimum treatment effect on the surrogate necessary to predict a non-zero effect on the true endpoint. For brevity, these thresholds are given only for MRD negative CR at 12 months. The values range from an odds ratio of 2.12 to 12.3, depending on endpoint and setting.

As an example, as shown in the plot below, an STE value of 2.12 suggests that in a randomized trial in which a 25 percent MRD negative CR rate is observed in the control arm, a 41 percent MRD negative CR rate in the treatment arm would be needed to predict a positive treatment effect on PFS. In general, the surrogate threshold effect can be calculated when there is sufficiently strong trial-level association and cannot be calculated if association is not present. Note that the surrogate threshold effect cannot be calculated for relapsed/refractory population due to small number of trials available in this setting.

This slide summarizes the results for the exploratory analysis of MRD negative CR at any time in the relapsed/refractory population. This endpoint is defined as achievement of MRD negativity at any time following achievement of CR. Only five trials were included in this analysis, and the results are similar to those for the MRD negative CR at 9 months or 12 months. For individual-level association, a strong association was demonstrated. For trial-level association, weak association was found for both R-squared values.

Based on the FDA's meta-analyses, we have the following statistical conclusions. Strong individual-level associations for MRD negative CR versus PFS and OS have been observed across all studies. This indicates that MRD negative CR is a strong prognostic factor for PFS and OS. Higher correlation was observed in the newly diagnosed transplant-ineligible population, although this was not replicated in other populations. Generally, weak to moderate trial-level associations were

observed for PFS. These associations were weaker for OS. Moderate associations for PFS were found in the pooled populations. The results for MRD negative CR at any time in the relapsed/refractory setting is similar to the results for MRD negative CR at 9 or 12 months in this setting; however, these results are based on only five trials.

I will stop here and turn it over to my clinical colleague, Dr. Rachel Ershler, to discuss the FDA's conclusions.

FDA Presentation - Rachel Ershler

DR. ERSHLER: Thank you, Dr. Zhang.

So where does this leave us? Based on the meta-analyses conducted by the applicants and the FDA, there was a lack of strong trial-level association for MRD and the clinical benefit endpoints of PFS and OS, indicating that MRD is not a validated surrogate endpoint; however, the strong individual-level association for MRD with PFS and OS did suggest that MRD is prognostic.

The analysis results provided robust data regarding the prognostic value of MRD, as noted

previously, data regarding the potential time points for MRD assessment, and information about how to potentially design future trials using MRD as an accelerated approval endpoint as part of a comprehensive development program.

So how can we potentially apply this information going forward when we think about designing future clinical trials? If we were to accept MRD as an intermediate endpoint for accelerated approval, we have two potential options for clinical trial design considerations to confirm clinical benefit.

Traditionally, the paradigm has been a two-trial approach that includes pursuing accelerated approval based on a single-arm trial in the late-line setting, followed by a randomized trial to confirm benefit and support regular approval. In this scenario, we could consider replacing ORR with MRD as an intermediate endpoint in support of accelerated approval. In this case, a minimum follow-up time should be specified. This would still be followed by a randomized trial in an

earlier line setting for confirmation of clinical benefit.

In the confirmatory trial, it would still be important to assess MRD -- for example, as a key secondary endpoint -- to continue to obtain information on how MRD affects long-term outcomes. Alternatively, we could consider a single-trial model in which data from an intermediate endpoint such as MRD, supported by duration of response, in a randomized trial in an earlier line setting could be used for initial accelerated approval.

In this scenario, patients could be followed for longer term outcomes of PFS and OS in the same trial for verification of clinical benefit for regular approval. Regardless of the clinical trial design used, confirmation of clinical benefit will be required, and accelerated approval may be withdrawn if benefit is not confirmed.

In general, the results of the individual-level associations were consistent across the 9-month and 12-month time points and for MRD negative CR at any time for both PFS and OS;

therefore, MRD assessment at any of these time points may be reasonable. The optimal timing of MRD assessment may depend on a particular disease setting. For example, in the newly diagnosed setting, MRD negativity at 12 months may be most appropriate, as it allows for assessment after multiple treatment components that impact the long-term outcomes, including induction and transplant; whereas in the relapsed/refractory patient population, MRD negative CR at any time may be more appropriate.

With regards to durability of response, durability may be inferred by MRD assessed at 9 months and 12 months; however, for MRD negative CR at any time, similar to ORR, durability of MRD negativity may be needed to support the robustness of this endpoint.

And finally, with regards to the MRD assay considerations, as noted previously, there are two general technologies used for bone marrow MRD assessment in multiple myeloma: multiparametric flow cytometry and next-generation sequencing. The

FDA is agnostic to which technology platform is used; however, the assay should be analytically validated for its context of use and should be sensitive to detect a prespecified MRD negativity threshold.

The data presented today show that there is a strong individual-level association of MRD with PFS and OS. This indicates that MRD is prognostic. The data also show weak to moderate trial-level association. MRD could potentially serve as an intermediate clinical endpoint instead of ORR, as it is a measure of a deeper level of response that can be measured early and may potentially support expedited drug development. However, there are still some residual uncertainties with the potential use of MRD.

First, there was a lack of strong trial-level association, and therefore, MRD was not established as a validated surrogate endpoint; however, most endpoints used to support accelerated approval have weak to moderate trial-level association with PFS and OS. Another uncertainty

is the lack of understanding of how this would be applied in different disease settings or with different treatment types.

Additionally, the magnitude of benefit is unknown, and there is also a potential safety consideration in that if new products are developed with the intention of targeting deeper levels of response, depending on the particular therapeutic, this may potentially lead to excessive toxicity.

So while there are some residual uncertainties regarding the use of MRD as an endpoint to support accelerated approval, it is important to note that there are risks associated with the use of any early endpoint. The accelerated approval paradigm addresses some of these risks by requiring confirmation of the anticipated clinical benefit. Recent FDORA legislation provides that the FDA may require, as appropriate, a study or studies to be underway prior to approval. And finally, the FDA has the authority to expeditiously withdraw an approval if the clinical benefit is not verified.

So in summary, multiple myeloma remains incurable and there is a need for alternate regulatory endpoints other than the traditionally accepted ORR and PFS that may be assessed earlier and potentially expedite drug development. The analyses presented today suggest that MRD negativity is prognostic in multiple myeloma. This is also supported by biologic plausibility in that it is biologically plausible that achieving a deeper level of response with MRD will be associated with improvement in long-term outcomes.

The accelerated approval pathway is intended to facilitate expedited approval of novel therapies based on an intermediate endpoint of clinical relevance that is reasonably likely to predict clinical benefit.

With that, we would like the committee to discuss the adequacy of the available data to support the use of MRD as an accelerated approval endpoint in multiple myeloma, as well as further assessment of MRD to advance its use in drug development. We would also like the committee to

discuss whether the available data supports the use of MRD as an endpoint in different disease settings, including newly diagnosed and relapsed/refractory multiple myeloma. And finally, we would like the committee to discuss the acceptability of the time points for MRD assessment and whether an assessment of durability should be required.

Finally, we would like the committee to consider the following voting question. Does the evidence support the use of MRD as an accelerated approval endpoint in multiple myeloma clinical trials?

Finally, we would like to thank all of the patients and investigators that participated in these trials, especially given the importance of the patient-level data for MRD in multiple myeloma. Thank you.

DR. NOWAKOWSKI: Thank you, Drs. Ershler and Zhang.

We will now take a quick break. Panel members, please remember there should not be

chatting or discussion of the meeting topics during the break. We'll resume at 11:25 Eastern time. Thank you.

(Whereupon, at 11:11 a.m., a recess was taken, and meeting resumed at 11:25 a.m.)

Clarifying Questions

DR. NOWAKOWSKI: We'll now resume, and we'll take clarifying questions to presenters. When acknowledged, please remember to state your name for the record before you speak and direct your questions to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with thank you, and the end of your follow-up question with, "That's all for my questions," so we can move to the next panel member.

Are there any clarifying questions for the presenters?

DR. NIEVA: Hi. This is Jorge Nieva from USC. My question is for Dr. Zhang.

There seems to be some discordance between individual-level associations and trial-level associations in interpreting these meta-analyses. In general, what are the advantages of trial-level associations versus using individual-level associations in order to try to get at these questions? Thank you.

DR. GORMLEY: This is Nicole Gormley. I'd like to have Dr. Zhang answer initially, and then we'll have additional comments from the FDA, if possible.

DR. VALLEJO: Yes, I can take that. This is Jonathon Vallejo, FDA. At the individual level, we're really talking about whether patients who respond live longer or have longer progression-free survival versus those who don't. In theory, this would translate to a treatment effect if you see higher response rates in one arm versus another. That's not always the case, so we tend to look across multiple trials to make sure that ends up translating from one treatment effect to the other.

So just because we see responders living

longer doesn't necessarily mean that that will translate at the treatment effect level, so that's the reason that we typically require multiple studies in meta-analyses with these kinds of effects.

Does that kind of get at your question?

DR. NIEVA: Almost. I guess on a more general basis, in terms of does one approach have a a certain reliability in one particular situation or another. I guess with the overall survival, we're getting at that there may be toxicity issues at the trial-level that interfere with survival, but are there any other general advantages to using one or the other?

DR. VALLEJO: In terms of --

DR. KANAPURU: Do you want to bring up slide 99?

DR. VALLEJO: Sure. I have a general presentation, small presentation, about this. Can we bring up backup slide 99?

As this is coming up, in terms of developing endpoints, probably the weakest rationale is just

biological rationale. The next step up would be individual-level correlation. So if you have biological rationale and individual patient-level association that's stronger, the strongest criteria would be trial level. So that's the strongest measure of an endpoint for surrogacy.

I can clarify further if you want to have a little more discussion about it.

Backup slide 99, please, if there's time. Maybe we'll have to circle back to that, but is that ok for now?

DR. NIEVA: Yes, that answers my question. Thank you.

DR. NOWAKOWSKI: I believe we have slide 99.

DR. VALLEJO: Right. Do you want me -- okay; sure

This is what we were just talking about, individual level, trial level.

Slide 100. Can you move forward one slide? So as we were talking about, you could just see one trial, and these are the types of curves we typically see. Responders do much better than

non-responders. You can see this just in a single trial.

In a randomized trial, you might say to yourself, "Well, what about by treatment? Does it vary by treatment?" So you can look at this and inspect within a single randomized trial whether one treatment has a different kind of association for responders and non-responders. So you see here red is treatment, blue is control, so treatment responders, control of responders, that kind of thing.

Ideally, this would translate to a treatment effect. If you increase the response rate, you would hope that you would see longer progression-free survival. This isn't always the case. We have a lot of cases in oncology where it doesn't translate. One reason this might be the case is we have therapies where if you're a non-responder in the control arm, you actually do much worse than you might do -- oh, sorry; in the treatment arm, you might actually do much worse than you would in the control arm.

So you can see in this case, responders do better regardless, but non-responders just do much worse on the treatment arm. So you can see in this particular example there's no effect on PFS or your long-term endpoint.

In general, what we're trying to do is see if you positively affect response rate, will that translate to a positive effect on PFS; or vice versa, if it's negative, will you see a negative trend? And if there's no effect, you hope that there's no effect on PFS. This is pretty stringent criteria.

So just to see that in action, here we have treatment versus control, and response rate is higher, PFS is higher. For another trial, ideally, if you see no difference in response rate, then you would see no difference in PFS. And similarly, if it's better than control, you would hope that the control has longer PFS.

Typically, in the meta-analysis, we're trying to collate these results across the three different trials or what I have here. Odds

ratio 2, hazard ratio of 0.5, and look at them as a conglomerate. So we take however many trials we have, and we plot these treatment effects. So odds ratios for the response rate, hazard ratio for PFS or survival. Here, odds ratio 2, hazard ratio of 0.5, and that's that dot down there. We plot them one by one, and then we hope to see a strong correlation where they fit around a straight line. So in this case, in this made-up example, this is like a relatively good correlation.

So that just gives you some intuition in terms of why the individual-level association is typically not enough, and why we need to see more at the trial-level and how it would translate. Does that make sense?

(Mr. Nieva nods yes.)

DR. NOWAKOWSKI: Dr. Vasan?

DR. VASAN: Hi. Neil Vasan, Columbia. Some more questions about the trial-level associations. I think it's clear from the briefing documents, this 0.8 value for the R-squared that was discussed by the FDA and the applicants, it's an arbitrary

number, and certainly that is a number that I think we're thinking about.

I'm thinking about the FDA slide 20, if that could be brought up. It seems that the real group that's driving the correlation here is the transplant-ineligible group, and I think that that is a theme we've seen with virtually all the data from both applicants and the FDA meta-analysis, is that in every analysis, the hazard ratios are lower -- excuse me, the R-squared values are lower for the transplant-eligible group compared to the ineligible group.

So I'm trying to understand, first of all, why that is. I do think that the numbers here are a more stark difference compared to the applicants' data, but this is a clear difference, and that R-squared here, hitting that 0.8 prespecified value, versus an R-squared of 0.35 is a large difference.

So I'd like to understand why that might be, and perhaps Dr. Landgren and Dr. Durie could discuss that from a clinical perspective. But then

also from a trial perspective, this designation of transplant eligible versus ineligible, is this a realistic way to be thinking about stratifying trials in the future from a regulatory endpoint perspective?

DR. GORMLEY: Thank you for that question. I'll actually ask Dr. Kanapuru to initially comment on the transplant eligible and ineligible, and then I'll perhaps have Dr. Vallejo mention some comments about some of the analyses that we've done in these subpopulations.

DR. KANAPURU: Thank you, Dr. Gormley, and thank you for that question.

Yes, as you have seen, at least the current paradigm for drug development in multiple myeloma is very distinct, so we do have drug development being conducted in transplant-eligible patients, and then transplant-ineligible patient populations; and part of this is also just related to how drug development is generally global. A lot of the trials from the transplant ineligible, they have very distinct eligibility criteria that are based

on age, so you have to meet a certain organ function to go on to those trials.

I think there's a lot of data that's now coming that some of these distinctions may be arbitrary; however, all of the trials that we have in the meta-analysis were based on these two distinct groups. Given the global drug development, it is thought that this is probably something that's going to continue; that the drug development could be potentially in these two distinct populations. And even if they're stratified, I think it's important to understand what the treatment effects are in the two different patient populations. Thank you.

DR. VALLEJO: In terms of why are they different, I don't think we know. I think that is an open question, something perhaps some of you all with multiple myeloma expertise could discuss or weigh in on. There are slight differences between what we did and the two applicants. One of the main differences here, in terms of trials included, is that we try to include everything. So there

were some trials that only had sensitivity 10 to the negative 4, and those are also included. So I think what was presented today was mostly just 10 to the negative 5th assays.

But regardless, I would tend to agree with you; it looks like the ineligible typically is driving this, but I don't know that we have an answer to that as to why that would be. And for these other populations, relapsed/refractory, yes, it says zero, but there are only four trials there, so I'm not sure we'd make too much of that. I wouldn't necessarily believe that there's no association, but I just don't think we have enough data to say exactly for that population what it would be.

DR. GORMLEY: This is Nicole Gormley, Division Director, DHM II. I would just add, I think just to underscore what Dr. Vallejo said, I think there's a robustness when we're looking at all the data, but if we start subsegmenting into different populations, as Dr. Vallejo mentioned, we have fewer and fewer trials, which decreases the

strength of our ability to detect any associations as well.

DR. NOWAKOWSKI: Dr. Hourigan?

DR. HOURIGAN: Thank you. Chris Hourigan. For the FDA, slide 36, please. So we've had wonderful, really diligent -- as you'd expect from our regulatory colleagues -- presentations on the levels of evidence required to go all the way through to a validated surrogate endpoint for regular approval. I wanted to just hone in on this residual uncertainty and say are these really uncertainties?

We're talking here about accelerated approval. Is the strong trial-level association required for an intermediate endpoint?

DR. ERSHLER: Rachel Ershler, FDA. No. So that is required for validation of a surrogate endpoint that could potentially, with totality of data, be used for regular approval. In the overall uncertainty in this, the meta-analysis that we did, did not provide that strong trial-level association; however, as we've commented on, most

endpoints in oncology do not meet that bar, particularly for accelerated approval.

DR. HOURIGAN: So just to restate, just so I'm really clear on the evidence, what you're telling us here is you don't believe the evidence is here for a regular approval as a validated endpoint. What we're discussing here is an accelerated approval where that strong trial-level association is not required; is that correct?

DR. ERSHLER: That is correct.

DR. HOURIGAN: Thank you. No more questions

DR. NOWAKOWSKI: Mr. Mitchell?

MR. MITCHELL: Yes. I would like to tease out a little more the difference between newly diagnosed and relapsed/refractory. Dr. Landgren's data, in his summary, he concludes the significant effect of new therapy on PFS and newly diagnosed multiple myeloma and did not talk specifically, in your conclusion, about relapsed/refractory. Then, in the subsequent data that was presented by the FDA, it appears that there's a weaker association, so I have two questions.

Should we be thinking about MRD as useful in both populations, and what do we do to make sure that we are continuing to design trials to examine more closely MRD with the relapsed/refractory population? So it's two things I'm asking, and anybody.

DR. GORMLEY: Yes. I think that you bring up, Mr. Mitchell, really great questions, and you are correct, that the strength of the association in the relapsed/refractory population was less. Dr. Landgren's analysis did not evaluate the relapsed/refractory patient population, and I don't want to speak for him, but that may explain why he didn't necessarily comment on that population.

I think, as we mentioned, our analysis was limited by the number of trials that were included in that there were really only four trials. So if you are going to use MRD in the relapsed/refractory setting, it really does require some extrapolation to say that we think that these associations are strong enough, generally, in multiple myeloma, and we don't see that many differences such that it

will be different in a newly diagnosed versus newly diagnosed transplant eligible, versus relapsed/refractory, that would prevent us from relying on this data. But that's somewhat of a judgment call, and that's one of the questions we would like for this committee to discuss further.

I would just add -- I'm not sure I'm fully addressing your second question. Could you restate it again?

MR. MITCHELL: The second question is, how do we design trials so that we are getting at the utility of MRD with the relapsed/refractory population, even if we're saying we don't have evidence for it now, or because we're saying we don't have enough evidence for it now, particularly at the trial level, with relapsed/refractory?

DR. GORMLEY: Thank you for jogging my memory. It's a really important question, and that's one of the things that we really want to highlight as well; that we think it's really important that subsequent trials continue to collect data on MRD as a secondary endpoint,

ideally with alpha allocation and statistical powering, such that we can really rely on those results, and then further refine or develop our understanding of how to best use MRD as an endpoint as well, throughout drug development, not just as an endpoint.

But I think what our thoughts are, is that, generally, this has been a really robust assessment thus far that's included multiple randomized-controlled trials and a meta-analysis, and multiple meta-analyses here that have evaluated the strength of data for MRD to be used as a potential endpoint. There are still some unknown areas, but we think that this is an opportunity to further collect this information in subsequent trials, subsequent randomized trials, to get additional data to help inform us how to best use this.

DR. KANAPURU: Yes. I just have one more comment just to add to what was said. Again, here we are talking about the use of MRD to support accelerated approval, and it was just pointed out,

this is going to be considered as an intermediate clinical endpoint, and we have evidence that achieving a deeper level of response is biological plausibility.

The individual associations were strong across all of the disease settings. The trial-level associations, yes, they were different, but again, as pointed out, we don't need that strong trial-level association for an accelerated approval endpoint.

MR. MITCHELL: For what?

DR. KANAPURU: For an accelerated approval endpoint, we don't need that strong trial-level association, and none of the current endpoints that are used for accelerated approval do not have or don't show strong trial-level association. Thanks.

MR. MITCHELL: Thank you.

DR. NOWAKOWSKI: Thank you.

Maybe I'll ask Dr. Landgren to comment on the issue, which was brought several times, this dichotomy in newly diagnosed patients for transplant eligible and transplant ineligible, and

how the field is changing in this regard with the new therapies.

DR. LANDGREN: Sorry. My Scandinavian gene pool is making me too tall here.

(Laughter.)

DR. LANDGREN: So the question is why do we see a stronger ALT ratio in the transplant in ineligible versus the transplant-eligible population? I don't think we know that for sure. We don't have any detailed information on that. But I think, as we heard from Dr. Gormley and the FDA team, the number of trials are, to begin with, quite small, and when we start slicing the data into further subgroups, we run into issues with statistical power. So I think the formal way to fully address the question will be to continue to capture data in future studies to better understand.

But I also would like to say that you have heard from our team today, from the EVIDENCE study, that there is a very strong correlation on a patient level between MRD as a surrogate endpoint

and progression-free survival, and you heard the same thing from the I2TEAMM team. So you heard two independent studies showing correlation.

The last thing I will also say is that in our statistical analysis plan, we have three primary endpoints: the transplant eligible, transplant ineligible, and also the relapsed/refractory patients. We chose to not include that in the briefing book, the last part, because the number of trials were small, but our results are very similar to what you heard from the I2TEAMM, so you have two studies showing the same thing also in the relapsed setting. Thank you.

DR. NOWAKOWSKI: Thank you.

Dr. Maurer?

DR. MAURER: Thanks. Matt Maurer, Mayo Clinic. If you could bring up the I2TEAMM slide 37? As that's coming up, one question I had is around the MRD negativity rate, across the different settings, transplant eligible, ineligible, and relapsed/refractory. It would be helpful if we could see per trial what the MRD

negativity rate is. I haven't seen that in any presentation yet, but I'll point out here that you see that it's a very low MRD negativity rate, especially in the transplant ineligible, as well as the relapsed/refractory.

So moving forward, I would be interested -- that has some implications, if we look at FDA slide 22 in terms of you're seeing some very large odds ratios for MRD because it's probably an uncommon event of MRD negativity in these settings.

So I guess my question is for the FDA. Moving forward, as we expect higher MRD negativity rates in the studies that we're doing, these studies done in scenarios with very low MRD negativity rates, how can we project that forward in future studies if we expect higher MRD negativity rates?

DR. GORMLEY: That's a good question. Nicole Gormley, FDA. I'll start. I think it is true that one of the challenges always with the use of a meta-analysis is looking at the data that you

currently have, and then figuring out how you're going to apply this to future clinical trials; and yes, we do expect and hope that MRD negativity rates will increase as the strength of our therapies do improve.

I think that the initial work that we've done, or that has been done, looking at the surrogate threshold effect will help provide a little bit of guidance in terms of the differential that would still be clinically meaningful, even if the absolute MRD rates are increasing. I think it's the differential between the MRD negativity rates, between arms, that would be most helpful and, again, underscoring, to some extent, the strength of randomized data as well, in particular, if it's a randomized trial that's being used.

DR. NOWAKOWSKI: Dr. Martin?

DR. MARTIN: First, a comment. I'd like to thank all the presenters, and it was really nice to see that all the presentations really harmonized with the end result, but I have a few questions for people.

Rachel, I have a question for you. The trial-level association for the non-transplant-eligible population, you assessed that as moderate to strong relationship for PFS, but I don't think for OS. So for surrogacy, does it have to meet it both for PFS and OS for regular approval?

DR. GORMLEY: This is Nicole Gormley. I'll start. Just to be transparent, if there were strong trial-level association demonstrated, typically we would compare that to endpoints that we use for regular approval now, but any association, if we were ever going to say that this is a validated surrogate, it would be the totality of data. So yes, we would look at the surrogacy for PFS as trial-level associations, and we would look as well at the trial-level associations for overall survival. And again, it would be the totality of data that would inform that decision.

I would just add to that, really underscoring the importance of even if it's a PFS endpoint, for example, that's used, or any

validated surrogate that's used for a regular approval, we still look at overall survival data. And that really was the purpose and underscored, in particular, at the overall survival workshop that we had this past July, the importance that even if the endpoint is not overall survival, if it's PFS even for regular approval, overall survival information is still evaluated because it is both an efficacy and safety endpoint.

At that workshop, in particular, we discussed ways to look at overall survival when it's not the primary endpoint and methods to look at it, in particular, to rule out harm, and there are multiple ways to do this, but also thinking about coming up with statistical criteria as well to prespecify how OS would be evaluated when it's not from an efficacy standpoint.

So that's a little bit of a long-winded question to your answer, but it's basically saying overall survival is important --

DR. MARTIN: Yes.

DR. GORMLEY: -- and that would be evaluated

in any context.

I don't know if others have anything to add.

DR. PAZDUR: Well, obviously, it depends on the context, if you're asking surrogacy for PFS or surrogacy for overall survival. They don't necessarily have to be concordant, obviously. One would want, obviously, surrogacy for overall survival because that's the true clinical benefit endpoint, but there may be reasons why one cannot show that -- numbers of patients, et cetera -- but, obviously, that's the stronger clinical endpoint, overall survival. You would ask yourself that question, and that's a matter of judgment on what we would take at that time, but we have used PFS as a full approval endpoint.

DR. MARTIN: Then maybe I can ask the I2TEAMM or the Miami team, in terms of the 9-month and the 12-month time frame for MRD, was that from the start? For the transplant-eligible patients, was that from the start of induction or was that from transplant? Just to get the time down.

DR. DEVLIN: Yes. Sean Devlin. So it's all

from the time of randomization.

DR. MARTIN: Okay.

DR. DEVLIN: So it's either 9 months or 12 months from the time of randomization.

DR. MARTIN: Okay.

So a question for the FDA on that -- because this is looking at early endpoint but, again, you'd want to have safety in the risk mitigated during this period of time -- if you look at the 9 month and the 12 month, because we've had some myeloma trials that have, unfortunately, had the results that we we really didn't want, is that 9-month or 12-month time point, is that good enough for us to look at the overall survival endpoint at that point in time and see the difference in overall survival? Is there any study that we would have missed in that if we had to wait longer?

DR. GORMLEY: Yes. I will say that we can often look at overall survival information if it's a randomized trial. So we can only assess overall survival if it's a randomized trial, and single-arm trials, we cannot, just because of the inherent

biases and differential information available.

So if it's a randomized trial, we sometimes can and do ask for information about overall survival at the time of any regulatory decision, even if it were based on MRD, or response rate, or PFS. The issue is, is that it's often not mature at that time point. So depending on where it is in the study, there may be interim analyses planned, or there may be enough information such that we can have an assessment, but I think that's the advantage, really, or strength of accelerated approval, is that there is that requirement for confirmatory benefit from a subsequent trial.

So if it's not available from that initial trial, whether that's a single-arm trial or a randomized trial with an early endpoint as the accelerated approval and an immature overall survival, we will be looking at it later at the time of a subsequent submission.

DR. PAZDUR: But to answer your question just briefly, a formal analysis for overall survival with adequate number of events probably

would not be done at that time. It would have not enough events.

DR. NOWAKOWSKI: Thank you.

Dr. Advani?

DR. ADVANI: Yes. Ranjana Advani, Stanford. I have a question for the Florida team; slide 32, please. Sorry. Slide 30.

DR. LANDGREN: Dr. Devlin will answer this question.

DR. ADVANI: I'm just a little confused as to the first bar there -- not this one.

DR. DEVLIN: I think you're on the wrong slide deck. It's for the EVIDENCE trial.

DR. ADVANI: It's a different slide deck, yes. The diagram of patients in the VGPR who were MRD negative at 12 months, why were they categorized as MRD positive?

DR. DEVLIN: Per our statistical analysis plan, for MRD evaluation, they would have to be in a complete response at the time of their MRD evaluation, even if they subsequently achieved a CR afterwards.

DR. ADVANI: And what was the percentage overall which fell into that category?

DR. DEVLIN: I don't know off the top of my head, but probably not a lot of patients in that category. I think I could defer to Dr. Landgren, who monitors patients and would probably know and could address that, how often that happens. But this was the decision we made in collaboration with advice from the FDA that we are only considering an MRD negative result if they had a previous complete response prior to that, which is following the IMWG response categorization.

DR. ADVANI: Because, clinically, I don't know if it matters that much, as long as you achieve a -- at some point, the outcomes probably will be the -- I don't know, and that's why the confusion.

DR. DEVLIN: Yes. I would be happy to defer that clinical question to Dr. Landgren.

DR. LANDGREN: I think that's an excellent question, and as a clinical treating physician, I would agree with you, but for the purpose of this

statistical analysis plan, with the FDA, we had a lot of discussions. It took us many years to arrive at the final version, and the decision was that we should have strict criteria. Only patients that had achieved a CR should be tested for MRD within this window of 12 months plus/minus 3 months as the criteria.

The consideration was that a patient that has a VGPR could have a residual 10 percent protein compared to the baseline protein, which could potentially indicate that there were some tumor cells left behind. But as a clinical doctor, I also know, treating thousands of patients with myeloma, that there is a delayed clearance of these proteins. Many times when you see these proteins and you test the patient, MRD could be negative, and a few weeks or months later, it will clear, so we've also delayed clearance. But just to make it very, very conservative for the purpose of the analysis, we used this approach.

We did sensitivity analyses when we included these patients, and there are many other examples.

You had patients who were tested for MRD before and after the time window, and they were in a CR. You could assume that they probably were MRD negative in the window but, again, sticking to the statistical plan, we worked with the FDA. This is how it was done, and I think that is how it should be done also.

DR. ADVANI: Thank you.

DR. NOWAKOWSKI: Dr. Maurer?

DR. MAURER: Matthew Maurer, Mayo Clinic. If you could bring up FDA slide 32, please? While that comes up, my question for the FDA, then, would be, are we considering MRD as a potential accelerated endpoint in a single-arm trial in this setting moving forward?

DR. GORMLEY: This is Nicole Gormley. Yes, and again, that's something we'd like for the committee to discuss. Currently, drug development within multiple myeloma, most commonly it's this sort of approach, where a single-arm trial is done in a more refractory patient population, and then a randomized trial in an earlier line is done to

confirm the clinical benefit.

We are advocating, and do advocate, the next slide, which shows a single trial be done that's randomized at the outset -- thank you -- for an initial MRD accelerated approval, and then following those patients in that same trial for progression-free survival and overall survival. But there are logistical challenges, in particular, disease-specific challenges with this sort of trial approach in terms of, specifically, in those earlier lines, is there enough data available to evaluate this in combination with other therapies, the appropriateness of the control arm of either a doublet or triplet in some of those earlier lines.

So there are unique circumstances in multiple myeloma where this type of trial approach would be reasonable, but we aren't able, I don't feel, to only have randomized trials in multiple myeloma, although I think there's the most amount of evidence gained for randomized trials, and in regards to efficacy, safety, there's the most amount of robust information gained from randomized

trials. But for MRD likely to be useful as an expedited endpoint, there would still probably need to be some use of single-arm trials.

DR. KANAPURU: Yes, and I'd just like to add, considering MRD as a deeper response, we've used overall response rates in single-arm trials because we know that this is probably measuring the activity of the drug, so similarly, if MRD is a response endpoint, it is probably reasonable to also use this in single-arm trials; but, obviously, there are limitations in that the safety without a control arm cannot be assessed. But as Dr. Gormley mentioned, having that confirmatory trial underway or following verification of benefit will mitigate some of those risks. Thank you.

DR. MAURER: If I could just follow up on that, then, is there sufficient evidence in this clinical setting to know what the bar would be for a clinical benefit or a positive study using MRD as an endpoint here?

DR. KANAPURU: Thank you for that question. I think you're asking about the magnitude of

benefit in MRD and myeloma?

DR. MAURER: Or with using a single-arm trial, do we have enough data to kind of know that this is a meaningful, efficacious study using this endpoint?

DR. KANAPURU: Yes, I think that's a very important question and, obviously, there is a lot of data from prior trials on how the MRD reads, at least from the current trials. I think you can still design a single-arm trial with a hypothesis for a specific MRD rate to show that your drug is actually beneficial, but I think that's still an open question and has to be decided on a case-by-case basis.

DR. PAZDUR: But you would also have the overall response rate, too --

DR. KANAPURU: Yes.

DR. PAZDUR: -- also in these trials, so you could get a feel of this. I think one of the issues most people have, we have a feel in oncology what a 30 percent response rate is compared to an 80 percent response rate, but we don't have that

necessary feel about MRD positivity or negativity. And here again, we need more experience with it, so you'd be taking a look at the total body of evidence that would come in.

DR. NOWAKOWSKI: Dr. Madan?

DR. MADAN: Thank you. Ravi Madan, National Cancer Institute. If we could put up Dr. Ershler's slide 33 again, about the hypothetical future trial designs; if guidance comes from the FDA that MRD is an accelerated approval endpoint, it changes the incentives for clinical or therapeutic development. So all of a sudden, perhaps, you could see a world where preclinical modeling is now more focused on the biologic and maybe less the clinical, as would the phase 1 and 2 development.

So in this pragmatic design, although there has been great concordance between MRD and PFS, that may not predict future results because the incentives have changed. So in that context, if there is not alignment with PFS, would that be the signal to remove the accelerated approval or would you still wait for OS?

Dr. Landgren and colleagues, if you want to comment on this scenario as well, but FDA, first, in terms of your thoughts on PFS being negative, if MRD is positive, would that be sufficient to remove the accelerated approval?

DR. GORMLEY: So we, unfortunately, at the FDA have had experience where we have had to pursue withdrawal of therapeutics, and when that has occurred, I'll just start off from the outset, it's a totality assessment. We're evaluating everything in that case. We're looking at the safety, we're looking at the death narratives, we're doing deep dive into -- I'll spare you the details, but multiple different types of analyses. It's a totality assessment at that point.

Oftentimes if the MRD is positive, and the same trial was followed up, and the PFS was negative, at that time, we would have information likely on overall survival. And even if it wasn't OS as an efficacy endpoint, we would have information on OS as a safety endpoint. So there would be likely information about OS that would

also help to inform that decision at that time.

So to answer your question, it would be pretty unlikely that we would be in a situation where we had information on PFS and no information on OS. We should have enough that could help inform that decision at that time to withdraw, if necessary. But it really is important that there's verification of clinical benefit from an initial accelerated approval to a regular approval because it's really important for multiple reasons. One, it's important for the validity and public trust in our approvals, and then also, we don't want to do harm to patients. It's really important that we get it right. So that's an assessment that we make at that time, but it's really based on the totality of data.

I don't know if others want to comment.

DR. THEORET: And just to add to that, one of the important factors to consider when we're looking at a confirmatory trial that did not verify clinical benefit, in addition to the safety considerations with overall survival, it's

increasingly difficult as there are more and more therapies, more and more effective therapies, that actually measure overall survival in a different context. But it's also very important to consider what is the therapeutic landscape and has that changed; has that therapeutic landscape changed for which the accelerated approval was actually granted? Are there more therapies that have been approved, more effective therapies, than the initial accelerated approval when that occurred? So that would be a consideration as well.

DR. MADAN: Yes. I think it could work the other way, too, right? You have MRD high, PFS is not what you would have hoped for, but the subsequent therapies balance that out. Again, we're changing the incentive structure when we move to these kind of endpoints, and I think that -- and I'd welcome the clinical input as well, in terms of if there is a disconnect between PFS and MRD specifically, how confident are you, then, that there is clinical benefit?

DR. LANDGREN: So may you kindly repeat the

exact question?

DR. MADAN: Yes. I'm just saying, as we move forward in kind of an MRD world, if that's where we're going, you changed the incentives to really target your trial designs and therapeutic development on maximizing MRD with maybe less emphasis on the backend clinical just because it's maybe not investigated as much before you decide to move forward. So how confident would you be if PFS didn't align with MRD; that you had to wait for some sort of signal from OS to say that maybe this isn't as effective as MRD suggested?

DR. LANDGREN: So my answer back is that drug development is very difficult. FDA has a difficult role making sure that they evaluate and approve drugs that are safe and effective and also to ensure expedited access to new therapies. It is a difficult task, but I think what we have provided here today is the body of evidence from the entire literature, for the entire available data sets and published literature from trials around the world. And I think you have seen in two independent

analyses consistent results that MRD negativity is a very strong predictor of progression-free survival. It fits the bill. It fits the bill of the regulation that the FDA has stipulated for a biomarker reasonably likely to predict clinical benefit. It's hard to speculate for me beyond that.

I think, also, the FDA has also highlighted the fact that MRD will be viewed as a totality, where progression-free and overall survival data also will be included in the determination. So the example of a trial eventually not reading out, I would assume that it would not be any different from a trial where ORR in the current landscape was done, and then the final endpoint didn't read out. So that would be in line with the example the FDA showed us. They would take back. It would not get the full approval.

So I would say MRD and ORR are not any different from each other. We are talking about an intermediate early endpoint for drug approval reasonably likely to predict clinical benefit.

There is no difference with ORR.

DR. MADAN: Okay. Thank you.

DR. NOWAKOWSKI: Thank you.

Mr. Mitchell?

MR. MITCHELL: Yes. Can we pull up the I2TEAMM slide number 18, please? And I have a question. Help this layperson patient understand the magic of 10 to the 5th power and why we are drawing a line there. Also, does this slide tell us something about the predictive power of MRD, given what we see happening with the plot?

DR. DURIE: David, I'll have Dr. Paiva respond to that.

DR. PAIVA: Thank you for the question. I think that this slide illustrates well the power of MRD in predicting clinical benefit in terms of progression-free survival, and what the slide is showing is that for patients achieving an MRD negative result -- and I will focus on 10 to the minus 5 -- it will translate into a reduction in the risk of progression and/or death of approximately 70 percent. So that is the magnitude

of clinical benefit that we have seen across different trials and patient populations, and drugs have the benefit of achieving an MRD negative result.

MR. MITCHELL: As a patient, wouldn't I prefer that that we draw the line at 10 to the 6th power because I'm going to get a deeper response, and we should be shooting for that? I still don't understand why 10 to the 5th power is the magic line.

DR. PAIVA: I appreciate the question.

MR. MITCHELL: Maybe it's me not understanding.

DR. PAIVA: From the patient point of view, the prognostic point of view, as well as from the clinical management, the more sensitive the MRD assessment, the better the prediction of clinical benefit, as shown in the slide, and this would speak for the 10 to the minus 6 sensitivity threshold. However, for the purpose of today's meeting that is to use MRD negative rates as a marker of reasonably likely to predict clinical

benefit, then you need to require or rely on a sensitivity threshold that can be achieved in all the patient samples that will be collected in that trial. And our accumulated evidence in the past 10 years using these methods in large multicenter clinical trials is that a 10 to the minus 5 sensitivity can be achieved in virtually all samples, and this is why this is a threshold that they selected for this purpose.

MR. MITCHELL: Thank you.

DR. NOWAKOWSKI: Thank you.

Mr. Riotto?

DR. KANAPURU: I'd just like to add a little bit.

Mr. Mitchell, thank you very much. I think that's a very important question, and I think from a patient point of view, I think it's very reasonable to ask for lower sensitivity threshold, but again, as pointed out, the majority of the data we have, really, to support the use of MRD as an endpoint is based on this 10 to the negative 5. There is emerging data that maybe having a lower

threshold like 10 to the negative 6 may be better, and that's why I think it's really important to evaluate that in all of the future trials as well. And this may change in the future as we get more data, but at the current time, the data supports the 10 to the negative 5 threshold. Thanks.

DR. GORMLEY: And just to add a little bit more, too, from a regulatory and a clinical trial perspective, you want a sensitivity level that allows you to discriminate between the two treatments, and 10 to the minus 6, just by way of example, you may only have one or two patients -- I'm just giving examples -- whereas if you use 10 to the minus 5, you might have 15 to 20 patients, and that might allow you more discriminating power as well. So there's a difference there between what you would want as an individual patient, and then what would be best for an endpoint for a clinical trial, perhaps, just because of the discrimination.

DR. NOWAKOWSKI: Mr. Riotto?

MR. RIOTTO: Michael Riotto, patient

representative. As a myeloma patient, time is always not on my side, shall we say. So the question is, both the Miami group and the I2TEAMM group both mentioned 10 years to get through a clinical trial. So if MRD negativity was approved as a surrogate endpoint, do you have a best guess at what the timeline would be to get a drug to market, then? Thank you.

DR. DURIE: Dr. Anderson will have an effort for this one.

DR. ANDERSON: No, I think it's a very, very good question, and, honestly, the reason we're here is that we need an earlier endpoint so that patients like you can get access to new drugs in a reasonable period of time. And you heard from the FDA and from us, and thank goodness, from all the work in this room, the response rates to the new drugs are very, very high nowadays, and the PFS, and even OS, is prolonged, so it isn't reasonable to do the same old paradigm in drug development. So CR, MRD negativity, seems like an early indicator that might move things more quickly.

I can't really speak to what that's going to mean now. I think in the past when accelerated approval has been used in myeloma, which it has been used very commonly, it got patients drugs two and a half years earlier than would have otherwise been the case. They went on to get their full approval, but the fact that they were accelerated approval let two and a half years worth of patients get that drug earlier.

So I think what you heard in our analysis, it was 9 to 12 months, and Miami 12 months, but we're going to get information on MRD within the first year. So my guess for you is that it is going to translate in us discriminating between arms and randomized trials much earlier. So earlier is key, but without it, honestly, we can't distinguish things very well anymore based on the overall response rate. We really need something that can discriminate better and as an earlier indicator, predict for PF, be associated with prolongation and PFS. So I think it's fair to say that you will know whether a drug is effective

earlier, and that should translate into earlier approval and earlier access for patients like you.

DR. NOWAKOWSKI: Thank you.

Dr. Martin? Okay.

Dr. Vasan?

DR. VASAN: Hi. Neil Vasan, Columbia. This is regarding I2TEAMM, slide CC-22. The data in the meta-analyses did not involve CAR T cells or any other cellular products, so these data obviously correlate, show that MRD negativity is correlating. So I think the question I have for Dr. Gormley is, MRD here was tested for antibodies and small molecules. Is this something that would need to be decades later, 10 years from now, redemonstrated in another formal meta-analysis, as today, for these newer therapies?

Obviously, this decision will have implications for the near and late future, and I say that because CAR T cells we know have late toxicities, and in a 9-month or 12-month assessment for MRD, that may or may not be reflected. So if there could be a little bit of speculation to the

decision we're making today and how that's going to affect therapies like CAR T cells, but even therapies 10 years from now that we may not know what they are.

DR. GORMLEY: No, that's a very pivotal question, so thank you. I think there are a few considerations here, and I think the way that I think of this is that this body of evidence and the data that we have now is really foundational to our understanding of how to use MRD, specifically in multiple myeloma. There are a lot of other settings, though, and you're correct, this analysis and these meta-analyses were limited to small molecules, antibodies, biologics, and there will be new therapies, including CAR T, that we don't know. And there are also additional populations that we don't know about, including smoldering multiple myeloma, and even earlier perhaps precursor states.

So how do we apply this body of evidence to other settings that are beyond the scope of this particular meta-analysis? I think from my perspective, it's not necessarily a complete redo

of all of the analyses, but it's perhaps looking at the strength of the data that we have in certain settings and what can be extrapolated. And I don't have the specific answers to you for specifically CAR T or specifically smoldering at this point, or other such extrapolations, but I do think that the evidence such as this shown here on the slide and other studies can help inform how reasonable it is to extrapolate the experience and the foundation that we have from this body of evidence to other settings.

So specifically, again, CAR T and products were not included in this analysis, but other information can help supplement and allow us to, within the regulatory agency, have confidence that it can be used in these other settings. So I don't think it's quite the same as a complete replication or a complete new analysis that needs to be only done with 10 randomized trials for CAR T therapy per se, but there can be other information that can help supplement our understanding.

DR. KANAPURU: And just to add to that, I do

think that it is important to understand because there are some differences. As we know, CAR T is a one-time treatment, and the drugs that we currently have are continuous. So it is really important to understand the kinetics of MRD response, as well as how these patients do in association with long-term outcomes. But as Dr. Gormley mentioned, I think we already have a body of evidence that we can build on, and it may not require the time that we took to get here to also consider the use of MRD in CAR T therapies. Thanks.

DR. VASAN: Thank you.

DR. THEORET: And just to add a bit, in terms of the accelerated approval pathway, it does reflect some uncertainty in terms of whether clinical benefit will ultimately be verified in that approval pathway. It also may speak to the importance, in general, of randomized trials, too. When you're evaluating a particular experimental therapy in the context of a standard of care, the accelerated approval pathway does take into context those available therapies, so differential

treatment effects may more easily be identified in that setting. And then, like Dr. Gormley had said previously, there really is a a very important assessment on overall survival as particularly a safety endpoint when we're looking at these earlier endpoints, and that randomized trial does allow us to have that assessment within the same trial.

DR. VASAN: I was also referring to it in terms of early and late toxicities as well, in addition to OS, which is obviously reflected in OS, but that that assessment obviously would be done as well for traditional approval.

DR. NOWAKOWSKI: Greg Nowakowski. I'd like to have a follow-up question for Dr. Anderson, and if we can pull the FDA slide 25?

Dr. Anderson, you made a case that MRD assessment can really help drug development; though, if you look at the magnitude of the benefit in reduction of the MRD negativity, it is quite significant to correlate to relatively modest differences in PFS in this modeling. So do you worry that the opposite effect can be seen; that

some of the trials which do not show the difference in MRD negativity early on can get terminated early or the interest in those drugs can actually drop?

DR. ANDERSON: No, I think it's a good point, and I do think we need to gain experience together as to the extent to which MRD negative CR does portend for the extent of progression-free survival advantage. I think we're open to that. We have some data on that. Dr. Bruno, perhaps, can talk about what MRD benefit we have seen and what it's been correlated with in terms of PFS to date, but I think we're open to understanding, in different settings, exactly what the increment and benefit will translate into.

Bruno, do you want to comment on your data?

DR. PAIVA: Yes, thank you. In terms of the magnitude of MRD negative rates in randomized clinical trials, we have seen, particularly in those that have led to drug approval in the past 5 to 10 years, a difference ranging from 20 to almost 30 percent. And what we have seen also in our analysis is that those trials showing an odds

ratio for PFS of 0.6 or less showed MRD negative rates higher than 20 percent, meaning that if you clearly see a difference between the investigational versus the control arm exceeding 10 or eventually 20 percent, this will most likely predict a benefit in PFS that will be greater than a 40 percent reduction in the risk of progression and/or death.

DR. NOWAKOWSKI: Thank you.

Dr. Frenkl?

DR. FRENKL: Thank you. Tara Frenkl. I'm the industry rep and work at Bayer Pharmaceuticals. I have a question for the clinical folks from the applicants' side, I believe, and if you could provide us with a little bit more context on what drives the timing of the MRD assessment. As we saw some variability in the scenarios that you progressed and how important clinically, I'd like to know is it important that there's flexibility in that timing, like between the 9- and the 12-month assessment.

DR. LANDGREN: This is Dr. Landgren. The

time point of 12 months, as mentioned before, for the timing of assessment of MRD plus/minus 3 months, was agreed upon jointly between the FDA and our study team, and it was something that really came out of the fact that the data sets we have, that's the data we have. We have to work with what we can work with.

When we looked across all the data sets, the agreement was that that would be a clinically reasonable time point. We focused on the newly diagnosed patients. As you heard previously from other presenters here today, clinically, patients with newly diagnosed myeloma get combination therapy for a certain number of cycles with or without transplantation. That may change in the future, but one year is a reasonable time point in this disease to capture MRD with a bone marrow biopsy. So it came out of a clinical scenario and also from availability of data, and it was discussed extensively with the FDA, and we jointly agreed.

We also lastly should say that that was also

the data point where there was least missingness, so that's how we came. And maybe I should say last that we did look at 9 months, and when we redid all our analyses, we see very similar results, as you heard from the I2TEAMM.

DR. NOWAKOWSKI: Thank you.

We'll now break --

DR. KANAPURU: I'd just like to make a comment. I just want to add to that. As we showed in our FDA analysis, FDA also looked at the MRD negative CR at any time in the relapsed/refractory patient population because, generally, we want to be able to assess it's similar to ORR. And ORR is generally assessed as best overall response rate, and at least in the individual patient level, the associations were similar to what we have seen for the 9 month and 12 month. So we can assess MRD negative CR at any time, at least in the relapsed/refractory data that we had. Thanks.

DR. NOWAKOWSKI: Thank you.

We'll now break for lunch. We'll reconvene again in this room at 1:15 pm Eastern time. Please

take any personal belongings you may want with you at this time. Panel members, please remember that there should be no chatting or discussion during the lunch break. Additionally, you should plan to reconvene around 1:05 to ensure that we are seated before we reconvene at 1:15. Thank you.

(Whereupon, at 12:25 p.m., a lunch recess was taken, and meeting resumed at 1:15 p.m.)

A F T E R N O O N S E S S I O N

(1:15 p.m.)

Open Public Hearing

DR. NOWAKOWSKI: We will now begin the open public hearing session.

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

For this reason, FDA encourages you to advise the committee of any financial relationship that you may have with the applicant. For example, this financial information may include the applicant's payment for your travel, lodging, or other expenses in connection with your participation in the meeting. Likewise, FDA encourages you to begin your statement and to advise the committee if you do not have such financial relationships. If you choose not to

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

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

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

Speaker number 1, please unmute and turn on your webcam. Will speaker number 1 begin and introduce yourself? Please state your name and organization you are representing for the record. You have five minutes for your presentation.

MS. AHLSTROM: My name is Jenny Ahlstrom.

I'm a multiple myeloma patient diagnosed in 2010, and I'm the founder and CEO of HealthTree Foundation, a patient advocacy organization supporting multiple myeloma. I have no financial interest in the outcome of this meeting.

Over the last 14 years, since my diagnosis, I've seen exceptional innovation in multiple myeloma. It's a disease that has attracted both the research community and investment into new therapies. What a major blessing it's been for the patient community to have the FDA approve a large number of new therapies and indications in this space, with last week's CAR T earlier approvals as our most recent example. I'm so grateful for FDA's work on these approvals because these new therapies and earlier use strategies are saving lives.

FDA has continued to contribute to the pace of innovation in myeloma with accelerated approvals that provide an earlier access path for new treatments. We have seen innovation affect the type of care that we receive as patients. I received tandem transplants back in 2010 because it

was my best shot at a curative treatment in the absence of powerful drugs that we have today. My initial approach would have been radically different had I been diagnosed today.

We've moved from these chemotherapies to a wide range of immunotherapies, including monoclonal antibodies, bispecific antibodies, CAR T therapies, and many others that are coming. This innovation has resulted in it being common for the majority of newly diagnosed patients to achieve 100 percent overall response rates.

As was discussed earlier in this meeting, overall response rates no longer have the power that it used to have. PFS and overall survival are traditionally used as clinical trial measures, but these measurements are becoming a bigger challenge the longer we live and the more therapies that we receive. For example, with overall survival, it's really challenging to determine which therapy impacted overall survival when patients have received multiple drug combinations, varied treatment sequencing, and have a wide variety of

genetics, especially in patients who have received 3, 5, or even 10 prior lines of therapy. Overall survival as an endpoint is becoming more convoluted as a key clinical trial data endpoint, especially for relapsed/refractory trials.

Now, with the acceleration of drug approvals, many patients are living 10-15 years instead of 3 to 5 years, although we still know that 40 percent of patients are still dying under 5 years. There is still no known cure, so the innovation needs to continue and we still have an urgent need.

The blessings of these new therapies have created a significant challenge in drug development. The time it takes to determine results without a new endpoint is too long. Ten-plus years to have the data readout for a single trial puts patients' lives at risk of dying before the results can be gathered, and that's just for a single trial, so we need new approaches, we need to continue innovating, and our need is still urgent.

Now, it's agreed by all attending this meeting that the use of newer MRD technology can better inform responses and that it correlates with PFS, the traditional measure. MRD testing is helpful for me as a patient in many ways. It provides me with the depth of response measurement to my initial therapy. It can help me detect early relapse. But it's most important use for me personally is that it can speed myeloma research to bring more drugs to market at a faster pace.

If the new average life expectancy is now 10 to 15 years, I'm coming to the end of that average being 14 years out. I've already taken advantage of CAR T, which is some of the latest and greatest therapy. I won't have another 10 years to wait for a single clinical trial to read out. I am playing beat the clock to access new therapies faster than my disease can relapse. So as a patient and a patient advocate, I ask the FDA to continue its remarkable gift of innovation in myeloma by approving the use of MRD as a new clinical trial endpoint at 10 to the minus 5, both

for newly diagnosed and relapsed/refractory myeloma. Thank you.

DR. NOWAKOWSKI: Thank you.

Speaker number 2, please unmute and turn on your webcam. Will speaker number 2 begin and introduce yourself? Please state your name and your organization you may be representing for the record. You have five minutes for your presentation.

MS. DeROME: Good afternoon. My name is Mary DeRome, and I'm the Senior Director of Medical Communications and Education for the Multiple Myeloma Research Foundation, or MMRF, and I have no financial relationships to disclose.

The MMRF is a national 501(c)(3) nonprofit organization, and our mission is to accelerate a cure for each and every myeloma patient. We are the number one private funder of myeloma research in the world and have raised over $600 million in support of this mission over the last 25 years. We are also the first and only nonprofit myeloma organization to foster and support yearly

scientific workshops on MRD in myeloma in collaboration with Dr. Ola Landgren, and always including the FDA, starting back in 2014. We thank the FDA for their partnership with the myeloma community. Their support has been instrumental in the treatment advances and patient benefits we have experienced over the past 20 plus years.

The MMRF supports all efforts to speed the availability of safe and effective new treatments to multiple myeloma patients. Despite recent improvements in the median overall survival of myeloma patients, which stem from the rigorous development and approval of new drugs and modalities, multiple myeloma remains an incurable cancer.

The application of minimal residual disease testing as a validated surrogate endpoint for progression-free and overall survival is one promising mechanism to facilitate the development and FDA approval of new therapies. It can help us answer questions faster, particularly in the newly diagnosed multiple myeloma setting, where due to

recent treatment advances, clinical studies can be lengthy and expensive to read out, potentially delaying availability of better treatments to the larger myeloma community.

There are several important considerations regarding the potential use of an MRD surrogate endpoint in multiple myeloma clinical trials, including that clear association of the surrogate endpoint with meaningful clinical endpoints such as PFS and OS is mandatory to ensuring efficient drug development for multiple myeloma patients.

We align with the FDA around use of the best correlation of MRD data to meaningful clinical endpoints. For example, sustained MRD negativity measured at prespecified time points of 9 or 12 months appears to correlate more closely with PFS compared to MRD measured at one time point. The applicability of a surrogate endpoint may be substantially different depending on the type of treatment such as targeted versus immune therapy and in combination or sequence therapy. Understanding these nuances is an unanswered

question, as the trials analyzed in these studies did not include the latest therapies and this should be further examined.

We are willing to work closely with FDA and the multiple myeloma community on the identification and validation of novel endpoints moving forward, and we emphasize the importance of mandatory completion of confirmatory clinical trials should MRD be a primary endpoint in a single-arm trial for an accelerated approval, as well as the continued inclusion of PFS and OS as endpoints in trials where MRD may be the primary endpoint.

And finally, it is imperative that the field commits to using the most accurate type of MRD measurement technology that is dependable and sensitive in order to ensure reliable and reproducible results regardless of the trial. In conclusion, on behalf of our patients, we would like to thank the FDA for their thoughtful and careful assessment of this important question. Thank you.

DR. NOWAKOWSKI: Thank you.

Speaker number 3, please unmute and turn on your webcam. Will speaker number 3 begin and introduce yourself? Please state your name and organization you're representing for the record. You have five minutes for your presentation.

DR. USMANI: Thank you so much to the ODAC chair and panel. My name is Saad Usmani. I'm the Chief of the Myeloma Service at Memorial Sloan Kettering Cancer Center. I'm also the chair of the NCTN Alliance Myeloma Committee, one of the three U.S. cooperative group mechanisms that conduct large randomized phase 3 studies in the United States. I'm speaking on my own behalf as a physician taking care of myeloma patients for over 17 years. I have in the distance past received research and consulting funding from Adaptive Technologies, but I'm not being compensated for speaking in this venue.

I would like to laud both my myeloma colleagues, as well as the FDA colleagues, for bringing attention to a very important topic

relevant to conducting clinical trials in the current scenario in the field, as well as patient advocates for providing their views and context. I would like to talk a little bit about the practicality of MRD testing in our clinical trials.

One of the key studies within the U.S. cooperative group mechanism that led to the acceptance of combination induction therapies in myeloma was the SWOG 777 trial that led to the 3-drug combination coming together as a standard of care. It took us over 10 years to get to the primary endpoint of progression-free survival, and that study actually was led by Dr. Brian Durie within the SWOG mechanism; and by that time, the practice had changed, and we were already asking other important questions in the field and trying to get accelerated approvals for this next wave of immunotherapy. So a trial that started in 2007 did not result in readout until 2017, and the field had moved on.

Fast forward to another important trial, the SWOG 18O3, which is asking a maintenance question

with over 1200 patients to be enrolled, and that study is a US-wide study being conducted across centers that include community centers, and MRD testing is being done across the board in this trial without any impediment. So I want to highlight that we are in an era where MRD testing can be conducted across the U.S. cooperative group mechanism as an endpoint to clinical trials.

Why is this important? This actually lends to the discussion we are having. We cannot wait for PFS or OS endpoints with the substantial survival benefits we've seen with therapies in recent years, and moving to MRD negativity as a clinical trial regulatory endpoint is very important for us.

You've already heard from patient advocates. I want to also highlight that our high-risk and functional high-risk patients are in still dire need of novel mechanisms and clinical trials, and need those answers faster so we can get access to those therapies for patients. So again, I truly appreciate the conversations and would lend my

support in having a favorable outcome in favor of using MRD as a regulatory endpoint in clinical trials. Thank you so much.

DR. NOWAKOWSKI: Thank you.

Speaker number 4, please unmute and turn on your webcam. Will speaker number 4 begin and introduce yourself? Please state your name and your organization you're representing for the record. You have five minutes for your presentation.

DR. SIDANA: Good afternoon, and thank you for the ODAC committee to give me this opportunity to speak to you all. I'm Surbhi Sidana. I'm a myeloma physician and researcher at Stanford University, and I really enjoyed hearing the viewpoints and presentations this morning, and it's great to see that we have very high overall response rates with our current therapies.

As has been discussed, overall response rate is the current endpoint we use for accelerated approval in multiple myeloma, and so far it has served us well, but now with the new therapies that

we have, with overall response rates of 80 to 90 percent in the newly diagnosed setting and very high response rate of 60 to 90 percent in the relapsed setting, we need an endpoint that can distinguish better. Because how do you practically design a trial where your control arm is 80 to 90 percent -- or your historical control is 80 to 90 percent?

Why is it important to still have newer therapies? As speakers before me have said, we're still not curing most patients with myeloma. Most patients still relapse, and it's the patients who have high-risk and functional high-risk disease that have a severe unmet need of getting these therapies. And we need to move these therapies from late line to earlier line as well, if they're safe and effective, because there is patient attrition at every level.

So there's still a lot of work that needs to be done to bring more newer effective therapies to the clinic for our patients, but we cannot wait for regular approval. As Dr. Usmani just illustrated,

it took 10-plus years for the SWOG VRd versus Rd trial to read out. We cannot wait 10 years for our patients, so we need the accelerated approval mechanism and an endpoint that reflects what we are doing currently in clinic. And we do know that it's not just achieving a response, it's achieving a deep response that really matters now that we have therapies that can lead to a deep response, and MRD negativity is the best tool that we have currently in 2024 to assess these deep responses.

We have more than one method to assess MRD negativity, but these have been validated analytically. We not only use them in clinical trials, as Dr. Usmani mentioned and that's routinely used, we also routinely use them in clinic all the time, and it is fairly straightforward to use them no matter which method you prefer, NGS or next-generation flow cytometry. These are reproducible and, as I said, widely available.

Today, we saw data from this tremendous effort by two teams, and I have to comment -- my

colleagues who have been working for years on this -- that MRD negativity at 10 to the power minus 5 has individual-level surrogacy to predict progression-free survival, which is the bar that the FDA has set for an accelerated approval endpoint. I do think there are a couple of issues that have been brought up that we will work on in the future. As Mr. Mitchell brought up, what about deeper endpoints, 10 to the power minus 6? Hopefully, we can get there in several years with the new and effective therapies we bring to clinic. What about sustained MRD negativity? And hopefully we'll have more data in the future.

But as of today, in April 2024, we have ample evidence that MRD negativity, regardless of how we measure it, NGS or flow cytometry, has individual-level surrogacy for progression-free survival, which is the bar that has been set by the FDA, and we know that it's more clinically meaningful than overall response rate, which is the current endpoint for accelerated approval. And therefore, I support wholeheartedly using MRD

negativity at 10 to the power of 5 for accelerated approval in multiple myeloma. Thank you for giving me this opportunity.

DR. NOWAKOWSKI: Thank you.

Speaker number 5, please unmute and turn on your webcam. Will speaker number 5 begin and introduce yourself? Please state your name and any organization you're representing for the record. You have five minutes for your presentation.

(No audible response.)

DR. NOWAKOWSKI: I think you're on mute, speaker number 5.

DR. RAJE: Sorry.

Thank you for this opportunity to present at this ODAC meeting. I truly appreciate the comments of some of my colleagues. My name is Noopur Raje. I'm a physician and a professor of medicine at Harvard Medical School, and I'm also the Director for the Center for Multiple Myeloma at Mass General in Boston. I'm also the NCI Chair Emeritus for the Myeloma Steering Committee, where we had the opportunity of reviewing and approving clinical

trial concepts through all of our cooperative groups. I'm providing my thoughts on the topic of minimal residual disease from the standpoint of a clinician and a clinical trialist who's been taking care of multiple myeloma patients now for more than 25 years. I have not been compensated by anyone for this presentation.

As you've heard so nicely this morning, we've made tremendous progress in the treatment of multiple myeloma, where close to 100 percent of our patients respond to current therapies. Moreover, these responses translate into disease control and progression-free survivals, which well exceed what we have been used to seeing. With this advance, our conventional response criteria are no longer able to ascertain depth of response.

Simply put, we need better tools to assess response in our patients, and minimal residual disease testing provides us with that very valuable tool. One can think of new MRD negative state as the new complete response in the context of all of our very effective treatments. In fact, MRD has

been able to discriminate between standard of care therapies and the quadruplets, where the old criteria of complete response has not been that useful.

MRD testing can quite easily be performed by either next-generation sequencing, as you've heard so nicely, as well as by flow cytometry in almost all patients. This is not only true for newly diagnosed multiple myeloma patients receiving triplets and quadruplets, which is the new standard, but also in the relapsed setting where we are using normal immunotherapeutic approaches such as bispecific antibodies, as well as CAR T cells, wherein we are seeing MRD negativity to the tune of 40 to 55 percent in this patient population. Most importantly, MRD negativity correlates with progression-free, as well as with overall survival.

Given that we've made a significant impact on both progression-free survival, as well as overall survival with our current therapies, the use of a sensitive tool such as MRD testing is critical to demonstrate efficacy of therapies and

provide early access to life-saving therapies for our patients. It in my mind is a true unmet need and truly facilitates drug development for our patients with myeloma.

Using CR and PFS is not adequate, nor is it practical anymore, specifically when the median PFS is expected to be close to 6 to 7 years from initial therapy. Using an early validated surrogate such as MRD will not only be practical, but also cost effective, and will facilitate drug development. For these reasons, we are already incorporating the use of NGS, or next-generation flow sequencing, for MRD testing in all of our ongoing clinical trials. We are also using MRD in ongoing clinical trials to tailor therapy in myeloma. Using MRD as a benchmark following initial therapy is already something we've incorporated in clinical trial practice, but more so in our real-world clinical practice as well.

Given all of the advances in the field of myeloma, I believe that the time is right to incorporate MRD testing and response assessment in

myeloma, and use it for accelerated approval of very effective therapies, and make them available to our patients in a timely fashion, and I do hope this committee will consider all of these factors. Thank you so much for this opportunity.

DR. NOWAKOWSKI: Thank you.

Speaker number 6, please unmute and turn on your webcam. Will speaker number 6 begin and introduce yourself? Please state your name and organization you are representing for the record. You have five minutes for your presentation.

DR. PRASAD: Can my slides be made available? Thank you.

I'm Vinay Prasad. I'm a practicing hemat doctor. I see myeloma every week at San Francisco General Hospital, and I'm professor here at UCSF, and I'm going to give you a different point of view on this decision for MRD for accelerated approval. The goal of drug approval by the U.S. FDA is to grant marketing authorization for patients with newly diagnosed multiple myeloma that result in living a longer life or a better life. We can't

forget longer or better.

MRD as an endpoint for accelerated approval is an error for five reasons. Number one, as the speakers have all said, the survival is terrific with newly diagnosed myeloma. It is not an unmet medical need. The 4-year overall survival in the PERSEUS study is 90 percent for dara-VRd. Keep in mind these are people who are in their 60s, late 60s, at the time of enrollment. The median survival was 10 years prior to this study. For a patient enrolling tomorrow in a clinical trial, I think it will be 15 years median survival.

In order to have an unmet medical need, you need no or limited treatment options. There are 17 treatment options endorsed by the National Comprehensive Cancer Network guidelines, 14 different FDA approved drugs, and 20 drugs are approved by the FDA in any line. There are many treatment options. Type 2 diabetes with cardiovascular risk factors would constitute an unmet medical need by this definition. Many disease states in biomedicine with a 90 percent

4-year survival for people in their late 60s would be an unmet medical need. We'll have accelerated approval for every disease if you allow this.

MRD as the basis for accelerated approval, the biggest problem is that unsafe drugs will come to the U.S. market. MRD testing may be assessed 1 to 3 years sooner than PFS. The other speakers think it'll come even faster, 5 years, 6 years, 7 years. Novel drugs will be eligible for accelerated approval less than 12 months after the trial begins. What fast approval means is these drugs, yes, they'll be active, they'll be very active, but they'll be very toxic as well, and you won't know the full toxicity profile.

CAR T-induced Parkinsonism was first noted in 2021. The first CAR T for myeloma was given in 2014. It took seven years. MRD as an accelerated approval endpoint will rush active but perhaps very toxic regimens to the frontline. When it comes to teclistamab and bispecific antibodies, 14 percent of people experienced grade 3 to 4 infections only 18 to 24 months after the initial dose. This is

very important for disease where the median survival is 15 years. You don't want 15 years of long-term neuropathy or toxicity for people enrolling in trials today.

The third point, we keep talking about MRD has some weak correlation with PFS in one of the three analyses in the non-transplant-eligible population, not in the other two, but progression-free survival itself does not predict living longer in myeloma, and MRD does not predict living longer either. PFS has a notably poor correlation with overall survival. This is work that I did with Mohyuddin and colleagues, showing the R-squared, the percent of variability captured by PFS, is less than 40 percent. Most of the variability is unexplained.

Surrogacy must only be assessed at the trial level and not the individual level. The question is not, do people who achieve MRD negativity do better? Of course, they do. They do better. But the question is, do regimens that increase the rate of MRD in an arm later improve overall survival in

that arm? And the answer is the trial-level correlations are poor. Most of the variability is not captured. That one positive PFS, it's 7 data points you're hanging your hat on. I mean, if you regress 2 data points, you're going to get a straight line. I mean, you need more data than 7 data points, okay? It's all weak across the board, these correlations, with both PFS and OS.

Myeloma trials have a huge problem that no one's discussing, which is the post-progression treatment in global registrations is far beneath the U.S. standard and unacceptable, and this gives you a big problem. In MAIA, which is dara-Rd versus Rd, which was a registration study accepted by the FDA, only 51 percent of patients in the control arm -- sorry, 50 percent of the patients in the control arm died without ever getting daratumumab, even though that was a U.S. standard of care. This problem plagues the triplet versus doublet registration studies and the quadruplet registration studies. Post-protocol reporting is poor.

In this paper, we've documented the post-protocol therapy in many, many myeloma studies. You see not reported as the most common thing, and when it is reported, it's not up to the U.S. standard. Here's why it's a problem. Here's why. This means that even if the FDA watches trials to exclude a deterioration in overall survival to prove that the drugs are safe, that's only in the context of poor post-protocol therapy. Drugs could come to the U.S. market that result in worse overall survival in the U.S. market, but that's hidden because the global care is beneath average. FDA must have better control arms, better post-progression therapy in their myeloma studies.

The biggest problem with MRD for accelerated approval is that you're taking people who are doing pretty well, great overall survival, a decade or more, and you're giving them drugs with very inadequate safety profiles. A little Parkinsonism, a little neurological damage and pain, and neuropathy will be catastrophic for someone living 15 years. This population needs to be shielded

from risk precisely because the outcomes are good.

This is why it shouldn't be eligible for accelerated approval. PFS buys you, in my estimation, 2 to 3 more years to collect vital safety information. The other speakers think it buys you even more years; that might be a little bit better. I think PFS is already permissive enough. I would not change the status quo. Okay. That's my closing thoughts. Thank you for the opportunity to speak. Sorry I had to go fast, appreciate your thoughts.

DR. NOWAKOWSKI: Thank you.

Speaker number 7, please unmute and turn on your webcam. Will speaker number 7 begin and introduce yourself? Please state your name and organization you are representing for the record. You have five minutes for your presentation.

MS. HUGUELET: Good afternoon. My name is Linda Huguelet, and I'm a multiple myeloma patient from Chattanooga, Tennessee. I have no financial relationships to disclose, and I'm speaking on my own behalf today. I thank you for allowing me to

speak to you today about the use of minimal residual disease as an endpoint in multiple myeloma clinical trials that intend to use MRD to support accelerated approval for new products and new indications.

I was diagnosed with multiple myeloma in April of 2010, almost exactly 14 years ago today. I was 46 years old at the time and had never heard of multiple myeloma. On my 14th wedding anniversary, April 27, 2010, I received my first round of treatment, including Revlimid, Velcade, and dexamethasone. I was also receiving bisphosphonate treatments to help stabilize the bone damage done to my spine by multiple myeloma.

My world was turned upside down, and I really had no clear thought on how long I would survive this incurable disease and what my quality of life would be. I had never had more than a sinus infection prior to being diagnosed with multiple myeloma, but quickly realized that I needed to be an advocate for myself, learn more about this disease, and more about the treatment

options that are available, and this all started for me by attending my local myeloma support group in May of 2010.

Only 10 months later, my husband and I began leading the group and have been doing so for the last 13 years, and during this time, I've met many, many patients in my community, and I work to educate them on the treatment options available, and also inspiring them with the hope that more options are on the horizon. Having treatment options is always key with this disease because relapse is almost inevitable for every patient.

Shortly after my diagnosis, one of my hematologists described the myeloma journey as a frog in a pond, leaping from lily pad to lily pad as other new treatments are needed. He said the goal is to maximize each treatment and to buy you time for more treatments, or lily pads, to become available. This analogy has remained with me for the last 14 years, as I've undergone 5 lines of treatment.

Leading the Chattanooga Multiple Myeloma

Networking Group opened my world to a host of resources and introduced me to myeloma support group leaders around the country, many of whom I've become close friends with and have learned so much about this disease from. This also opened the door for me to attend the American Society of Hematology Annual Meeting for the last 11 years. During these 11 years, I've heard hundreds of abstracts on multiple myeloma and seeing how MRD testing has worked its way into clinical trials. Not only have I learned about how researchers are approaching the treatment of this disease, but I've witnessed their passion for bringing more lily pads to the pond and ultimately finding a cure for multiple myeloma.

In early 2013, I was relapsing again and experiencing life-limiting back pain. In April of last year, I was overwhelmed with joy when I was able to secure a Carvykti CAR T cell slot at Emory's Winship Cancer Center in Atlanta, Georgia. On my 28th wedding anniversary, we harvested my T cells and my treatment was completed by late June. I'm now looking forward to my one-year

evaluation and further assessment with MRD testing. I know that an MRD negative indication has shown to correlate with great, longer progression-free survival, so I'm anxious for these results and looking forward to many more anniversaries with my husband.

I'm optimistic but also realistic that at this point in my journey, I have used up many of the lily pads in the pond, so having additional treatment options is very personal to me and to all myeloma patients. Although I'm not a doctor, I am a well-educated patient, advocating for myself and other patients today, and I urge you to support the use of MRD testing in an effort to accelerate approval for new treatment options. Thank you for allowing me to share the patient perspective with you today.

DR. NOWAKOWSKI: Thank you.

Speaker number 8, please unmute and turn on your webcam. Will speaker number 8 begin and introduce yourself? Please state your name and organization you are representing for the record.

You have five minutes for your presentation.

MR. MORELLI: Thank you. I am Frank Morelli, a multiple myeloma patient diagnosed in November of 2012, and I have no financial relationship or interest in the outcome of today's event. I would like to thank ODAC and the FDA for the opportunity to speak before the committee today, not only on behalf of myself, but the entire myeloma community as well. Our community is comprised of patients, family members, friends, medical teams, and of course our care partners that have been thrust into a life-altering situation that one was never really fully prepared for.

As a multiple myeloma patient, like many patients, I was blindsided and devastated with a cancer diagnosis, and one that I had very little knowledge of as well. I learned quickly to adapt to my new way of life, started to learn a new language, recognized what was important in life and how to manage the role of myeloma, and that I was now a newly enlisted lifetime member. I've been a multiple myeloma support group leader as well for

the past seven years. During this time, I've valued and learned more about patients' and families' and members' concerns, their anxiety, and what the future may or may not be. I am firmly embedded in the myeloma community.

What I did realize in the early stages of my diagnosis was how rapidly my disease can change and how I could go from being in remission one day, with the next set of labs reflecting I have relapsed and refractory to the most recent combination of therapies I've been on. This was completely disheartening and frightening as a patient. Refractory. What does that mean to me? Are there sufficient number of treatments for me now and in the future, in the years ahead? Do I have a future? What if I run out of therapy options? Are newer therapy options keeping pace and being approved to sustain patients' hopes and aspirations?

Almost recently, I was involved in the Pfizer MAGNETISMM-2 clinical trial in December of 2021, involving elranatamab, a bispecific. MRD

testing was done at the 6-month mark, post-initial treatment, and one year post-start of my trial as well. I did reach MRD both times, and subsequent testing has concluded, and I remain MRD as of February of 2024. As a patient reaching MRD, that is the gold standard of being in remission. This was an affirmation that my medical team and I made the right choice at that time, predicated on my myeloma history and overall medical profile.

Reaching MRD was initially a relief and a feeling of gratification that the trial therapy was effective. I never thought of it as any type of false hope, as over time, now over 11 years since my diagnosis, there are certain intervening realities one may have to confront during our journey. The potential of relapse is real, and one must recognize and be prepared should that occur.

With my MRD situation, I take a pragmatic approach that I should take advantage of my current health status and just enjoy life the best I can. I have reached MRD several times prior to this trial as well, which really solidifies hope for the

future. After numerous lines of treatment prior to this trial and still being capable of MRD, that does provide for quite a bit of optimism. For one reason, we continue to hear that after each remission, there is a high probability your next remission will have a much shorter duration. After over 11 years of various treatments and clinical trials, now reaching MRD once again speaks to the advances that are being made and newer and developing therapies that are in the pipeline.

For me personally, if MRD can be used to accelerate those therapies in clinical trials that would allow for broader options in the future and extend survival rates, it must be strongly considered. In addition, with the use of various combination therapies today, such as triplets and quadruplets, they have added another positive dimension to the treatments by successfully improving outcomes of the quality of life for many myeloma patients, and this is important. But ultimately, can these therapies and patients becoming refractory to these combinations result in

limited future therapy choices as well?

As myeloma therapies are enhanced and combination therapies are becoming more routine, MRD testing in trials can guide research to accelerate the pace to safely offset this concern of limited future life-saving choices, and specifically for patients that may be refractory to many, many drug combinations. And finally, reaching MRD is always a wonderful outcome and should be tempered with certain realities, as I've said. For one, it's very difficult to determine how long that status will remain; but also, if you got there once, you could get there again with the encouraging advances that are currently being made in research.

I may not always reach MRD; however, if I know my entire multiple myeloma medical research community is using MRD, supported by the FDA decisions as one of its baseline measurements to accelerate delivery of treatments to the myeloma community, that in and of itself offers hope, optimism, and a positive outlook for all of us.

Thank you very much.

Questions to the Committee and Discussion

DR. NOWAKOWSKI: Thank you.

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

We'll now proceed with the questions to the committee and panel discussions. I would 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. After I read each question, we'll pause for any questions or comments concerning the wording.

This is discussion question number 1. Discuss the adequacy of the available data to support the use of minimal residual disease, MRD, as an accelerated approval endpoint in multiple myeloma.

Are there any concerns or comments about this question, about the wording itself?

(No response.)

DR. NOWAKOWSKI: If there are no further questions or comments concerning the wording of the question, we will now open the question for discussion.

Dr. Lieu?

DR. LIEU: This is Chris Lieu from University of Colorado. It'll be interesting to see how much of our comments are similar, but as somebody who does not treat multiple myeloma, I have to tell you, for the applicants, I think you should be commended on what I think is an aspirational data collection, data analysis, and collaboration, and I'm very, very impressed, and jealous, as a solid-tumor oncologist.

But what I would say is that when you look at the data, especially the patient-level data, I think that's clear that it meets the criteria for accelerated approval. I think that this is one of the most prognostic tests that we've seen in the

disease. I think we'd all like to see the trial-level data show more correlation, but that's not the bar that's set for accelerated approval.

It will be interesting to see, as we gather another decade -- you guys have done a decade of research and data collection -- in the coming years, there may be that level of data to correlate this endpoint with overall survival, which is obviously what we would like to see, but as it stands right now, I do believe that it meets the criteria for accelerated approval. I would like to see this endpoint correlated with quality of life, as well as time on treatment, which I think addresses some of this toxicity issue. Does that mean that if somebody's MRD negative and CR, that they feel better, that they are not having undue toxicities from drugs? That's just an additional area of investigation that I'd like to see. Thank you.

DR. MARTIN: Yes. Tom Martin from UCSF. I think I'm the myeloma person on the committee, so maybe I'll just put it in perspective just a little

bit so that people realize also. Presentations were excellent, but let me just give another layer of stuff. When patients present with a protein in their blood in the urine, it has to go down by more than 90 percent in the blood in the urine for us to get a VGPR. That's when we're thinking about doing MRD testing. In fact, CR is when the proteins are gone.

If you do an MRD test in some patients that are in CR, by the clonaSEQ assay, you might get a thousand to 10,000 cells in the bone marrow, but MRD negative is 1, 10 to the minus 6 or less than 10. So it's really a significant bar. It's really way down in terms of the biologic significance. We heard about the biologic significance. There certainly is the biologic correlation that if you get that low with your MRD, you're probably going to have a longer -- your responders do better; that's kind of the thing.

So your question is what is the quality of life? Well, myeloma, we treat forever, until progression, so sometimes the quality of life, they

feel better because they know their numbers are really low, but the truth of the matter is, it would be nice if we can get them off therapy. So I think in this context, for us, we have to think about MRD in the later-line settings, the relapsed/refractory; in the accelerated approval space, is it going to meet surrogacy so that we can actually have accelerated approval in the late-line setting, or in the early relapse, like the example we got from the FDA, the 1 to 3 prior lines of therapy? And if so, if it's approved in that line of therapy, we probably are, like Dr. Anderson said, two to three years ahead the approval of what we would expect if we let the trial go through.

But in the frontline setting, it's a whole different thing, in my mind, so we do have to keep two things in consideration. One is, the drugs that are used for frontline therapy right now, the 4-drug combination, each individual drug had a response rate in the order of 20 to 30 percent, and when you put them all together, it's over 100 percent. Well, these new immunotherapeutics

have single-agent response rates that's 60-70 percent, so when we throw those in the mix, it's probably really going to, I think, enhance the number of people achieving that MRD negativity. But as we've heard from some of the comments, we do have to worry about toxicity and how does that change the toxicity envelope.

But in the frontline setting, what, basically, Dr. Landgren presented, that's our best chance to do our best therapy for people, thinking that they're going to be in remission for the longest. If we actually use it as an accelerated marker in frontline, it actually could be 5 to 7 years earlier than the PFS readout. So we have to think of it in those contexts, too, I think, frontline, early relapse, late-line relapse, and that this marker has really a lot of biologic data behind it. Also, as we've seen -- again, it's nice to see everybody put the data together; that individual-level association is pretty strong throughout. I was a little surprised that we didn't get a little more trial-level surrogacy, but

it is what it is. The data is what the data is, and we need to do more data. We need to have more MRD data.

DR. NOWAKOWSKI: Thank you.

DR. NIEVA: So I really do want to commend the applicant and the FDA for all the work that was done in putting together this data set because, really, it's somewhat of a simple question. We're just not saying that response isn't a predictor of outcome; we're deciding what the depth of response has to be, and whether it's 50 percent for PR, 90 percent for a VGPR, or 99 percent or 99.9999 percent, really, we're just changing the the bar, in fact, raising the bar, or what the bar has to be in order for a new therapeutic to show efficacy as an early indicator because our therapies are better.

I do want to echo a point that Dr. Madan alluded to earlier, and that is a concern about gamesmanship. I worry that people will say, "Well, all that matters now is going to be MRD at 12 months, so my new therapy is going to be

6 drugs for 12 months, and then nothing after that." So I am concerned about the focus on a single time point and not looking at MRD at multiple time points, or time to loss of MRD, or some other metric to discourage that type of gamesmanship that companies may engage in.

Then one last thing I'd just like to say, I'm concerned if there are people out there that have an attitude that, "Well, everyone's doing really well, so we don't need to come up with new drugs, or we don't need to bring them to market faster." I also get very concerned that if we create a scenario where the time to market is so long that drug companies have to recover their sunk costs over a very short period of time, only 2 to 3, 4 years of patent life, that we're going to find ourselves in a situation where drug costs will necessarily become more astronomical than they already are because the costs aren't able to be recovered over a longer period of patent life. So I do think there is a very good justification for continuing to use an accelerated approval

mechanism, in part, to make sure that we have an opportunity for the very difficult costs associated with drug development to be recovered. Thank you.

DR. NOWAKOWSKI: Thank you.

Dr. Madan?

DR. MADAN: Yes. I think there's a lot of concordance in the conversations today with the disease experts and the FDA in terms of the adequacy of the data, but I think, again, changing the incentive structure here is an important consideration, especially if the timelines are changed by the magnitudes we're talking about.

I think we just have to understand that if we go into this world, you may see higher degrees of agents that don't meet the criteria for full approval. And I know it's hard when that happens for patients and providers to really accept that a drug that, at least in their hands, has been effective is now being removed because of reasons that maybe didn't necessarily coincide with the initial approvals, but I think it's something we have to accept if we use an endpoint like this.

But it should be something that is acceptable to all the players, and especially the patients, because in the end, that's who stand to benefit the most from this, but also potentially can be hurt by this if the vigilance isn't there. Thank you.

DR. NOWAKOWSKI: Thank you.

Dr. Vasan?

DR. VASAN: Neil Vasan, Columbia. I'd also like to congratulate the applicants, and also all the partnerships I think that were necessary for such a long-term endeavor. I'm a breast oncologist, and the analogy that I have been thinking about this whole time is on pathologic complete response, which of course has had a tremendous number of ODACs and discussion around this endpoint. I came back to the original meta-analysis that was performed by the FDA and Dr. Cortazar, with the R-squared for DFS of only point .03 at the trial level. The R-squared's we're talking about here are so much higher than that. So while this is apples and oranges, clearly to me this is, from an analytical point of view, a

better endpoint.

I will say that I share my colleagues' concerns regarding gamesmanship, but I am assuaged by the fact of the recent 2023 Consolidated Appropriations Act and really gives the FDA a muscular policy to enforce accelerated approval, with multiple safeguards in place to nudge companies to comply, so that gives me faith in this process.

Finally, on this point of innovation, I do think it's very important -- again, I'm a breast oncologist. We have many trials in our field, especially in ER positive metastatic breast cancer that take years to accrue their PFS endpoint, and because the field is so fast-moving, by the time that trial reports, it can sometimes be irrelevant. Maybe the control arm is one we wouldn't use now and other mitigating factors. So having more endpoints in different diseases will help spur innovation, undoubtedly.

DR. NOWAKOWSKI: Mr. Riotto?

MR. RIOTTO: Michael Riotto, patient.

Dr. Madan just mentioned something a few minutes, and he said it is about the patients, and I'm a patient. He said we could hurt a patient, and we can also really help a patient, and you think about going back to the timeline of what I mentioned earlier, my time is infinite.

Speaker number 6 -- and I'll be honest with you -- really annoyed me when he said, "Well, you've got 15 years." Well, I want to live 50 years, or 60 years, or 70 years, and having MRD negative -- and I really appreciate everything that everyone has done, I really do -- if it can bring a drug to market faster, as an educated patient, I'll take that risk. That's what clinical trials are all about. I'll take that risk. If I'm at my last resort, and there's a drug out there that's on a clinical trial, and MRD negativity is its endpoint, and it's going to give me maybe 18 months or 24 months, I'm going to jump at it. Thank you.

DR. NOWAKOWSKI: Thank you.

Dr. Maurer?

DR. MAURER: Thanks. Matt Maurer, Mayo

Clinic. I would also like to echo the comments in the room, and really commend the sponsors for the work to put this together, as well as the FDA. As we saw on the slides, this was over a decade of work to do this, and it's not a small undertaking to assemble data sets like this.

In regards to the adequacy of the available data, doing a surrogacy analysis of this sort means you're always going to be a few years behind because you need the randomized trials, it's a limitation, you need adequate follow-up, and then you need the time to assemble the data and do the analysis. So I have no concerns with the analysis that's been done. I think it's a very strong work by all of the people involved. I think one of the challenges, though, is with four studies in the relapsed/refractory setting, I would have liked to have seen more, especially given the low MRD negativity rate in those studies. But again, this is what is available when we have the time to do the analysis. So that's more of a flaw of maybe where we're at from the drug development standpoint

in terms of having those data, as opposed to the work by all the people involved.

DR. NOWAKOWSKI: Thank you.

Dr. Advani?

DR. ADVANI: So like everybody else, congratulations on this immense amount of work, both by you all, as well as the FDA. It's rare to have this kind of a discussion where it's all academic and with a great amount of integrity of data, so congratulations.

I think at the patient level, it's very, very clear. And while I am concerned about some of the toxicity concerns, I do think that you'll have safeguards built into it, especially being able to pull things out if approval is very early based on this, and it turns out to be toxic like you did for the PI3 kinase inhibitors and other such drugs; that you have safeguards in place.

I also think this sets a precedent for actually moving the field forward, not only for patients to get the drug earlier, but can we stop therapy based on MRD if the duration of MRD is

longer with better treatments. It kind of opens up a whole other way of maybe treating patients, where you don't have this continuous, where you can get treatment gaps like you do in solid tumors. So I think it's commendable that we're able to get to this stage. Thank you for that.

DR. NOWAKOWSKI: Dr. Hourigan?

DR. HOURIGAN: So Chris Hourigan. In answer to your question, yes, and I think it's great to be in a situation where there's no discordance between what the data is teaching us. The current standard for accelerated approval is response, so measurable residual disease is a direct measure of anti-tumor response.

I think the biological plausibility, we all agree, the individual association with response, we all agree, and I think we're in actually a much better situation, looking at this in the context of this FDA commitment, for safety monitoring and robust compliance for clinical benefit confirmation studies. I think we think a lot about the risks of action. I think, also, we need to consider the

risk of inaction.

You imagine the future of drug developments where we're using a non-high sensitivity measure of anti-myeloma response. We can't push any new entities forward in those trials with drug development because we don't have the appropriate tools to measure the efficacy of those therapies. There's harm to inaction.

So, again, to reflect to the fast-talking man in the T-shirt and the sweatshirt, I think we're right to consider risks. We have trust in the regulators, but also I think there's great harm to not acting, and I think this data gives us confidence that all three bodies came to, essentially, the same conclusions.

DR. NOWAKOWSKI: Dr. Martin?

DR. MARTIN: Yes. Tom Martin again, UCSF. Just to come back to you guys' comments about gaming this scenario, that doesn't seem to me to be so much of a risk. That would be that we're going to even see a higher bar of MRD negativity. I think we are, and that is our measure of response.

It is all of our jobs, everybody in this room, to actually have safeguards in for the trial for the next thing, and these patients who potentially had a great response with MRD and we do get accelerated approval, they're going to be followed for other side effects. That's what we're saying. They're going to be followed for PFS for that downstream thing.

Just what Chris just said also, there are risks on both sides of it. There's the risk of downstream toxicity, but there's also the risk that the patients themselves have to wait this amount of time to actually get access to this therapy. And I'll go back to what Dr. Landgren said, is our best chance is frontline, our best chance to actually get the deepest, the best, and hopefully the longest remission. And I do think we cure a fraction of the patients, and maybe to get even that C word out there even more would be for us to actually get these drugs to the frontline as soon as possible.

DR. NOWAKOWSKI: Thank you.

Dr. Pazdur?

DR. PAZDUR: The safeguard, really, is the randomized trial that will happen subsequently because we've seen in the development of drugs in this disease, the drugs that we took off the market, they mostly came off the market because people had incorrect doses. They just were looking at how to get the highest response rate, and then put the results in a risk-benefit context. And then when they looked at it in a randomized study against a therapy that had a much more favorable toxicity profile, then it showed detrimental survivals. So that is really the safeguard that is put in place, and that's why we're so insistent that these trials be done in an expeditious manner, really, as part of a comprehensive plan.

We've written about this extensively, and I don't know how many of you follow our discussions on the whole accelerated approval program, but what we're really looking for is the sponsors to come in with a comprehensive development plan, with not only the accelerated approval discussion of the

trial that they're going to use for accelerated approval, but also what their plans are for the confirmatory study, right up front, as well as the timelines for that, et cetera. So we really do not want a sequential approach; we want a comprehensive plan using this.

There's one other thing from a regulatory point of view that I want to point out. The whole picture of multiple myeloma is really a true picture of the success of the accelerated approval program. We have, I think, 13 drugs -- 17, excuse me -- and almost all of them were approved on accelerated approval. All of them were approved on non-survival endpoints, and we have many critics that say, "Oh, the world is falling apart because these drugs have not been approved on an overall survival basis." But what you've seen with this disease is a dramatic improvement in the disease itself and what the options are for the patients, and I think that this really represents the true meaning of the accelerated approval program.

People get fixated on one drug and, no, it

hasn't shown a survival advantage, and I'd like to point out that a failed trial does not necessarily mean a failed drug. There are many reasons why a trial can fail, and when you really take a look at what has happened here, you have drugs that were basically all approved on non-survival endpoints, that when used together have demonstrated profound effects on overall survival and have transformed this disease. And this is the true success story of accelerated approval, and probably in oncology the best example of that in a disease that when I started out had only melphalan and prednisone for its use in the 1970s and 1980s.

The other point that Dr. Martin made that I really want to talk about is also the upfront use of this drug, of drugs, in the accelerated approval. Many times we are just focused on the most refractory disease setting, but the whole idea behind this Project FrontRunner project of the OCE is to try to move these drugs up as soon as possible when we have, obviously, the appropriate safety information to use them in a previously

untreated population.

But that's really where we're going to see the benefit, and we do really want sponsors to move these drugs up as quickly as possible using accelerated approval, and this would be a great opportunity to use the one-trial initiative where you get accelerated approval on a surrogate endpoint, or a earlier clinical endpoint I should say, and then follow them up for PFS or overall survival.

DR. NOWAKOWSKI: Thank you. That's why from the FDA presentation of the potential pathways for approval and different trials, the one which actually speaks the closest to my heart is the single-trial model where you randomize up front and you have accelerated approval based on MRD, which removes some of the assay variability as well and lets you capture early toxicity in this randomized site comparison, and then the trial continues. It's efficient, allows you early readout, and really accelerates drug development.

DR. PAZDUR: If I could make one more point,

we love randomized trials, obviously, but even people that want to come in with a single-arm trial, where you do have problems with dose -- and here again, there's a tremendous rush to get these drugs approved and we really want people to have adequate dosing information as they develop their drugs -- is to do a randomized study of dose, and once you decide what is your dose, continue that arm out, so to speak, so you're not wasting patients' resources but continuing those out; but you do have early randomized information on dosing.

Many people don't realize that the need for, really, looking at dose early on -- and that was, again, one of the projects that we're looking at in the OCE -- is really to encourage better dosing of these drugs so we don't run into problems as we have with having to take drugs off the market because they probably had the wrong dose and subsequently failed in the randomized study; not that they didn't have efficacy, but they were just too overly toxic.

DR. NOWAKOWSKI: This is something which we

didn't discuss here much, the potential impact of MRD assessment of Project Optimus and how do you select the dose because, presumptively, you would consider it to be a part of the totality of evidence of more efficient therapy in this setting.

Mr. Mitchell?

MR. MITCHELL: Yes. I'm David Mitchell. I'm the consumer rep and a myeloma patient. I want to echo what Dr. Pazdur said. I think I'm part of that success story. If I'm not mistaken, bortezomib, pomalidomide, and daratumumab were all approved under accelerated approval and are now converted. Those are the drugs literally keeping me alive, and I got them sooner because of the accelerated approval pathway. So I see the accelerated approval pathway is something that is for patients, and it's worked for me.

The FDA, in participating in these meetings, I think has taught me that the only way we're going to know for sure about safety is randomized clinical trials, looking at overall survival. That's how we ultimately know whether they're doing

what we want them to do and not delivering toxicities that are doing more harm than good. And we're not changing any of that by looking at this; we're only saying here's another predictor that seems to have strength in utility and will help us advance these drugs coming to market.

As a patient, I do want to emphasize the point that Dr. Madan made a moment ago -- I think it was Dr. Madan; it might have been Dr. Lieu -- that we need to be tracking toxicities closely. And if we only have 12 months before we measure MRD, we better have really good tight data on what's having an impact on patients in terms of the quality of life and the things that cancer patients have to put up with, whether it's peripheral neuropathy or diarrhea, or something worse. But we need to be looking at all of those things.

I do want to respond to Dr. Prasad and to say maybe there is no unmet need, in his view, at diagnosis, but beauty is truly in the eyes of the beholder. When I was diagnosed, median survival

was maybe 6 to 8 years; now 10-plus. Maybe we could say -- I don't know what the most recent numbers are. I think it's also true the research shows that a strong early response is a predictor of longevity, so having better drugs that have more power and effectiveness early on can be beneficial to patients and extend their lives, if I'm interpreting that data correctly.

So I don't see us as looking at an unmet need; I see us as trying to get access to superior therapies. Where there's clearly unmet need is in relapsed and refractory disease, and it's kind of ironic that that, in this discussion, is where we have the least clarity in terms of applying MRD. But that doesn't mean we shouldn't, especially when you take into account all of the surrounding variables that you always look at when you ask us to consider risk versus benefit.

So I think we are addressing unmet need, both at the front end and at the back end. It just depends on what your need is. So I think that the adequacy, going to this from my perspective, is it

does support the use of MRD. Thanks, and I'm done.

DR. PAZDUR: Just to follow up on David's comments, the actual legislation says, "for serious and life-threatening disease," not "unmet medical need," and I don't think any rational person would say that multiple myeloma is not a serious and life-threatening disease. So it's not in the legislation, the congressional mandate.

DR. NOWAKOWSKI: Thank you.

Dr. Conaway?

DR. CONAWAY: Yes. I just wanted to echo what Dr. Pazdur said about the use of this in early-phase trials. I tend to do more of those than late phase. We're talking about this in accelerated approval. But long-term outcomes are just not feasible in these early-dose optimization trials, so I think we shouldn't lose sight of this endpoint across the spectrum of drug development.

DR. NOWAKOWSKI: Thank you.

So let me finally summarize this discussion. What we've heard here is that the sponsors and FDA needs to be really commended for this effort on

looking at patients and trying to establish MRD as the endpoint in clinical trials in multiple myeloma. It is very difficult, as we've seen by the timeline, but a very important effort.

It was felt that, indeed, MRD represents a major opportunity for acceleration of drug development, particularly in a frontline setting. There is some concern about catching toxicity and quality of life in this setting, and some worries that maybe this emphasis on early endpoint can decrease the emphasis on the later endpoints, including PFS and overall survival, although within the frames of the accelerated approval process, this is usually mitigated by requirement for additional randomized studies.

Also further, this accelerated drug development may have a favorable impact on acceleration of the drug development overall and possibly decreasing the cost of care; and we also heard to minimize toxicity and looking at the optimal dose for patients, along with Project Optimus, this MRD assessment could be also a very

valuable method in this regard.

We'll now move to question 2, also a discussion question. Discuss whether the available data supports the use of MRD as an endpoint in different multiple myeloma disease settings, specifically newly diagnosed multiple myeloma and relapsed/refractory multiple myeloma.

Are there any questions or comments regarding the wording of the question or concerns?

(No response.)

DR. NOWAKOWSKI: I don't hear any, so we'll now move to the discussion of this question.

Dr. Vasan?

DR. VASAN: Neil Vasan, Columbia. I think many of us brought up some of these issues. Obviously, I think it just comes down to the fact that this is a large meta-analysis. The number of representative data points of trials in the newly diagnosed setting versus the relapsed/refractory setting, it is a countable number. It is a small number. We have to both draw large-scale conclusions from that small finite number of data

points, as well as try to figure out which is just overfitting the data. I think that many of the correlations for the relapsed/refractory setting were weaker than in the newly diagnosed setting, so I think that's just something that we're going to have to deal with by the field, and that the field will continue to use these biomarkers in these trials.

DR. NOWAKOWSKI: Dr. Lieu?

DR. LIEU: This is Chris Lieu, University of Colorado. I agree completely with Dr. Vasan. I think that, obviously, the data in the relapsed/refractory setting is the weakest, and I think that's just really a power issue. I think when we think about this setting, the rates are going to be pretty low -- I assume, not being an expert in disease of MRD negative CR -- and I would really encourage the experts in the field to consider what change in MRD negativity would be clinically meaningful.

I have no idea what that is. But in that setting where the rates are low, is it a 1 to 2

percent difference? Is that what's clinically relevant, or is it like a 10 to 15 percent difference? I think those are all, obviously, some of the assumptions and the things that have to be worked out in protocol development to determine, well, what's the bar and what would be a meaningful bar here in that setting?

DR. MARTIN: Tom Martin, UCSF. Again, I'll give you the myeloma perspective here. So there were just a few studies, so it's very difficult, and the studies that were part of the briefing documents, in fact, were good studies. They are good relapsed/refractory myeloma studies, but mostly were antibody based and other non-immune-therapy based studies, which to your question, the level of MRD negativity was not that high.

I do think it's going to be a change of 20-plus, maybe 30-plus percent MRD negativity, what we're going to see in the relapsed setting. You get so many years from frontline therapy of remission duration, you get a much shorter

remission duration in the relapsed/refractory setting, and as you get really relapsed/refractory, it's even shorter. So to show that difference, you'd probably need a lot of studies to do that, not just four studies. So again, we do have to use the totality of the data to say do we think it still would work in relapsed/refractory knowing what we know about newly diagnosed, so it is a different group of patients for sure.

DR. FRENKL: I guess when I'm looking at the data, And we're focusing here just on the individual-level association to meet the bar of accelerated approval -- the odds ratios are still super high, or very high I'll say, for relapsed/refractory and are still statistically significant in that there's no crossing of the 1. So that's what I am kind of focusing on when I'm looking at newly diagnosed and relapsed/refractory, and they both seem to meet that bar for today.

DR. NOWAKOWSKI: Dr. Nieva?

DR. NIEVA: Yes. I think it just comes down to biological plausibility. It doesn't really make

any sense that it would be important in newly diagnosed and not important in relapsed/refractory patients. It really just is a threshold thing, and I don't think anybody here would think that a drug that increased the MRD rate by 30 percent in the relapsed/refractory setting isn't something that's a major advance in the way of activity. So I do think that we have enough data here, enough biological plausibility data, and enough that we can extrapolate from the newly diagnosed setting to say, yes, we should be able to move forward in that context.

DR. NOWAKOWSKI: Dr. Vasan?

DR. VASAN: Neil Vasan, Columbia. I agree with everything that's been said, and I think also adding that, again, for people in the field, I think what's interesting about MRD as a biomarker, there's a bit of an avant garde-ness in the sense that it's not fixed, again, as compared to pathologic complete response in breast cancer, which really is a fixed definition, and I doubt that will ever change. This is more quantitative.

It has multiple NGS flow cytometry. We've talked about a lot of these variables.

So it's possible that more optimization of this, resetting the threshold -- maybe the threshold like Mr. Mitchell pointed out, this 10 to the negative 6 threshold -- could be relevant for the relapsed/refractory. All these details, I know that the field will work these out, but I think that those details are going to be very important as this biomarker develops.

DR. NOWAKOWSKI: To follow up on your comment, though, do you think with the change in the field and the level of detection, it might get more challenging to compare some of the historical results with the single-arm studies potentially in the relapsed/refractory space?

DR. VASAN: Yes, I agree with that. And one of the strengths of the meta-analysis I think is that the number of trials that was included span decades, if I'm correct. I think this also provides a playbook for the future, as well as for involving trials that cover the span of years.

DR. NOWAKOWSKI: Dr. Maurer?

DR. MAURER: Matt Maurer, Mayo Clinic. I have a question for our patient representatives. With the accelerated approval process, there's a risk-benefit. The benefit is you're getting earlier access to drugs; the risk is there's maybe less evidence about the safety and effectiveness of those drugs. What we're really talking about, as someone mentioned earlier, is that MRD is a more sensitive response rate.

Could you speak maybe to how that translates to you as a patient in terms of your understanding of your benefit in terms of this? I think we're used to dealing with response rates that this drug, or this agent, or this regimen is more likely to shrink your tumor. MRD, is that meaningful to you as a patient in terms of your personal understanding of the risk-benefit of this, if we're approving things on it in an accelerated basis?

MR. RIOTTO: Mike Riotto, a patient. In a one-word answer, yes, because whether I'm looking at progression-free survival or overall survival,

and all the statistics that you can look at it for dara or Sarclisa, if my doctor is telling me that, "Hey, I can give you this particular drug, and it's so far has shown that it's going to give you MRD negativity to the 10 minus 5," I'm going to go for it. I just think most patients are going to look at that. They're going to look at the fact that as the data keeps accumulating, that MRD negativity becomes more of a common word.

I mean, every support group that I tend to, every conference I go to, it's talked about extensively, everywhere. So I would probably say that most myeloma patients are well aware of it. Do they understand it all? Probably not yet, but as it becomes more mainstream, they will. And, yes, if you come back, and my healthcare team says I can give you this and it's going to get you here, I would definitely say yes. I think that's so important.

As far as the risk, as I mentioned a little while ago, if there's any drug out there that's going to give me a longer life, I'm going to take

it. I mean, I am willing to take that risk because what's the alternative? You know? What's the alternative? It's not good.

DR. NOWAKOWSKI: Thank you.

MR. MITCHELL: I'm going to exercise patient prerogative here. Even though he asked him, and I'm a consumer rep --

DR. MAURER: I asked both of you, well, I guess from a patient --

MR. MITCHELL: -- I'm not in the same place as you are. I don't want a drug that makes me blind, for example, but will extend my life. I don't know that I'm willing to make that trade, for example. And I'm talking about a specific drug right now, and I don't know that I would. That's something I have to think about hard. So longer life at what cost is a factor for me and, fortunately, I haven't had to cross that bridge yet, and I don't ever want to cross that bridge if I don't have to.

As far as minimum residual disease, I have light chains now that are more than measurable. I

have an M spike, but I don't have any other symptoms. My CBCs are perfect. They're picture perfect. My bone marrow is doing its work. I did a PET CT scan a couple of months ago, and there's nothing really happening that is worthy of addressing right now. But at the point in time that my physician says we need to consider another option, "look at your numbers, they're trending too much and we have to arrest them," I'm very heavily pretreated. If I get like a treatment, whatever it may be -- CAR T -- and it scrubs me out and leaves me with clean pipes, I would consider that a big triumph because that wasn't possible, mainly, a few years ago.

All of the drugs for relapsed and refractory multiple myeloma were inferior. Inferior is the wrong word. They weren't as optimistic in terms of the results that they could achieve for whatever number of patients. So "minimum residual disease" is a useful term for me to think about, that this treatment could put me back in a place, although I'm heavily pretreated, that I sort of start over,

in my head. These are my own personal interpretations, so for me, it's an effective concept as a patient, minimum residual disease at negative 5, 10 to the negative 5.

MR. RIOTTO: Alright, David. So we're going to agree to disagree, but I would think that the FDA has enough safeguards in place that I wouldn't have to worry about going blind; that they would have already looked at that, and we would be ok.

I want to go back to Dr. Pazdur, if I get it right. When I was diagnosed, I was an infant way back then, three drugs. And you're right, there are 17 now, and most of those are all through the accelerated approval program. So MRD negativity means a tremendous amount to me as I move forward in my journey at 12-plus years now.

And we don't talk about it much, or we didn't talk about it much. We talked about unmet need and everything out there. You're living with a disease that's going to kill you, and you know that. I don't know how you feel about it, David, but you're living with a disease that's going to

kill you, and that's a really hard thing to deal with every day. And if there's just a little bit out there, MRD negativity, to move a clinical trial ahead a little bit, to get a drug ahead a little bit, it's a beautiful thing.

DR. NOWAKOWSKI: Thank you.

Those are great and very valuable comments. I'm a little bit concerned, just from the drug development perspective, because we're all talking about acceleration of the drug development, but I can imagine if we have examples of the trials -- for example lymphoma, where the response rate was not necessarily higher and MRD results were looking negative, yet PFS was actually different later on in a trial -- would it be a possibility that if somebody doesn't see this early signal, would we actually abandoned potentially promising therapy, which could then affect PFS or maybe even overall survival? I wonder if folks have any comments.

DR. PAZDUR: That's why we want the single-trial approach because we have seen in other

therapeutic areas, with the PD-1 therapies, for example, that response rate and PFS are not good predictors of overall survival. And if you went down that pathway of, "Oh, let's just look at overall response rate," you may miss a drug and true therapeutic advances.

So if you had the single-trial approach, basically, you would keep the trial going on and witness an overall survival advantage. We have seen that, and this is one of the things that we are cautioning people about repeatedly, is not to put all of their eggs in one basket as far as this response rate, genuflecting in front of this altar of response rate, basically, to put it in Catholic terms.

DR. NOWAKOWSKI: Thank you.

Dr. Frenkl?

DR. FRENKL: I guess I was going to offer a different perspective in that the prognostic value of it being positive -- and we all want to bring a new drug to market for the hope of patients, and we all hope it's positive. But the other fight is if

we really believe in the negative prognostic value of this as well, it's also beneficial for patients, for pharma, for FDA, because we can make an early stop and not waste patients' time, not waste resources, and everybody can use it towards things that will actually move forward, and I see that potential with this in the data that we have as well.

DR. GORMLEY: One other thing that I just really want to underscore, and I believe -- I can't remember -- maybe it was Dr. Nieva who mentioned this. This is one more tool. We're not getting rid of the other tools. We're not getting rid of our PK/PD assessments. We're not getting rid of overall response. We're not getting rid of toxicity, safety assessments, SAEs, adverse events, dosing information. It's one other piece to the whole complete armamentarium of the data that we'll have available.

DR. NOWAKOWSKI: Thank you.

Dr. Vasan?

DR. VASAN: To echo off of Dr. Frenkl's

comments, again, just bringing it back to the breast cancer example, the prognostic value of path CR in breast cancer, if a patient does not achieve a path CR, years ago, we treated those patients exactly the same as if they did have a path CR. But then more recently in the past five years, now we escalate therapies in the adjuvant setting, and that was because of the strong development of a biomarker that everyone agreed on, and everyone agreed had prognostic value. That was the only reason those trials could have been designed, and now we have data that those drugs, when added, improve overall survival in some settings.

DR. NOWAKOWSKI: Thank you.

As a general reminder, when you're speaking, please introduce yourself just for the recordkeeping.

If no other comments, let me summarize this part of the discussion. I think the committee has seen MRD assessment favorably, both in the frontline setting and in the relapsed/refractory

setting, pointing out that some of the analyses showing less association were probably confounded by a smaller number of patients and inevaluable trials. Importantly, biologically, biological significance appears to be the same in both settings. There was some concern, however, that there is technology drift, which can result in different assessments of MRD in the future, and therefore this is something to consider while interpreting trial results in the future as well.

It appears that the benefit and gain in MRD negativity is very meaningful. There were patient advocates, particularly knowing the association with the prognosis. And finally, we should not be putting all the eggs in one basket. It's clear that MRD is just one of the endpoints. We should be still looking at duration of response, progression and survival, overall survival, and all the other classical endpoints in the trials, including overall response rate and CR rates, which we have done in the past.

Now, we'll move to question 3. It is also a

discussion question. Discuss the applicability of the time points for MRD assessment, 9 months, 12 months, MRD negative complete response at anytime, and the requirement for assessment of durability, and we'll start a discussion now.

DR. MARTIN: Okay. I'll start. Tom Martin, UCSF. As a treating myeloma physician and a person who's done MRD for the last 5 or 10 years -- and Dr. Landgren brought this up in his discussion also -- the M protein after therapy for myeloma has a half-life, and you have to actually give people therapy for 6 months to 12 months before you truly would get rid of that M protein. So certainly, a distal of 6 months is an important time frame to follow MRD so that you could actually get MRD CR. I think most time points after that, 12 months or after, are actually all applicable in terms of measuring MRD negativity because at that point, they should be NCR and MRD negative.

I don't think there was enough data -- that was one of the questions I was going to ask earlier, and I forgot to ask it, about sustained

MRD negativity because that's the next hurrah for us. It's not just this one time point of MRD negativity, but 6 months of MRD negativity, or 12 months of MRD negativity. Many of our relapsed trials, we've looked at those time frames, and you actually get better PFS and better overall survival, obviously, the longer the MRD. Again, it's a biology thing. You're MRD for a longer period of time and you're a longer responder, you're going to have longer PFS and OS.

I would say that, for me, anything 9 months or forward would be an appropriate time. So 9 months and 12 months I think is fine, or later, for MRD, and I think we should actually consider sustained MRD negativity as an endpoint in some clinical trials as we move forward.

DR. NOWAKOWSKI: Thank you.

MR. RIOTTO: Mike Riotto, patient. My thoughts as a patient -- and this goes back to what we talked about a minute ago -- say I'm newly diagnosed, I would like to know what my MRD is when I'm newly diagnosed. I'd like to know what it is

right after induction therapy. I'd like to know what it is if I go through transplant, right after transplant, and then probably every year after that, like I do a bone marrow biopsy every year after that just to see where it's at.

Is that what you're all thinking? Am I kind of on the same wavelength there?

DR. MARTIN: So maybe I can answer that for you. There are many reasons to test MRD for a patient like yourself because you want to see the response. You want to see how good you're doing with the various therapies, et cetera. But for this point of looking at accelerated approval, we're picking a time point where this is the time point that we're going to say, "Okay, this is where we're going to measure one arm versus the other arm or do they achieve that endpoint." We do have to choose a time frame, so we want a time frame that's going to be, quote/unquote, "maybe the best time frame for us to make that."

It doesn't mean that we can't do it at 6 months, or at 9 months, or at 12 months, if you

want to go through that many bone marrows -- I don't know -- but it is the one time frame that we're looking at when do we do our assessment to say, "Okay, this is enough to say that we can have accelerated approval for this drug." That's more of it.

MR. RIOTTO: Can I follow up? Would it only be the one time, then, only at 12 months, and you wouldn't follow up after that?

DR. MARTIN: Well, I think that's what this discussion is. That's what we want to talk about in this discussion, and that's why doing sustained MRD negative, too. So you do it at 3 months after transplant and 9 months after transplant, and you have sustained MRD negativity; that is also a measure.

DR. KANAPURU: Yes. This is Dr. Kanapuru. Just to clarify, I think we sort of discussed this. But to answer the first point, yes, the current data analysis did not have data points to assess sustained MRD negativity and the impact on long-term outcomes. In regards to your question,

Mr. Riotto, we are asking you to discuss if there is a need to actually assess at multiple time points but, really, at the 9 month and 12 month is where we're trying to assess in terms of an endpoint to see if there's a difference between the two arms.

One aspect to consider is that for a 9-month and 12-month endpoint, you already have that period from the time you started treatment, so you're really looking at already the duration. It's not the duration from the time of achieving MRD, but you've already had the period where you've been without progression because you're still MRD negative at 9 months or you're MRD negative at 12 months. But we would want you to discuss, in addition to that assessment at 9 months and 12 months, would it be helpful to have additional time points to measure so that you can actually look at whether the MRD is durable. So that's something that we want you to discuss here.

DR. NOWAKOWSKI: Dr. Advani?

DR. ADVANI: Dr. Advani, Stanford. I think

it comes with the responsibility to do that. So this is, yes, one time point for accelerated approval, and I think the 9 and 12 month has been well studied, and well vetted, and it takes that much time to bring the protein down. But moving forward beyond that, I do think as clinicians or researchers, it's a responsibility to test it further on to see how durable it is and whether it correlates with longer term outcomes as well.

DR. NOWAKOWSKI: Dr. Hourigan?

DR. HOURIGAN: Yes. Just to answer your question, I spend a lot of time thinking about measurable residual disease in other settings, and I think it's really important to uncouple the different use cases for these really powerful tools. So the high sensitivity assessment of residual disease can be used for many different things, and I think the way it's used in clinical practice may be different than the way it's used in a regulatory context to approve new drugs.

I think this is ultimately a choice. Any landmark assessment when there's continuous therapy

is going to be a choice, and I think the choice made here is reasonable based on the data available. Your clinician, however, may very reasonably decide to track you for many other purposes at different landmarks. I think this is just a landmark choice as a starting point for the purposes of testing the efficacy of drugs against each other, in randomized trials in particular.

DR. NOWAKOWSKI: Yes. Greg Nowakowski. I think that over time, the assessment will be important. As Dr. Advani pointed out, it's almost our responsibility to establish if the dynamic of the MRD actually is even a better predictor of the outcome in the long term. In addition, in other tumors, we also know that the rapidity of normalization or achieving MRD negativity is actually very important as well, so I have no doubt that in the future, this field will develop even more.

Dr. Lieu?

DR. LIEU: This is Chris Lieu, University of Colorado. The use of accelerated approval here,

the data are so strong at 9 months and 12 months, and there is a little bit of a difference, but the data are so strong at a patient level that I think that that endpoint is reasonable to use. To use an extreme example, if you require durability of response -- let's just say you require, an extreme example, 5 years of durability of MRD negativity -- obviously, we assume that that would be associated with improved overall survival, but then the length of time to approval is obviously quite long.

So I think the data are strong enough at these earlier time points to use them, and while I agree that assessment of durability is obviously a critical part of the assessment of, obviously, the entire trial population, the use of a 9-month MRD assessment time point for accelerated approval seems very reasonable to me.

DR. NOWAKOWSKI: Dr. Nieva?

DR. NIEVA: Jorge Nieva, USC. I'm at two minds on this. One is, the 12-month point seems somewhat arbitrary, and we don't have comparisons

of what it would look like at one time or another. And while I think durability is a good thing to know, I have this tremendous fear that this is going to mean every myeloma protocol has a marrow biopsy every 6 weeks on the patients forever. And I just want to make sure that as sponsors think about designing their trials, they're not thinking, "Oh, yeah. All we need to do is do more bone marrows, and then we'll have this much additional statistical power to show a difference between the two arms because now we can do a Kaplan-Meier plot of loss of MRD," and I just don't want to see that happen. So I think we need to balance these two things.

DR. NOWAKOWSKI: That's an extremely important point.

Dr. Maurer?

DR. MAURER: Matt Maurer, Mayo Clinic. I think the results are strong, equally for 9 and 12 months, so I would encourage, based on the clinical therapy, being able to make decisions about either 9 or 12 months, depending on the

length of therapy, consolidation, and/or maintenance. So having some clinical judgment in terms of picking either of those I think would be warranted.

DR. GORMLEY: Could we comment as well?

DR. NOWAKOWSKI: Yes. Dr. Gormley?

DR. GORMLEY: Nicole Gormley, FDA. These are really important concepts, and I think there were analyses looking at MRD at 9 months, MRD at 12 months, and MRD at any time. And all of these, other than the MRD at any time, the 9 and 12 months, have a little bit of durability built into them just because of when they are set; although the MRD at any time also had some durability built into it as well just because that's when most MRD is actually assessed. It's when you achieve CR, which is a little bit later on. I think all of these time points in and of themselves had strong individual prognostic level associations, so that's an important consideration.

In terms of the durability, the IMWG defines sustained MRD as MRD sustained for 12 months, so

that would be later than our 12-month MRD assessment because it's reaching MRD and then sustaining that for 12 months, and as we mentioned earlier, the data is not robust yet enough to assess that. And I think, as was mentioned, there will be continued assessment of this over time, looking at the MRD kinetics across the board, time to attaining MRD, and durability of MRD.

So I think that we will, over time, know more information about the kinetics, but I think the question is, the data that we have really suggest that just MRD in and of itself, at 9 months, 12 months, and at any time even, were strong prognostic individual associations. So this is a little bit of a deviation, perhaps, than how we have traditionally treated response rate, and that's been response rate with durability, but I think that the MRD data that we have thus far has not looked at that yet, and I think we will over time. But MRD, even at these time points, was a strong individual prognostic association.

DR. NOWAKOWSKI: Greg Nowakowski. I

completely agree with this. I think this goes back a little bit to our love of randomized studies because if you imagine this scenario as a single randomized study, you can probably pick up different points and compare them in the same time. If you're looking at single-arm studies as refractory space and comparing to historical control, the most currently available and most robust would be 9 and 12 months, so it also depends on the scenario.

The other thing, there is a movement now, which is good to see for our patients, of trying to get more of a time-limited therapy or time-defined therapy than therapy forever. So depending what will be the duration of this therapy, the timing of MRD assessment can change as well. But you're absolutely right; it does have this element of durability itself already at 9 to 12 months.

Dr. Hourigan?

DR. HOURIGAN: Chris Hourigan. Because we're all agreeing so much, just to put in a cancer example, just in terms of data collection and

harmonization for future across different efforts, as we're picking an arbitrary landmark, is there any utility in picking one, given 9 and 12 month both seem to have a similar prognostic association and individual level? Futurecasting 10 years into the future, is there some value in just putting a stake in the ground and saying we're going to say 12-month assessments are the assessment and giving help to our next generation of colleagues, are we going to do a similar meaning to this to move forward?

The only thing I'd add is unlike other measures of response assessment, this is highly quantitative, so you will collect data at this 10 to the minus 5 cut point in your future technologies. When we go to 10 to the minus 6 to 10 to the minus 9 -- to your point, Mr. Mitchell -- to 10 to the minus 20, we'll still have data at this 10 to the minus 5 cut point, but the timing may be important.

DR. GORMLEY: No, that's a good point. Nicole Gormley, FDA. I would just add, I think

that there is probably value in standardization, just generally. I will say, though, even though there may be one time point that's chosen as the primary endpoint, often in the clinical trials, we do have some assessment of other time points as well. So similar to your comment about the depth of response, I think over time as well, we'll gather more information from several of these trials about the appropriate time point and kinetics, just generally with MRD.

DR. NOWAKOWSKI: Dr. Frenkl?

DR. FRENKL: Actually, Dr. Gormley said everything that was on my mind just a few minutes ago with all of her comments. Thanks.

DR. NOWAKOWSKI: Thank you.

Dr. Martin?

DR. MARTIN: Tom Martin, UCSF. I would actually say that we should keep it a little bit open because of the design of the trial. And 9 months, I honestly don't think there's a big difference in 9 months versus 12 months. For transplant trials, where they get 4 cycles of

induction and then a transplant, that might take 3 or 4 months, and then a couple cycles of consolidation, 12 months might be the sweet spot. But in a new newly diagnosed transplant-ineligible population that gets 6 or 8 cycles of induction, then the 9-month frame might be the best one.

So I think we should let the trial decide on what's going to be the best time point for, this is where my analysis is going to be, based on the data that's been sent, and like you said, we have good data at 9 and 12 months. It's the sustained one that'll be really interesting to see down the road as we get more data, that maybe that is the best predictor and that can be the the next level for us.

DR. PAZDUR: I agree with some flexibility here because, here again, we're basing everything on existing therapies, and there may be other therapies that come out that require additional time here. And to say, well, we're only going to look at this at this point may be cutting off our nose, basically, here because we really need to

have some flexibility here; and here again, benefits of a randomized study, you could specify that.

DR. NOWAKOWSKI: Dr. Hourigan?

DR. HOURIGAN: Just in terms of line stepping, I know clinical investigators will always push the envelope. So the date of analysis seemed to be 12 months plus or minus 3 months versus 9 months plus or minus 3 months. You can imagine that, then, we're trying to compare 6-month time points with 12-month time points, which may be very different. So just to split the difference, would 12 months plus or minus 3 months be a window that's acceptable to -- Dr. Martin, you're the myeloma expert. Is that a reasonable --

DR. GORMLEY: Nicole Gormley, FDA again. And that was sort of the reason why we had the additional assessment. We added MRD negative CR at any time to allow a little bit more flexibility because the clinical trial protocol may have just designated that once a patient achieves CR, we will assess MRD negativity, and that actually, as well,

still demonstrated a good amount of individual prognostic association.

So again, I think we may be arguing a little bit over -- not arguing, but this may not be needed at this level. I think where we're coming from is does the committee deem that all of these times are adequate? And a lot of this, I think as Dr. Martin mentioned, will really be driven by the specific therapy and the patient setting for a specific trial. And that's not to say, again, this will just be the designation of the primary endpoint. I suspect that multiple MRD time points within any given trial will still be collected such that even if one is designated as the primary endpoint, even if it's MRD negative CR at anytime, we would still get information from these other time points as well, which will add to our information we have later on.

DR. NOWAKOWSKI: Dr. Hourigan?

DR. HOURIGAN: Just for the record, I can see the point, and I'd like to also say I was playing devil's advocate.

(Laughter.)

DR. NOWAKOWSKI: Any other comments or discussion points?

(No response.)

DR. NOWAKOWSKI: If not, let me summarize the discussion at this point by the committee. So the answer in brief is it depends, depends on the trial design and depends on the timing of therapy. But the 9 to 12-month endpoint currently for an MRD appears to be the most validated for current use. There was a definite indication that other time points in other trials, particularly in randomized comparisons, could be also explored and adequate.

There was also understanding that this is technology which is in development and will change, so understanding the dynamic of how MRD has changed, the durability, would be something which we should encourage in clinical trials. Again, we have to be mindful here, though, to minimize the burden for the patients, which could be related to the ongoing bone marrow biopsies. Then, we also recognize that technology may change as well in

terms of the limit of detection of the cells, so additional studies in the future will inform MRD assessment even more.

Well, thank you. We'll now proceed to question 4, which is a voting question for today. We'll be using an electronic voting system for this meeting. Once we begin to vote, the buttons will start flashing, and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The designated federal officer, Dr. Stevenson, will read the vote on the screen into the record. 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. We'll continue in the same manner until

all questions have been answered or discussed.

This is the voting question. Does the evidence support the use of MRD as an accelerated approval endpoint in multiple myeloma trials? And before we proceed, I would like to ask if there are any comments or concerns about the wording of the question. Does anybody have any concerns or comments about the wording of the question?

(No response.)

DR. NOWAKOWSKI: It sounds like it's pretty clear to the committee.

So if there are no further questions or comments concerning the wording of the question, we'll now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly after you have made your selection. The light will continue to flash. If you are unsure of your vote or wish to change your vote, please press the corresponding button again before the voting is closed.

(Voting)

DR. STEVENSON: Takyiah speaking, DFO. For the record, there are 12 yeses, 0 noes, and 0 abstentions. Thank you. I'll hand it back to the chair. Thank you.

DR. NOWAKOWSKI: Thank you.

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 the way you did into the record. We'll start from Dr. Lieu and go around the table.

DR. LIEU: This is Chris Lieu, University of Colorado. I voted yes. There's a clear clinical need and unmet need for an endpoint here. This is a wonderful problem to have. Your overall response rate is too high; progression-free survival is too long. What a great issue to be discussing today. But the landscape is changing, and we've got to adapt to that landscape, and we need to incorporate novel technologies, and that's what the FDA is doing, and that's what the applicants have done with their analyses, and they should be commended

on that.

Dr. Hourigan had made this point. Does MRD fulfill the criteria outlined by the FDA guidance in terms of biological plausibility? Yes; prognostic impact, yes, and then clinical evidence, certainly at the patient level, the answer is yes. I think we're all concerned that, of course, MRD negativity is not going to correlate perfectly with overall survival, and I think this is a legitimate concern. And the question at hand is, does the currently available evidence support that the benefits of using this endpoint in the accelerated approval fashion outweigh the risks? And, to me, the answer is yes. Thank you.

DR. MADAN: Ravi Madan, National Cancer Institute. I think the FDA showed that MRD does fall short of true surrogacy, but that's a high bar, and that wasn't the question today. I think our clinical experts and the FDA both agree that MRD does meet the criteria for accelerated approval, and that's why I voted yes.

That said, I think we need to be cautious

that once FDA guidance, if that's the choice, gets out that MRD is acceptable for accelerated approval, it will change the incentive structure for preclinical modeling, clinical development, early clinical trials, so that requires the FDA to be vigilant. We talked a little bit about how that may lead to throwing the baby out with the bathwater, as financial incentives may pressure industry to hit the MRD mark or not decide to continue.

On the flip side, it could raise other concerns that hitting MRD may not translate into long-term clinical efficacy, so therefore, the FDA needs to pay close attention, as it always does, to safety, progression-free survival, and other relevant endpoints like survival. But again, I commend everybody on the efforts here, which took 15 years. It's easy to sit in awe of the work done today.

DR. NOWAKOWSKI: Thank you.

And just as a reminder, please state your vote just for the record in addition to your name.

DR. MADAN: Sorry. For the record, I voted yes.

MR. MITCHELL: I'm David Mitchell, consumer representative. I voted yes, and Dr. Lieu and Dr. Madan really said everything I would have said.

MR. RIOTTO: Michael Riotto, patient representative. I voted yes. I voted yes because I'm hoping that MRD negativity, as a surrogate in a clinical trial, will lead to a cure. There might be a drug out there that will be a cure for me and all the other myeloma patients.

DR. NIEVA: Jorge Nieva. I voted yes, and I voted yes because I've actually never before seen this level of data presented on simply moving the bar on response. We have three independent statistical analyses from thousands of patients, showing that it does in fact correlate very nicely with long-term outcomes. And I think if ever there was an endpoint that showed a good statistical association, this is the one that does.

DR. VASAN: Neil Vasan from Columbia. I voted yes. I'd like to congratulate the applicants

here. This was a Herculean effort. I think it really changes the playbook for how we think about biomarkers across all cancer types. To me, the important word was "reasonable." Is this a reasonable surrogate endpoint? Is this a reasonable intermediate endpoint? And I think it is more than reasonable.

I think, just big picture, it is a wonderful thing to be able to learn from all of the patients, from this critical mass of patients who've been involved in phase 3 trials all over the world over many, many years. This is a wonderful aspirational approach that I think all oncologists can refer to. Thank you.

DR. HOURIGAN: Christopher Hourigan. I voted yes. Measurable residual disease negativity, determined using a validated assay capable of detection down to 10 to the minus 5, is an important measure of reduction of tumor burden, and has been shown to be clearly strongly associated, at an individual level, with progression-free and overall survival in patients with multiply myeloma.

Because we live in the real world, the evidence for a trial-level association is less robust. We're always going to be looking in the rearview mirror, looking at data from drugs and assays that don't reflect the current state of the art and confounded by post-trial realities. It's messy.

This reasonably likely intermediate endpoint will not perfectly capture clinical benefit in all scenarios, and may sometimes mislead us, but that's why we're talking about accelerated approval, and I'm reassured by the robust safety monitoring and this requirement for the confirmation of clinical benefit.

There is harm to inaction. We're not currently curing people of multiple myeloma, and I'm not willing to make patients wait on principle for a theoretical perfect that may never come. Our responsibility to accept the world is messy and be agile enough to adapt and iterate as the evidence develops, rather than create barriers to the work of discovering effective new therapies for these

patients.

DR. MARTIN: Hi. Tom Martin, UCSF. I voted yes, and I would like to applaud the FDA and the applicants for actually doing all the work over the last 10 years with all the meetings and everything that's done to bring us to this day, and also to all the investigators across the world who basically put in the data, the individual patient-level data, for these analyses.

The analyses all showed that this is a reasonable approach to look for accelerated approval. It took over 10 years to get to this point. I think this day actually will mark that in the next 2 to 5 years, we'll have way more data, just based on this meeting and based on this approval today, on MRD, and it will take us to the next level. And finally, just the patients, I'd like to thank all the patients for doing all the bone marrow biopsies for all these analyses. Thank you.

DR. MAURER: Matt Maurer, Mayo Clinic. I voted yes. Again, I echo everyone's comments in

here about the strength of the work that's been done over the last 10 years to really move endpoints forward in multiple myeloma, so congratulations to the the team and all people involved, but the teams, as well as the FDA. I think it brought up that the accelerated approval process has been a big success in myeloma, and I think this, essentially, with MRD, continues to move that forward.

I think MRD, from the data presented, clearly met the criteria of an intermediate clinical endpoint. I think the agency has shown that they know how to use the accelerated approval process within myeloma given this broad success. So if we think in the big picture, this mechanism has really worked, and I think this will help continue to move this forward for patients with myeloma.

DR. NOWAKOWSKI: Dr. Advani?

DR. ADVANI: So I voted yes because I think it doesn't get rid of the traditional endpoints. It raises the bar higher. I have full faith in the

system that there are safeguards in place to prevent bad things from happening, like if there's toxicity, there are endpoints. And I do think technology is advancing, and that hopefully these tests are not going to need bone marrows every 2 months or so, but we can do it in a simple blood test.

DR. NOWAKOWSKI: Thank you. And if I can ask you, Dr. Advani, just state your name for the record.

DR. ADVANI: Dr. Advani, and I voted yes.

DR. NOWAKOWSKI: Thank you.

DR. CONAWAY: Mark Conaway, University of Virginia, and I, too, want to congratulate the teams for the Herculean effort of harmonizing data across so many clinical trials, and an Herculean task describes it. I do think this could well serve as a blueprint for developing endpoints in the future. So for all those reasons, and the reasons expressed by other panel members, yes, I voted yes.

DR. NOWAKOWSKI: Thank you.

Greg Nowakowski. I voted yes, and I voted yes with confidence because of the way the accelerated approval process is designed. There is a safety net to require confirmatory studies and require long-term toxicity and benefits of other time-dependent endpoints. So the way the system is designed, it really facilitates rapid drug development while providing these long-term confirmatory studies to assure our patients safety, and also for the other reasons already mentioned.

So this concludes this part. Before we adjourn, I would like to make a couple of comments. First, I would like to also applaud the sponsors and FDA for all the work which was done to really bring the MRD as an endpoint in multiple myeloma. We've seen the timelines. It took a lot of effort. It took a lot of international collaboration and a lot of investigators working together, but we really believe that this is going to drive the field forward. I'd particularly like to also thank FDA for hosting here and allowing us to have this discussion. We would like to thank the public and

also the open public hearing presenters for all their comments to the panel. We always find those very useful in our deliberations at this committee.

And a personal comment, and I've heard it from many of the members as well, I'd like to thank FDA for your combined briefing document. With two sponsors and FDA comments, it made the interpretation of the results much easier in tracking for us. So you definitely improved our ability to really quickly understand the major points in the discussion, and I will open it to FDA for your comments.

DR. PAZDUR: First of all, I want to thank everybody for making the travel here, and hopefully we're somewhat back to normal and we'll continue in-person meetings. This was the first advisory committee out of any therapeutic area that was done live, so this is a groundbreaking thing after the COVID infection. But we wanted to really talk about the briefing document also.

I want to emphasize that these are separate documents, basically, separate inputs. We're not

working in collaboration with the sponsor on this. The sponsor does theirs, we do ours, and I think that's important for people to realize. But I wanted to get people's viewpoints on this because we really want this to be the default position for these briefing documents.

Many times -- many of the standing members know this -- they get two briefing documents that may be well over 100 pages, and it's hard, really, to digest all this information. I assume that people like this unified briefing document. If they don't, please tell me, because we plan on trying to make sponsors take the default position, and if they don't want to do it, I'll be asking them at this meeting, why not? So to put them on the hot seat, so to speak.

But really, we want this, and this is a public opportunity to announce that this is where we want this to move, and if they're not willing to do it, be prepared to answer why you're not doing it because I think this simplifies the process and puts the arguments in counterpoint point, so to

speak. And the real name of this project was Point Counterpoint; yes? And here again, we really want simplified documents to really illustrate where we're going and where the company is going.

So if I don't hear from anybody, I assume that there is uniform agreement that we should move forward? Okay. So without any dissent, companies beware. This is what we expect, and Dr. Pazdur will be on you if you don't do this.

DR. GORMLEY: Great. Yes. I just wanted to take a minute to thank both the Miami group and the I2TEAMM team. As everyone has mentioned, this was a very large collaborative effort, and I think it really helped to advance the field of myeloma, so thank you for all the work that you did.

I also really want to thank all the committee members for joining us here in person today and all of your really thoughtful comments and discussion. It's really, really valued, and we take all of this back and really listen to all of your comments. So thank you for your time and all of your really rich discussion that was had today.

Thank you.

Adjournment

DR. NOWAKOWSKI: Thank you, Dr. Gormley.

If no other comments, we'll now adjourn the meeting. So thanks again for your participation.

(Whereupon, at 3:19 p.m., the meeting was adjourned.)