FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

(ODAC)

Virtual Meeting

Morning Session

Friday, March 15, 2024

8:30 a.m. to 1:00 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Joyce Frimpong, PharmD
Division of Advisory Committee and
Consultant Management
Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Ranjana H. Advani, MD
Saul A. Rosenberg Professor of Lymphoma
Division of Oncology
Stanford University School of Medicine
Stanford, California

William J. Gradishar, MD
Professor of Medicine/Betsy Bramsen Professor of
Breast Oncology
Chief, Hematology/Oncology
Robert H. Lurie Comprehensive Cancer Center
Feinberg School of Medicine at
Northwestern University
Chicago, Illinois

Christopher H. Lieu, MD

Associate Professor of Medicine

Associate Director for Clinical Research

Director, Gastrointestinal Medical Oncology Program

University of Colorado

Aurora, Colorado

Ravi A. Madan, MD

(Chairperson)

Senior Clinician

Head, Prostate Cancer Clinical Research Section

Genitourinary Malignancies Branch

Center for Cancer Research

National Cancer Institute

National Institutes of Health (NIH)

Bethesda, Maryland

Jorge J. Nieva, MD

Associate Professor of Clinical Medicine

Section Head, Solid Tumors

University of Southern California (USC)

Norris Comprehensive Cancer Center

Keck School of Medicine of USC

Los Angeles, California

Daniel Spratt, MD

Vincent K Smith Chair, Department of

Radiation Oncology

Professor of Radiation Oncology and Urology

University Hospitals Seidman Cancer Center

Case Western Reserve University

Cleveland, Ohio

Neil Vasan, MD, PhD

Assistant Professor

Division of Hematology & Oncology

Department of Medicine

Herbert Irving Comprehensive Cancer Center

Columbia University Medical Center

New York, New York

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBER

(Non-Voting)

Tara Frenkl, MD, MPH

Senior Vice President, Head of Oncology Development

Bayer Pharmaceuticals

Whippany, New Jersey

TEMPORARY MEMBERS (Voting)

John Deflice, MD

(Patient Representative)

Albuquerque, New Mexico

Sally Hunsberger, PhD

Mathematical Statistician

Biostatistics Research Branch

National Institute of Allergy and

Infectious Diseases

NIH

Bethesda, Maryland

Mary Kwok, MD

Clinical Associate Professor

Division of Hematology-Oncology

University of Washington

Seattle, Washington

Susan Lattimore, RN, GCPH

Assistant Professor, Pediatrics

Associate Director – The Hemostasis &

Thrombosis Center

Oregon Health & Science University

Portland, Oregon

FDA PARTICIPANTS (Non-Voting)

Marc Theoret, MD

Deputy Center Director, OCE

Supervisory Associate Director (Acting)

OOD, OND, CDER, FDA

Nicole Verdun, MD

Super Office Director

Office of Therapeutic Products (OTP)

Center for Biologics Evaluation and Research (CBER)

FDA

Bindu Kanapuru, MD

Clinical Team Leader

Division of Hematologic Malignancies II (DHMII)

OOD, OND, CDER, FDA

Robert Sokolic, MD

Branch Chief

Malignant Hematology Branch (MHB)

Division of Clinical Evaluation Hematology (DCEH)

Office of Clinical Evaluation (OCE)

OTP, CBER, FDA

Helkha Peredo-Pinto, MD, MPH

(Morning session only)

Clinical Reviewer

MHB, DCEH, OCE, OTP, CBER, FDA

Cong Wang, PhD

(Morning session only)

Statistical Reviewer

Therapeutics Evaluation Branch 1 (TEB1)

Division of Biostatistics (DB)

Office of Biostatistics and Pharmacovigilance

(OBPV), CBER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:30 a.m.)

Call to Order

DR. MADAN: Good morning, and welcome. I would first like to remind everyone to please mute your line when you are not speaking. For media and press, the FDA press contact is Lauren-Jei McCarthy, and her e-mail is displayed currently. Thank you.

My name is Ravi Madan, and I will be chairing today's meeting. I will now call the morning session of the March 15, 2024 Oncologic Drugs Advisory Committee meeting to order. Dr. Joyce Frimpong is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. FRIMPONG: Good morning. My name is Joyce Frimpong, and I'm the acting designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation. We will start with the

standing members.

Dr. Advani?

DR. ADVANI: Ranjana Advani, Stanford.

DR. FRIMPONG: Thank you. Good morning.

Dr. Gradishar?

DR. GRADISHAR: Bill Gradishar, medical oncology, Northwestern University.

DR. FRIMPONG: Thank you.

Dr. Lieu?

DR. LIEU: Good morning, everybody. I'm Chris Lieu. I'm a GI medical oncologist from the University of Colorado Cancer Center.

DR. FRIMPONG: Thank you.

Our chairperson, Dr. Madan.

DR. MADAN: Good morning. Ravi Madan, medical oncologist, National Cancer Institute.

DR. FRIMPONG: Thank you.

Dr. Nieva?

DR. NIEVA: Good morning. Jorge Nieva, thoracic medical oncologist, University of Southern California, Norris Comprehensive Cancer Center.

DR. FRIMPONG: Thank you.

Dr. Spratt?

DR. SPRATT: Dr. Dan Spratt, Chair of Radiation Oncology at University Hospitals Seidman Cancer Center and Case Western Reserve University.

DR. FRIMPONG: Thank you.

Dr. Vasan?

DR. VASAN: Neil Vasan. I'm a breast medical oncologist at Columbia University Medical Center.

DR. FRIMPONG: Thank you.

And for our industry representative, Dr. Frenkl?

DR. FRENKL: Good morning. I'm Dr. Tara Frenkl, Head of Oncology Development at Bayer Pharmaceuticals.

DR. FRIMPONG: And now for our temporary voting members, Dr. Deflice?

DR. DEFLICE: Hello. I'm John Deflice. I'm a gastroenterologist and I have a 13-year history of multiple myeloma. I'm a patient advocate.

DR. FRIMPONG: Thank you.

Dr. Hunsberger?

DR. HUNSBERGER: Good morning. I'm Sally Hunsberger. I'm a biostatistician at NIH NIAID. Thank you.

DR. FRIMPONG: Dr. Kwok?

DR. KWOK: I am Mary Kwok. I am a multiple myeloma physician at the University of Washington and Fred Hutch Cancer Center.

DR. FRIMPONG: And for our consumer representative, Ms. Lattimore?

MS. LATTIMORE: Good morning. I'm Susan Lattimore from Oregon Health & Science University in Portland.

DR. FRIMPONG: And now I will do our FDA participants. I would first start with Dr. Theoret.

DR. THEORET: Yes. Hi. Good morning. My name is Mark Theoret. I'm a hematologist/oncologist and Deputy Center Director of the Oncology Center of Excellence.

DR. FRIMPONG: Dr. Kanapuru?

DR. KANAPURU: Hi. Good morning. I'm Bindu Kanapuru. I'm a hematologist/oncologist and the

medical oncology review team lead.

DR. FRIMPONG: Dr. Sokolic?

DR. SOKOLIC: Hi. Rob Sokolic. I'm the Branch Chief for Hematologic Malignancy in CBER.

DR. FRIMPONG: Dr. Peredo-Pinto?

DR. PEDERO-PINTO: Good morning. I'm Dr. Helkha Pedereo-Pinto, a pediatric hematologist/ oncologist in the Division of Clinical Hematology Evaluation in CBER and the primary clinical reviewer for this product. Thank you.

DR. FRIMPONG: And Dr. Wang?

DR. WANG: Good morning, everyone. I'm Cong Wang, biostatistical reviewer for the Carvykti application. I'm from the Division of Biostatistics, CBER, FDA.

DR. FRIMPONG: Thank you, everyone.

Dr. Madan, I'll hand it back over to you.

DR. MADAN: Thank you, Dr. Frimpong.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are strongly held. Our goal is that this meeting will have a fair and open

forum to discuss these 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 this meeting.

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

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

Conflict of Interest Statement

DR. FRIMPONG: Thank you, Dr. Madan.

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

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal

employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs their potential financial conflicts 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 a discussion of supplemental biologics license application, sBLA, 125746.74 for Carvykti, ciltacabtagene autoleucel,

suspension for intravenous infusion, submitted by Janssen Biotech, Incorporated. The proposed indication for this product is for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and are refractory to lenalidomide.

The committee will have a general discussion focused on the overall survival data in the Study MMY3002, CARTITUDE-4, and the risk and benefit of ciltacabtagene autoleucel in the intended population. This is a particular matters meeting during which specific matters related to Janssen Biotech's sBLA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting numbers, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Mary Kwok. Dr. Kwok's waiver involves a consulting interest under negotiation with a competing firm. The

waiver also involves 10 of the employer's research contracts for various studies funded by the party to the matter or competing firm. Dr. Kwok's employer receives between $0 and $50,000 per year for each of the four studies from Janssen, Seagen, Celgene, and a competing firm; between $50,000 and $100,000 per patient enrolled for one study from Regeneron Pharmaceuticals; between $100,000 and $300,000 per year for each of the two total studies from Janssen and Sanofi; between $100,000 and $300,000 per enrolled patients for each of the two total studies from Janssen Research & Development and TeneoOne and AbbVie; and $300,000 and $500,000 per year for one study from Harpoon Therapeutics.

The waiver allows this individual to participate fully in today's deliberations. FDA's reason for issuing the waiver are described in the waiver document, which is posted on the FDA's website on the advisory committee meeting page, which can be found at www.fda.gov and by searching on March 15, 2024 ODAC. Copies of the waiver may also be obtained by submitting a written request to

the agency's Freedom of Information Division, 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements they have made concerning the product at issue. With respect to the 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.

For the record, Dr. Sham Mailankody, an employee of Memorial Sloan Kettering Cancer Center, has acknowledged having contracts for grants from Bristol-Myers Squibb and being a principal investigator or co-investigator on studies with Janssen Oncology; Takeda Oncology; Bristol-Myers

Squibb; Allogene Therapeutics; BAIT Therapeutics; and Caribou Therapeutics. Dr. Mailankody has also acknowledged receiving consulting fees from Janssen Oncology; Bristol-Myers Squibb; Arcellx; AbbVie; Optimum Oncology; and Sanofi-Aventis. As a guest speaker, Dr. Mailankody will not participate in committee deliberations, nor will he vote.

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

Dr. Madan, I'll hand it back to you.

DR. MADAN: Thank you, Dr. Frimpong.

We will now proceed with the FDA introductory remarks from Dr. Robert Sokolic.

FDA Opening Remarks - Robert Sokolic

DR. SOKOLIC: Good morning. My name is Rob Sokolic. I'm the chief of the malignant hematology branch in the Office of Clinical Evaluation at CBER. I'm going to briefly introduce the purpose of this convening of the Oncology Drug Advisory Committee meeting.

During this meeting, we'll be discussing the clinical development program for ciltacabtagene autoleucel, also known as cilta-cel, and Carvykti for the treatment of relapsed multiple myeloma. cilta-cel is an autologous T-cell immunotherapy for the treatment of multiple myeloma. Cells are engineered to express a chimeric antigen receptor directed against BCMA, a protein expressed by benign and malignant plasma cells. Cilta-cel is currently approved for the treatment of adults with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and then an anti-CD38 monoclonal antibody.

The applicant, Janssen, submitted a

supplemental biologics license application, or BLA, seeking expansion of the cilta-cel indication to read, "Carvykti is a B-cell maturation antigen directed, genetically modified, autologous T-cell immunotherapy, indicated for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least one prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent, and who are refractory to lenalidomide."

So during my brief remarks, I'll describe the meeting purpose, provide an overview of the trial, whose results provide the basis for the applicant's request for approval, and conclude with questions for which we're asking the committee's discussion.

The applicant submitted the results of the CARTITUDE-4 trial to provide the evidence of safety and effectiveness of cilta-cel for the proposed indication. CARTITUDE-4 demonstrated improvement in progression-free survival in patients randomized to cilta-cel compared to patients randomized to

standard of care treatment. During the review of the application, FDA identified the higher rate of early deaths in the cilta-cel arm compared to the standard therapy arm as a major review issue. Specifically, visual inspection of the Kaplan-Meier curves for overall survival indicates a crossing hazards pattern with an early decrement in overall survival through the first 10 months. As you'll hear from my colleagues in the subsequent FDA presentations, the crossing hazards pattern renders the average hazard ratio uninterpretable.

We ask the members of the committee to discuss and provide input on the adequacy of the data from the CARTITUDE-4 trial to demonstrate the safety and effectiveness of cilta-cel for the proposed indication, taking into account the effects on progression-free survival and the increased rate of early deaths observed in the cilta-cel arm.

I'll now briefly review the CARTITUDE-4 trial. CARTITUDE-4 is an ongoing, open-label, randomized, phase 3 clinical trial. A total of

419 participants with relapsed or refractory multiple myeloma who are refractory to lenalidomide were randomized to either a single infusion of cilta-cel after lymphapheresis, bespoke product manufacturing, and lymphodepleting chemotherapy, or to standard of care immunochemotherapy until progression or intolerance. Treatment response is assessed in CARTITUDE-4 using the 2016 IMWG criteria.

Shown here is the Kaplan-Meier plot for progression-free survival for the intention-to-treat population at the first interim analysis. CARTITUDE-4 demonstrated a statistically significant effect on progression-free survival with a hazard ratio of 0.41, indicating a 59 percent decrease in hazard rate of progression for patients randomized to cilta-cel compared to patients randomized to the standard of care. The median progression-free survival was not reached in the cilta-cel arm and was 12 months in the standard of care arm.

CARTITUDE-4 demonstrated a numerically

increased overall survival in the cilta-cel arm, although the crossing hazards pattern makes the hazard ratio uninterpretable. The median overall survival was not reached in the cilta-cel arm and was 26.7 months for the standard of care arm. My colleague, Dr. Peredo-Pinto, will review these data in greater detail in the body of the presentation.

I'll now present the questions for the committee. The review issues are that ciltacabtagene autoleucel led to a significantly improved rate of progression-free survival, but with a decrement in overall survival in the first 10 months of the trial. The decrement in overall survival calls into question whether the risk-benefit assessment is favorable. We ask the members of committee to discuss whether the observed increased risk of early deaths in the cilta-cel arm of CARTITUDE-4 is offset by the statistically significant improvement in progression-free survival.

Shown here is the voting question, which I will read. Is the risk-benefit assessment for

ciltacabtagene autoleucel, for the proposed indication, favorable?

Thank you for your attention. I'll now invite FDA's guest speaker, Dr. Sham Mailankody, the Clinical Director of the Cellular Therapy Service at Memorial Sloan Kettering Cancer Center, who will provide an overview of current management of multiple myeloma.

DR. MADAN: Thank you, Dr. Sokolic.

We'll now proceed with our guest speaker presentation from Dr. Sham Mailankody.

Guest Speaker Presentation - Sham Mailankody

DR. MAILANKODY: Thank you.

I'm going to try to summarize the current management of multiple myeloma in the next 20 or so minutes. These are my disclosures.

To begin with, incidence and prevalence of multiple myeloma, as many of you may know, this is the second most common blood cancer amongst adults in the U.S. There is probably about 35,000 patients being diagnosed with multiple myeloma every year, and the prevalence or the

number of patients living with this disease is almost 160,000. Myeloma represents about 1.8 percent of all new cancer cases in the United States, and it's primarily seen in older adults. The median age is 69 years.

We stage myeloma using either the revised ISS staging or the R2-ISS staging, and as shown here, there are 1 to 3 or 1 to 4 different stages. We don't necessarily change treatments based on staging, at least currently, but suffice it to say that higher stages generally are associated with less optimal outcomes. The other point to note is these staging systems incorporate a cytogenetic risk factor, so about 25 percent of our patients have one or more high-risk cytogenetic factors, which again is associated with somewhat less optimal outcomes. Most trials that we will discuss and we have reported so far report the R-ISS staging, although the R2-ISS is a further refinement of this R-ISS staging.

This is one of several examples of population-based studies that have shown a

consistent improvement in survival for patients with multiple myeloma over the last 30 or so years, and this improvement has been seen across age groups. It includes patients younger than 65, 65 to 74, as well as 75-plus years, and this data only goes up to 2012, after which we've had many more new treatments become available. So it's expected that patients diagnosed with multiple myeloma in 2023 will have an average life expectancy of 10 or more years, and this is largely driven by new drug development.

Over the last 25 or so years, we have had multiple classes of treatments become available for our patients, starting with immunomodulatory drugs and proteasome inhibitors in the 2000s, and then monoclonal antibodies targeting CD38 and SLAMF7, and then in the last five or so years, the introduction of T-cell redirecting therapies. This is not an all inclusive but a pretty comprehensive list of treatments we have available for myeloma. The three major classes we have are listed in the top here -- proteasome inhibitors, immunomodulatory

drugs, CD38 antibodies -- and then the last seven or so years, we've had the development of T-cell redirecting therapies. Those are CAR T cells or bispecific antibodies. On the bottom right listed here are the five currently approved products.

Starting with newly diagnosed myeloma, when the patient is diagnosed with myeloma for the very first time, the first determination that happens after initial screening and testing is to determine whether a patient is transplant eligible or ineligible, and this is based on several factors including age, comorbidities, general organ function, and other clinical factors. So patients who are transplant eligible are typically treated with induction therapy, followed by consolidation, which is typically autologous stem-cell transplant, and this is then followed by maintenance treatment.

For patients who are transplant ineligible, they receive initial therapy with a combination of drugs, followed by maintenance. As is standard for most of oncology, supportive care is given throughout the course of these treatments, and

eventually when patients relapse, they go on to receiving treatments for their relapse disease.

Starting with management of newly diagnosed multiple myeloma, this is a busy slide by intent because we have a lot of data here, but listed here are probably six of the major clinical trials that inform our current practice of managing patients with multiple myeloma. As shown here, most of these treatments are looking at either combinations of 3-drug induction compared to 2 drugs or 4 drugs compared to 3 drugs; and one example, endurance in the middle, looking at a 3-drug versus 3-drug comparison.

The second point to note is some of these studies were for patients who were transplant eligible, some for transplant ineligible patients, and two studies where transplant was not intended but was feasible to do in the studies. Then looking at response rates and complete response rates, I won't go through each of these columns individually, but suffice it to say three drugs typically get better responses than two, and four

drugs provide better responses than three. And for the one 3 to 3 drug comparison, the response rates were quite similar.

The next two rows look at PFS and OS, median PFS and median OS, and red highlights statistically significant results, and blue are those that have not yet met statistical significance. And again, as shown here, every time a 3 drug is compared to 2 drugs or a 4 drug is compared to 3 drugs, the progression-free survival is improved statistically significantly, and in some of these studies we're also seeing overall survival benefit.

So in general, it's believed that 3 drugs are generally superior to 2 drugs, and with the extreme right two columns, increasingly emerging data for induction therapy with 4 drugs. And when you use 4 drugs as part of induction, you're using a proteasome inhibitor, an immunomodulatory drug, and a CD38 antibody, all as part of the initial induction treatment.

So as mentioned, for patients who are transplant eligible, there's a consideration of

doing a consolidated autologous transplant after initial induction, and there are currently two major clinical trials that inform the practice of transplant, and both studies looked at the use of autologous transplant in the early or upfront setting or deferred, i.e., at the time of relapse. The first study is IFM-2009. This is from the French myeloma group, and the second study is from the DETERMINATION study done here in the United States. In both studies, patients received induction therapy with the standard 3-drug induction of bortezomib, lenalidomide, and dexamethasone, and thereafter, patients were randomized to receive either transplant in the early setting or transplant that was deferred.

Regardless of the transplant status, all patients received lenalidomide maintenance for 2 years in the IFM study and indefinitely in the DETERMINATION study. As shown here, both studies showed a pretty significant improvement in the median progression-free survival; however, with 8 years of follow for the IFM study and almost

5 years for the DETERMINATION study, there was no difference in overall survival. In summary, it's clear with modern induction therapies that the autologous transplant continues to improve progression-free survival, but not quite yet any difference in overall survival in either of these two studies.

To the bottom panel are the four relevant studies for maintenance treatment. So again, regardless of whether patients get consolidation or not, most patients then move on to maintenance. The only approved treatment for maintenance currently in the United States is lenalidomide, and that is based on these four large clinical trials, and each of these studies showed a significant improvement in the median progression-free survival with the use of lenalidomide as maintenance compared to placebo, and one of the studies has also shown an overall survival benefit.

This is the U.S. study CALGB100104, but also a meta-analysis of all these four studies has shown an improvement in overall survival, suggesting

again that lenalidomide maintenance with or without consolidation is the the default standard of care for patients with newly diagnosed multiple myeloma.

So to summarize this section, standard induction therapy for patients with multiple myeloma is either a combination of three or increasingly four drugs, and when you use four drugs, all three major classes of our treatments are incorporated, proteasome inhibitors, immunomodulatory drugs, and CD38 antibodies. The role of autologous transplantation as consolidation is evolving. This is based on data that PFS is improved but similar OS, and therefore increasingly, fewer transplant-eligible patients, especially here in the U.S., are receiving upfront autologous transplantation, although it remains an important treatment consideration.

Maintenance, particularly with lenalidomide, remains the current standard of care. It has consistently improved progression-free survival in multiple, larger randomized studies, and meta-analysis also shows an improvement in overall

survival. Although the number is evolving, I think it's fair to say that median progression-free survival, based on all of these clinical trials and some of the real-world data, for patients receiving first-line therapy is currently estimated to be about 4 to 7 years.

So I come back to the slide to say that these are the same 18 or so drugs we have that we can use for patients with relapsed myeloma, and when patients relapse, there are a plethora of choices you have in front of you because of different combinations of these 18 drugs that you can use. I've listed, I think, 42 different choices here, but there may be others as well.

One thing to note here is there's a lot of overlap between these regimens. As you can see, all the alphabets are kind of overlapping, and therefore, while there are 42 choices, most patients have been exposed to some of these treatments or classes of these treatments previously, and there's a significant amount of cross resistance across the different classes of

drugs and agents used, such that subsequent lines of therapies generally become more and more challenging.

So how do we use these 42 regimens, or more than 42 regimens, for the patient sitting in front of us? I guess we use different factors. For instance, what's the nature of relapse? Is it symptomatic, asymptomatic? How aggressive is the patient's relapse? Should we be using high-dose chemotherapy to control aggressive relapse?

We also look at side effect profiles for these drugs, as well as patients' own history of side effects. Peripheral neuropathy, for instance, may steer us towards using some drugs versus others; cardiac dysfunction, renal dysfunction, cytopenias, immune function, all of these play into our choices of which regimens to use. Patient factors like frailty; how far does the patient live from the treatment center; does the patient prefer an oral drug compared to infusions; eligibility for clinical trial participation, those are also factors.

And finally, mechanism of action, has the patient received the same treatment previously or a different drug from the same class? What was the response to that treatment previously? Could we use an alternate mechanism of action? And refractoriness or exposure to a class of drug are all factors we use to determine what treatments to use in the relapsed/refractory setting.

Again, when we have patients who have relapsed myeloma, we generally think of patients as being either lenalidomide refractory or not refractory, and listed here are the key clinical trials that inform the management of patients who are not lenalidomide refractory.

I'll note that as more and more patients receive lenalidomide maintenance in the initial setting, we increasingly have patients who are lenalidomide refractory at the time of relapse, but in the rare instances that a patient is not lenalidomide refractory, one of these four clinical trials using the lenalidomide backbone may inform the practice of what to do next.

Each of these trials look as a combination of 3 drugs compared to 2 drugs, and in every instance, the progression-free survival is better for the 3 drugs compared to 2 drugs. And in most of these cases, as shown here, the overall survival has also improved with the 3-drug combination compared to 2 drugs; so in general, 3-drug combinations are better than 2 drugs, both for PFS and OS in this setting.

If you have patients who are lenalidomide refractory, which increasingly is the more common scenario when patients relapse, there are several clinical trials that inform. Again, most of these studies are looking at a 3-drug combination compared to 2 drugs. I've listed here the different treatment regimens, and these trials are largely for patients with either 1 to 3 or more than 2 lines of treatment. And in every case, 3 drugs provide better responses and better complete responses compared to 2 drugs; and in every case, the 3-drug regimen has a better progression-free survival compared to 2 drugs.

In a couple of instances, we also have overall survival benefit to the 3 drugs versus 2 drugs, and in some other instances, either the data is not mature enough or have not demonstrated an overall survival benefit, highlighting some of the challenges of multiple subsequent lines of treatment and other challenges with long-term follow-up for overall survival in these clinical trials.

So one final thought about relapsed/refractory myeloma in this setting is attrition through lines of therapy, and we do have several choices for treatment; however, not every patient who gets diagnosed with multiple myeloma receives 3rd, 4th, or 5th lines of therapy. This is one example from a U.S. claims-based data set that was published by Dr. Fonseca and colleagues a few years back, looking at non-transplant patients who received first-line treatment. Only about 8 percent of those patients received a 5th line of treatment, although we have several treatments now approved for 5th line, and for transplant patients,

that number is about 22 percent.

The study tries to look into what might be some of the reasons for attrition, and that's harder to do with insurance claims data, but one of the reasons is, unfortunately, death. But that's not actually the most common reason for attrition across lines. Some of the purported reasons could be the patients drop off, or have side effects, or can't access treatments, and other reasons for drop off. This is data from a U.S. claims database, but similar data has been reported from Europe and Australia as well, suggesting that a fair amount of patients who get newly diagnosed myeloma do not receive 3rd, 4th, or 5th lines of treatment despite multiple approvals and choices available.

So what about triple-class exposed patients, patients who have already been exposed to or refractory to one proteasome inhibitor, one immunomodulatory drug, and one CD38 antibody? We don't have a lot of perspective randomized data in this setting, but two observational data

sets -- again one international and one here in the U.S., the MAMMOTH here from a US-based observational study, and LocoMMotion more international -- both of them show that with conventional treatments, less than 30 percent of patients respond to next line of treatment if they're already triple-class exposed. The median progression-free survival in this setting is under 6 months and median survival is somewhere between 9 to 12 months.

I highlight, again, that these are both observational data sets and we don't currently have a lot of prospective long-term data for triple-class exposed patients; however, whatever limited data we have available would suggest a response rate with conventional treatments of around 30 percent and a median PFS of less than 6 months.

So that's before we had T-cell redirecting therapies, and CAR T cells are on the left here and bispecific antibodies. CAR T cells are autologous, gene engineered T cells that target tumor-specific

antigens. Bispecific antibodies on the other hand are off-the-shelf drugs that target, on the one hand, a tumor-specific antigen, and on the other side, binds to CD3, which is present on T cells, and redirects these T cells towards the tumor cells.

We have now five different T-cell redirecting therapies, immune therapies, that are approved for patients with four or more prior lines of treatment. Each of these treatments have been approved based on single-arm, pivotal studies, so not randomized comparisons. None of these treatments have been compared head to head so far, and each of these treatments, like I said, are approved for patients with very advanced multiple myeloma, and in these studies, a median of 5 to 6 prior lines of treatments, but showing a very high response rate, in the order of 60 to 95-98 percent for each of these products, and complete response rates in the order of 30 to 83 percent. The median progression-free survival, again, in this non-randomized, single-arm study is

between 8 months, 8 and a half months, to 35 months.

In terms of safety, while these treatments have high efficacy, they also come with toxicity concerns, for instance, cytokine release syndrome, and neurologic symptoms are class effects for these drugs. Shown here are the rates of CRS and ICANS, and immune compromised and infections are another particularly challenging side effect with many of these treatments.

So for holding in on some of these side effects, which will be discussed later today at the meeting as well I'm sure, number one, is cytokine release syndrome or CRS. This has been reported with most T-cell directed therapies, and not only in myeloma but across disease settings and across treatment modalities, and the key symptoms include fever, hypoxia, and hypotension. Any grade CRS, as shown in the previous slide, is 70 to 95 percent of patients; grade 3 or higher, though, is less than 5 percent with each of these products. Our management of CRS has improved dramatically in the

last 10 or so years with the use of IL-6 blocking drugs like tocilizumab and steroids like dexamethasone, and there are some patients with each of these products that develop a more severe form of inflammation called hemophagocytic syndromes as well.

On the right are features of immune effector cell-associated neurologic toxicities or ICANS. Again, symptoms here include lethargy, confusion, somnolence, seizures, and any grade ICANS is 20 to 25 percent, and grade 3 or higher, less than 5 percent. Treatments here include steroids or anakinra. There are some patients with these products that also develop a distinct neurologic syndrome that's somewhat delayed by weeks to months and presents in the form of either Parkinson's like features or cranial neuropathies, and doesn't fit into the classical ICANS definition or timeline.

Then looking at, I guess, really, logistics of CAR T cells, it is a pretty unique treatment in that it's customized and it's individualized, so there are multiple steps involved in providing

these treatments to patients, and bottlenecks also that are associated with these steps. There's initial screening when we see the patient to determine whether they're eligible, and then we have to find a slot available for them to collect their T cells. We also have to work with logistics like donor room, catheter placement, treatment washouts, and all of these may take 2 to 4 weeks.

After all of this, we apherese or collect their T cells. This is a single-day process and takes about 3 to 4 hours. Once the collection is done, many patients, especially in the advanced setting where patients have had four or more lines of treatment, need bridging therapy because they're rapidly progressing. The challenge here is we have very limited bridging options in this setting because many of these patients have already been exposed to most available treatments, and the choices for bridging that we have have low responses and typically high toxicities, which becomes a challenge.

Then we have to consider treatment washout

before CAR T cell infusion, so the current time from the apheresis, to bridging, to CAR T infusion can be 4 to 8 weeks. So all in all, from the time when we see the patient to them actually getting the CAR T cell can be upwards of 8 to 12 weeks in the current scenario for the currently approved CAR T cells. And when you give CAR T cells to patients with high burden of disease, as often happens with advanced multiple myeloma, we also recognize that there's higher incidence of toxicities with refractory disease and high burden of disease.

So these are all some of the challenges we're facing with the currently approved indications for CAR T cells, and some of that may steer us towards using bispecific antibodies due to ease of access and ready availability of these treatments in the advanced setting.

There are other challenges as well to both these treatments, the need for specialized centers; inpatient management and the management of toxicities; availability as I mentioned for CAR T

cells; the turnaround time; the efficacy is high but so is cost, and the access is limited; and then finally, bridging therapy, which is particularly, as indicated previously, needed for CAR T cells but obviously not needed for bispecific antibodies.

So to summarize the section on relapsed/refractory myeloma, we have multiple available options but significant overlap in mechanisms. Cross resistance and attrition through lines of therapy limits choices. Triple-class exposed patients remain a particular challenge and whether we have limited data for long-term survival. T-cell redirecting therapies in the form of CAR T cells or bispecific antibodies have high responses in this setting, and to date, I guess until recently, had limited long-term and randomized data for safety and survival.

To summarize the entire talk, I would say we've made substantial progress in the treatment of multiple myeloma. By some counts, we have 19 different FDA-approved treatments for myeloma and most of these treatments became available in

the last two decades. This has directly led to consistent improvements in survival, both in our clinical trials as well as population-based studies, but despite these improvements, it's somewhat sobering to say that most patients who have a diagnosis of multiple myeloma will die from the diagnosis. Thank you very much.

Clarifying Questions to Guest Speaker

DR. MADAN: Thank you, Dr. Mailankody.

We will now take clarifying questions for our guest speaker, Dr. Mailankody. Please use the raise-hand icon to indicate that you have a question and remember to lower your hand by clicking the raise-hand icon after you have asked your question. When acknowledged by the chair, please remember to state your name for the record before you speak and direct your question to Dr. Mailankody. I guess you'd be the speaker here.

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 a thank

you or, "That's the end of my question for now," so we can move on to the next member.

I don't know if we have any questions for Dr. Mailankody, but now would be an opportunity.

Dr. Vasan?

DR. VASAN: Hi. That was a really elucidating presentation. Thank you. I had a question. I'm a solid tumor oncologist, and one thing we think a lot about is disease-free intervals in solid tumor oncology, and there are many studies that correlate disease-free intervals, especially in long indolent diseases like myeloma or ER positive breast cancer, with improved or decreased responses to subsequent therapies.

I was wondering if any of the therapies -- I know you presented so many different regimens, but if that theme is manifest in in myeloma.

DR. MAILANKODY: Thank you, Dr. Vasan. I would say that our management of multiple myeloma involves some form of treatment -- at least the current management. All of the treatments involve either a component of maintenance or a component of

continuous treatments in the relapsed/refractory setting such that many of my patients in clinic really don't get a complete treatment-free interval throughout the course of the disease.

Now, the intensity of the treatment may vary. They start with combinations of drugs, and then single drug maintenance, but most of the regimens we have available -- both newly diagnosed, as well as relapsed myeloma -- involve ongoing treatments, with the exception, I guess, of the 4-plus lines with the recent approval of CAR T cells. Those patients generally are monitored without any additional treatments after.

So yes, we do have disease-free intervals where patients are in remission or response, but there is benefit to continuing ongoing treatments for many of these regimens, so there's really no treatment-free interval for many of our patients.

DR. VASAN: For instance, you presented a trial where there's indefinite lenalidomide maintenance. Let's still consider that a disease-free interval in a way --

DR. MAILANKODY: Yes.

DR. VASAN: -- because we're calling it maintenance therapy. It's micrometastatic or some microscopic disease, so let's just call it that. Even with that, is there a correlation?

DR. MAILANKODY: Correlation with --

DR. VASAN: With improved response to subsequent therapies.

DR. MAILANKODY: Oh, sure. So I guess the question is, if you have a good response to a prior therapy, would you respond also with -- is that indicative of a good response for the next line of therapy? In general, yes, but the classes of treatments change very dramatically. So for instance, we have patients who get CAR T cells or bispecific that have never received the T-cell redirecting therapies that are refractory to all other available classes that have had a very long response to it. So I don't know, because the classes are so different and there are so many different classes, that a response or duration of response to a previous line fully informs next-line

response.

That said, there are some common themes to patients who don't respond; for instance, patients with high-risk cytogenetics, patients who have extramedullary disease, patients who have RSS stage 3 disease, and fewer of those patients respond and respond to a shorter period of time, largely agnostic of the treatment classes that we have available.

DR. VASAN: Thank you.

DR. MADAN: Thank you, Dr. Vasan.

Dr. Frenkl?

DR. FRENKL: Hi. Thank you so much. I was wondering if you could expand a little bit on the bridging therapies. I saw that you said low response and limited options. So could you just tell us a little bit more about how physicians go about that, and why the options are limited when it seems like there are so many drugs available?

DR. MAILANKODY: Yes.

DR. FRENKL: Thank you.

DR. MAILANKODY: I think the slide that

refers to the current use of CAR T cells, which is for patients who have received four or more lines of treatment, this is a patient on 5th line that is coming to us to just get CAR T cells. Invariably, they have received a proteasome inhibitor, an immunomodulatory drug, and CD38 antibody previously; that's the requirement. Many of them have actually received more than one immunomodulatory drug, more than one PI, and a CD38 antibody, so a large proportion of these patients are definitely triple-class refractory. Many of what we would consider as penta-refractory, which means that they're refractory to five different drugs that are the backbone of many of our treatments.

I also mentioned that increasingly we're using all three classes of drugs in the first- and certainly in the second-line treatment, so you can imagine by the time they come to 5th line, we don't have a lot of effective treatment choices. We have a lot of choices, but they're not necessarily effective. Many of these patients are also

progressing on available treatment, and like I said, there is about 8 to 12 weeks that we need, when I think about giving somebody a CAR T cell, to them actually getting a CAR T cell because of various logistical or other bottlenecks.

So in that setting, our choices of effective bridging is somewhat limited, and this is borne out by clinical trials. So that led to the approval where bridging therapy was used for these trials, and response rates are under 30-40 percent. That's also borne out by real-world experience and our own experience here, and those responses don't tend to be particularly robust or durable.

The second challenge is, in our attempt to get deeper responses, if you use multidrug traditional chemotherapy, which we sometimes do, that can lead to cytopenias, infections in some cases, and further delays in patients getting CAR T cells. So our ability to get a good response and our ability to manage toxicities in this setting is somewhat limited such that, invariably, some of our patients are going into these treatments with

rapidly progressing disease, or symptomatic disease, or ongoing toxicities from their bridging therapy. So I would say it is one of the key challenges as we think about using these treatments in clinic.

DR. FRENKL: Thank you.

DR. MADAN: Thank you.

Dr. Lieu?

DR. LIEU: Hi. This is Chris Lieu, University of Colorado. Thank you so much for that outstanding talk. You showed a lot of different trials in different settings, and one of the things that struck me was this difference in progression-free survival, which in some cases were extreme differences between treatment arms, but then when you look at overall survival, several of the studies have either no significant difference in overall survival or, despite a humongous difference in progression-free survival, the overall survival difference is sometimes somewhat marginal in comparison.

I understand that in an indolent

disease -- and I'm a solid tumor oncologist, so I think about this like a neuroendocrine tumor. I just want to hear your impression about how you as a clinician treating patients interpret this difference in progression-free survival knowing that overall survival may be marginally different, or in some cases not different at all, and how you perceive the benefit to your patients when thinking about these options if you're not massively increasing overall survival but you have this long progression-free survival period.

DR. MAILANKODY: Thank you. I'll give you my perspective. This is obviously very important, and I don't know that I know all the answers, but my perspective is the following, which is if you look at the earliest randomized studies -- those were some of the first studies I presented in relapsed/refractory refractive multiple myeloma, before we had the plethora of treatment choices we had available -- these are the studies that looked at lenalidomide and dexamethasone as a control arm and adding a novel drug or a new drug as

combination.

There were four studies that I highlighted. Each of them, the initial reports showed PFS and no difference in OS. And now with extended follow-up, three out of those four studies have also shown overall survival benefit. So I think that reflects that in an era when these studies were done, where there were limited post-progression treatment choices both here in the U.S. and internationally where these studies are done, it was a little bit easier to follow patients long enough and have a relatively accurate estimate of long-term overall survival.

What has changed in the last 5 to 7 years is that, number one, patients are living longer, which is a great challenge to have, and they're living longer because they can get multiple other lines of treatments. So increasingly common, the patients are progressing.

DR. FRIMPONG: Sorry, Dr. Mailankody. At this moment, there shouldn't be any discussion in regards to questions that's geared towards the

committee from your end.

DR. MAILANKODY: Oh, fair enough. Sorry.

DR. FRIMPONG: No problem.

Dr. Madan, I hand it back to you.

DR. MADAN: No problem.

Go ahead. Okay, continue with that guidance, Dr. Mailankody.

DR. MAILANKODY: So should I speak about that or --

DR. FASHOYIN-AJE: May I interrupt, please?

DR. MADAN: Go ahead. Who is this?

DR. FASHOYIN-AJE: Yes. Hi. Good morning. This is Lola Fashoyin-Aje from the Office of Clinical Evaluation in CBER. I would like to interrupt just to remind the committee and the chair that Dr. Mailankody is an FDA invited guest, and the purview and the scope of his participation today is to provide the disease overview, and he should not be weighing in on any questions related to the reason we are convening this ODAC today. Thank you.

DR. MADAN: Okay.

So I think we've got two -- well, let me see. I think we have two more questions here. Are hands still raised?

Dr. Lattimore?

MS. LATTIMORE: Hi. Thank you. Thank you for that background, though; it was incredibly helpful. You showed a slide that had 5th-line treatments or you showed a progression over time of where uptake of subsequent treatments waned over time and the use of subsequent treatments really narrowed, and you mentioned, in particular, access issues and access to CAR T in particular.

Can you share a little bit and expand on contributing factors to access to this treatment and what might play into that a little bit more?

DR. MAILANKODY: I will clarify that the data I presented from the study was from 2020, so the CAR T cells were not quite widely available quite yet, but the same themes hold true. What the data showed was that I think as you go further in lines of treatment, fewer and fewer patients get subsequent lines of treatment, and the reasons are

probably, one, is patients unfortunately die. Second is the median age, as I showed, is about 69 years for patients with multiple myeloma, so accrual of toxicities; inability to travel to treatment sites; and other reasons may preclude getting other lines of treatment.

Specifically about access to CAR T cells, I would say the challenges are that at this point, CAR T cells are available in limited specialized centers, so it's not every oncology practice or every oncologist that can give his or her patient CAR T cells currently; and therefore, patients need to be referred to specialized centers that have access to CAR T cells, number one.

The second is these are autologous CAR T cells, so there's somewhat limited availability of slots to apherese and manufacture that we hope will improve over time, but that also leads to a bottleneck. And the third, I guess, is that there are significant disruptions to patients own life. They have to sometimes relocate to a different city and live here for 4, 6, 8 weeks to get these

treatments, which may not be feasible for all patients or may not be considered for all patients. So all of those factors put together, I think the use of treatments like CAR T cells, particularly, and access to them continues to be a significant challenge.

MS. LATTIMORE: And can you give me an understanding of how many specialty centers exist currently?

DR. MAILANKODY: I think it's different for different products. I don't know the exact number, but I would guess it's somewhere between 50 to 100 sites across the U.S., but that's my estimate. And it's different for different products because different hospitals and health centers have licensing agreements with different products, and fact declaration is required for many of them; But I would say for the different approved indications for CAR T cells in myeloma and other diseases is somewhere between 50 to 100 sites perhaps, and they're all largely focused in larger cities and less access in rural areas and smaller cities. So

there are certain parts of the country where people may have to travel 2-3 hours before they get to the closest CAR T cell center.

DR. MADAN: Okay. Thank you, Dr. Mailankody, for that presentation and question and answer session. I think it informed the audience and our panel as well.

DR. MAILANKODY: Thank you.

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

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

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

So with that, we will now proceed with the Janssen Biotech presentation. I turn the floor over to you.

Applicant Presentation - Sen Zhuang

DR. ZHUANG: Good morning, Mr. Chair, members of the advisory committee, and members of the FDA. Sen Zhuang, Vice President of Oncology Research and Development from Johnson & Johnson. Thank you for the opportunity today to review the data supporting Carvykti, which will be referred to as cilta-cel, for the treatment of patients with relapsed and lenalidomide refractory multiple myeloma.

Cilta-cel is a BCMA or B cell maturation antigen direct CAR T therapy that is genetically

engineered from patients' own T cells to target multiple myeloma. It was approved by the U.S. FDA in February of 2022 for the treatment of patients with relapsed or refractory multiple myeloma who have received four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

Cilta-cel is among one of the most active agents ever developed for multiple myeloma. In the pivotal CARTITUDE-1 study, 97 patients with highly advanced multiple myeloma was treated with cilta-cel. The overall response rate was 98 percent and stringent complete response rate was over 80 percent. With extended follow-up, the median profession-free survival was 34.9 months compared with historic control of approximately 3 to 5 months in a similar patient population.

Today we are here to discuss the CARTITUDE-4 study and to seek an expanded indication for the treatment of patients with relapsed and lenalidomide refractory multi myeloma. The

CARTITUDE-4 study is an international, randomized-controlled, phase 3 study of cilta-cel in patients with relapsed or refractory multi myeloma who have received 1 to 3 prior lines of therapy and whose disease are refractory lenalidomide. This is a patient population with high unmet medical need, with a median progression-free survival of approximately 12 months with the current standard of care.

A one-time infusion of cilta-cel demonstrates clinically meaningful and highly statistical significant improvement in progression-free survival, the primary endpoint, and key secondary endpoints of overall response rate, complete response rate, MRD, or minimum residual disease, negativity rate compared with continuous standard therapy.

These deep and durable responses are not attainable by the standard treatment modalities, and with additional follow-up has translated into a strong trend in improvement of overall survival that has further strengthened as data mature.

Additionally, subgroup analyses demonstrate consistent benefit of cilta-cel in both progression-free survival and overall survival across all subgroups. You will hear that a safety profile observed in the cilta-cel CARTITUDE-4 study is consistent with its known safety profile in the approved label and is consistent with the mechanism of action as CAR T therapy.

The observed early imbalance of the progression-free survival and overall survival events are driven by patients who did not receive cilta-cel, and it was not due to cilta-cel toxicity. In totality, the data we will present today will support a positive benefit and risk for cilta-cel for the treatment of patients with a relapse in lenalidomide refractory multiple myeloma. Consistent with the study population of the CARTITUDE-4 study, the proposed indication is cilta-cel for the treatment of patients with relapsed or refractory multiple myeloma who have received at least one prior lines of therapy and whose disease is refractory to lenalidomide.

With this information in mind, here is the agenda of today's presentation. Dr. Irene Ghobrial from Dana-Farber Cancer Institute will discuss the continued unmet medical need for the treatment of patients with relapsed and refractory multiple myeloma, particularly in the area of lenalidomide refractory multiple myeloma, then Dr. Jordan Schecter from Johnson & Johnson will review the efficacy and safety data supporting today's application.

Finally, we have Dr. Sundar Jagannath from Mount Sinai in New York City who will conclude the presentation with his clinical perspectives. With us here are additional experts to help answer potential questions you may have. All outside experts have been compensated for their time for today's meeting. Thank you, and I'll now turn the presentation to Dr. Ghobrial.

Applicant Presentation - Irene Ghobrial

DR. GHOBRIAL: Thank you. My name is Irene Ghobrial. I'm a Professor of Medicine at Dana-Farber Cancer Institute, Harvard Medical

School. I'm a physician scientist working at Dana-Farber now for over 19 years. In addition to my work with patients with multiple myeloma, I run a translational lab, and I am currently the principal investigator of a clinical trial with cilta-cel in high-risk, smoldering myeloma. I'm happy to be here to review the background of multiple myeloma and the clear unmet need for this patient population.

Multiple myeloma is the second most common hematological malignancy. Over the last 15 years, survival has improved significantly. Before 2010, our patients only survived between 2 to 5 years. Since 2011, patients are living a median of 10 years and longer. This improvement is due to the use of ongoing combinations of therapy and the new era of immunotherapy, including CAR T therapy and bispecific antibodies. This has further strengthened the survival of our patients. Despite all of these advances, myeloma is still an incurable disease. We owe it to our patients to keep improving our therapies.

You've already heard about CARTITUDE-1 data and how CAR T therapy has emerged as an important late line treatment in multiple myeloma and has truly changed the landscape of patient care. The question we need to consider now is do we need to use this beneficial therapy once patients become lenalidomide refractory rather than the current indication following 4 lines of therapy.

I would personally say yes for several reasons. Multiple studies have shown that the use of our best therapy in earlier setting can lead to deeper remission and longer outcome for our patients with myeloma. We also know that patients are lost to attrition with each line of therapy. Biologically, T cells become more exhausted with advanced disease and subsequent lines of therapy; therefore, the development of CAR T cells from less exhausted T cells in an earlier disease setting would lead to the development of more robust CAR T cells, which would indicate that those T cells would have better long-term outcome. Additionally, the current standard of care in first relapse is

used indefinitely and is associated with its own toxicity profile. Using one-and-done CAR T therapy earlier helps improve the benefit for our patients.

Let me review each of these points more closely. Initial treatment is the best chance for deep and durable remission. You can see here the high attrition and death rate, which underscores the need to use more effective treatments earlier. Our patients may not live to the 4th or 5th line of therapy. With the current indication, as few as 15 percent of patients are able to receive cilta-cel as a treatment option.

Multiple studies have shown that the T cell repertoire changes over the course of the disease. This is a key research focus in my lab, where we are studying single cell sequencing of immune cells. Changes occur in the immune system during disease progression with a significant increase in exhausted T cells with each progression. We see that there are more terminally differentiated T cells at the later stages of the disease. Developing CAR T cells from less exhausted T cells

is beneficial.

Several studies have shown that naive-like, central memory T cells that are enriched in earlier disease stages are associated with a better clinical response. In addition, the longer PFS observed in CARTITUDE-1 was directly associated with a less exhausted stem-cell-like phenotype of the CAR product.

Here are the current treatment options in the second line of therapy, and many of them are not as effective in lenalidomide refractory disease. All of these options require continuous therapy and therefore come with added toxicity and added burden for the patient who has to think of their disease every day of their life. The potential benefit I can see using cilta-cel earlier is not only to provide patients a high response rate, but also a life without continuous therapy.

Here's a schematic to better understand the patient's journey with cilta-cel in the CARTITUDE-4 study. Upon relapse, we look to see if CAR T is a viable option for our patients with myeloma. Once

selected, we collect the T cells by doing apheresis, which is a simple one day outpatient procedure. Then all patients are put on at least one cycle of bridging therapy to control disease. In the CARTITUDE-4 protocol, this was specified to be one of two standards of care triplets; however, in clinical practice, the bridging therapy would be tailored to the individual needs of the patient.

The choice of bridging therapy continues to evolve. Our goal is to control the disease with bridging therapy before the patient receives CAR T therapy. Once we have all the T cells back, we perform lymphodepletion for 3 days with fludarabine and cyclophosphamide, and then we infuse the CAR T cells, and finally we closely monitor the patients for toxicities of the CAR T center.

With each successive relapse, symptoms return, quality of life worsens, and the chance and deterioration of response decreases. Patients with lenalidomide refractory multiple myeloma have poor outcomes with current standard therapy; therefore, there remains a significant and critical unmet need

for new therapeutic options in these patients to be used earlier in the treatment sequence. I can't emphasize enough that we should provide our patients with the best treatments as early as possible. This would help improve their outcomes, as they, unfortunately, may never get to later lines of therapy. CAR T offers our patients a great opportunity to have a deeper remission and a better long-term outcome.

Thank you. I'll turn the presentation to Dr. Schechter to review the clinical data.

Applicant Presentation - Jordan Schecter

DR. SCHECTER: Thank you, Dr. Ghobrial.

My name is Jordan Schechter. I am the Vice President for Clinical Development of Myeloma at Johnson & Johnson, and I'm pleased to present the clinical efficacy and safety data supporting cilta-cel based on the CARTITUDE-4 study. This study was designed in consultation with the FDA and other regulatory authorities worldwide. The study population in CARTITUDE-4 includes adults diagnosed with multiple myeloma who've received between

1 and 3 prior lines of therapy, including prior exposure to a proteasome inhibitor, an immunomodulatory drug, and additionally who are refractory to lenalidomide.

Prior to randomization, investigators selected the standard of care for each patient. With this decision, patients were to be randomized 1 to 1 to receive either standard of care or cilta-cel. Standard of care therapy consisted of the investigators' choice of either PVD, which is pomalidomide, bortezomib, and dexamethasone, or DPD, daratumumab, pomalidomide, and dexamethasone.

Patients randomized to cilta-cel underwent apheresis to acquire peripheral blood mononuclear cells, followed by at least one cycle of bridging therapy with the aforementioned standard of care triplet. Thereafter, patients received lymphodepletion consisting of cyclophosphamide and fludarabine for 3 days. Cilta-cel was then administered days 5 through 7 after the start of the conditioning regimen. Crossover was not part of the study design; that is, patients randomized

to standard of care did not have cilta-cel automatically offered at progression, although some patients did receive commercial or investigational CAR T at the discretion of the treating physician.

The primary endpoint of the study was progression-free survival. Key secondary endpoints included complete response or better; overall response; MRD negativity; and overall survival. The primary endpoint and major secondary response-related endpoints were assessed by the International Myeloma Working Group criteria using a computerized algorithm and also an independent review committee.

As you can see on this slide, the two arms were well balanced in terms of baseline demographics, disease characteristics, including patients with higher risk disease. The median age of study participants was around 61, with slightly greater proportion of male patients in both groups. Most patients in both arms had a baseline ECOG status of zero and an ISS stage of 1. Soft tissue plasmocytomas, which are known to be a high-risk

feature, were slightly higher in cilta-cel patients compared to standard of care patients.

The median time for myeloma diagnosis to randomization was 3 years, with approximately one-third of patients having one prior line and two-thirds having between 2 and 3 prior lines. About 60 percent of patients had high-risk cytogenetics and all were refractory to lenalidomide as per study entry criteria. About a quarter of patients were refractory to an anti-CD38 monoclonal antibody.

Here you can see the CONSORT diagram. The ITT analysis consisted of 419 patients randomized, 208 to cilta-cel, 211 to standard of care. Of these, 416 patients received any part of study treatment. This comprises our safety analysis set. Three patients were randomized to standard of care but were not treated. Of the 208 patients randomized to cilta-cel, 32 patients experienced disease progression or died prior to receiving cilta-cel as study treatment. Of those, 20 patients received cilta-cel as subsequent

therapy after disease progression. This leaves us with 176 patients in the as-treated patient population subset. There are currently 143 cilta-cel-treated patients who are still in ongoing follow-up for progression compared to only 77 patients who received standard of care.

Now, let's turn to our results starting with our primary endpoint. A one-time infusion of cilta-cel demonstrated clinically meaningful and statistically significant improvement in the primary endpoint of progression-free survival as compared to continuous therapy with standard of care. The median progression-free survival for cilta-cel was not reached. This compares to 11.8 months with standard of care.

In consultation with the FDA, we analyzed the primary endpoint in two ways. The prespecified primary analysis resulted in a weighted hazard ratio of 0.26. This indicates a 74 percent reduction in the risk of death or progression compared to standard of care. A weighted hazard ratio includes events which occur after 8 weeks.

The standard unweighted, intent-to-treat analysis, including all events, resulted in a hazard ratio for PFS of 0.40.

Now, the PFS curves do cross. This depicts an earlier balance of PFS events. In the first 8 weeks of the study, 22 PFS events were observed in the cilta-cel arm compared with eight in the standard of care arm; however, during this initial period, both arms were prescribed the same exact standard of care treatments; in fact, all 22 events in the cilta-cel arm occurred prior to cilta-cel infusion.

We'll review the crossing of the curves in more detail shortly. First, let's look at the overall data across subgroups. You can see that the cilta-cel benefit was consistent across every single subgroup test step. These data reaffirm that all patients have the potential to experience a meaningful benefit in terms of progression-free survival.

The progression-free survival results are supported by robust secondary endpoints, all

favoring cilta-cel versus standard of care. Cilta-cel demonstrated deep and durable responses following the single infusion. This resulted in a statistically significant odds ratio for obtaining a complete response or better of 10.3 between cilta-cel and the standard of care for the ITT population. In terms of overall response rate, 85 percent of all patients randomized to cilta-cel obtained the response compared to only 67 percent with standard of care.

Importantly, when we consider the 176 patients who received cilta-cel as study treatment, 99 percent, or 175 out of the 176 patients, had an overall response. The depth and durability of response observed with cilta-cel is something not observed with any other modality, and it is important for long-term outcomes such as progression-free survival and, of course, overall survival.

Now, let's look at the DOR curves. Duration of response includes patients who achieve the response of PR or better. The DOR is calculated

from the start of a response to the first documented evidence of disease progression or death, whichever comes first. Median DOR was not reached for cilta-cel and was 16.6 months for standard of care. Eighty-five percent of the patients in the cilta-cel arm were in response at 12 months compared to only 63 percent in the standard of care arm.

The endpoint of MRD, or minimal residual disease, was also met, with an odds ratio of 8.7 and a significant p-value of less than 0.0001 in the ITT population. MRD negativity is highly indicative of long-term outcomes, and therefore it's a very meaningful measure for patients. In patients evaluable for MRD, 88 percent in the cilta-cel arm achieved MRD negativity at 10 to the minus 5 threshold compared to only 33 percent in the standard of care.

Now, of course, overall survival is a key secondary endpoint, so let's take a look at the most recent data. Our most recent data cut for overall survival was in December of 2023. This was

conducted at the request of the European Medicines Agency. At this point, we've observed 48 deaths in the cilta-cel arm, 77 deaths in the standard of care arm, and the resulting hazard ratio for OS is 0.57. Now, additional follow-up will not change the early portion of the curve; however, we see an increasing separation of the OS curves over time. And when we look at the forest plot in OS using the most recent data cut, we also see consistent effect favoring cilta-cel for each and every subgroup assessed.

Looking further into the deaths, the only period in which we see more deaths on the experimental alarm versus standard of care arm is between 0 and 3 months. There were 7 deaths in the experimental arm and one death in the standard of care arm. Recall that most patients who progressed early did so prior to cilta-cel treatment, so a more informative way to look at these data is to break it out by cilta-cel exposure.

Here you can see that six out of the seven deaths prior to 3 months were in patients

randomized to cilta-cel but progressed prior to the infusion, and thus never received cilta-cel. There was one patient who received cilta-cel as a subsequent therapy post-disease progression. Now, it is this imbalance that is driving the initial crossing of the OS curves; thereafter, OS events are balanced between months 3 and 6 and then tend towards improvement, with fewer deaths observed in the experimental arm compared to the standard of care.

Let's take a closer look at these early deaths by cause. This slide presents the ITT analysis, including all events occurring after randomization. We see that most early deaths occurred in patients randomized but did not yet receive cilta-cel, and this was driven by early progression of disease. As you can see, more patients progressed on the standard of care arm compared to those who were actually treated with cilta-cel.

Five out of the eight AEs leading to death were in patients with progressive disease and

received cilta-cel in subsequent therapy. As I will review in the safety section, these rapidly progressing patients are more vulnerable, and thus more likely to experience serious AEs. This helps reinforce the value of disease control prior to lymphodepletion and cilta-cel infusion.

In patients that obtained disease control and received cilta-cel as study treatment, there were only 3 AEs leading to death, and these were all due to COVID-19 infections. Importantly, these deaths occurred during the height of the pandemic and also occurred in patients who are not fully vaccinated.

The same trends are seen in PFS, with the imbalance in progression occurring early, within the first 2 months in patients that either never received cilta-cel or those who received cilta-cel as subsequent therapy after disease progression. None of the 22 patients who progressed within the first 8 weeks actually received cilta-cel treatment. By month 2 and beyond, we start to see more PFS events occurring in the standard of care

arm.

Now, we've performed an extensive analysis to see if any parameters explain the imbalance in early progression on the cilta-cel arm prior to the cilta-cel infusion. Some of the parameters we assessed are listed here, but now let me show you a schematic to help visualize these investigations and also provide a summary of our findings.

As shown previously, the baseline demographics and disease characteristics, even those indicative of higher risk disease, were well balanced at study baseline. We also looked at study related factors such as the apheresis procedure and the time for randomization to start of therapy. The median time from randomization to start of therapy was 6 days in standard of care compared to 7 days in the cilta-cel arm, and this was all within the protocol-specified, 7-day randomization window.

We assessed the CAR T cells manufacturing time as well. The median time from apheresis to product release for patients with early PFS versus

those without early PFS was 59 days versus 57 days. The median number of days patients spent off bridging therapy prior to progression was zero, ranging from 0 to 15. This indicates that most patients were actively receiving bridging therapy at the time of disease progression; therefore, it is unlikely that manufacturing time played a major role in the early PFS events. Patients who had early PFS events did not start lymphodepletion, so exposure to lymphodepletion could not have been a cause of early progression.

Finally, we looked at the dose intensity of bridging therapy. Of the many analyses we conducted, we found that the lower relative dose intensity of bridging therapy may have contributed to the imbalance in early progression, although to what extent is unclear. Per protocol, doses of bridging therapy can be decreased secondary to patient tolerability and at the discretion of the treating physician.

We evaluated the relationship between dose of bridging therapy and the occurrence of early PFS

events. You can see that there was a lower relative dose intensity of pomalidomide, as well as a lower relative dose intensity of bortezomib in patients randomized to cilta-cel compared to standard of care. The doses of dexamethasone and daratumumab were well balanced between the arms, and then when we looked at patients who had early PFS events across both treatment arms, a lower relative dose intensity of pomalidomide or bortezomib may have been associated with a higher risk of progression.

Again, the clinical impact of these differences is unclear, but these differences do emphasize the need to optimize bridging therapy and provide standard doses of bridging therapy to help control disease before lymphodepletion and CAR T administration.

Now, to summarize the efficacy findings, a one-time infusion of cilta-cel demonstrated deep responses with statistically significant and clinically meaningful improvement in progression-free survival that's expected to contribute to

prolonged overall survival. The primary endpoints of PFS achieved a hazard ratio of 0.40, indicating a 60 percent reduction in the risk of death or progression for cilta-cel compared to standard of care. Additionally, cilta-cel showed significant improvement in measurements of disease burden, and while the overall survival data are still maturing, the data we have to date suggests an improving trend for prolonged survival with cilta-cel versus standard of care, and importantly, the beneficial results were consistently observed across every subgroup that we assessed.

Now, let's turn our attention to the safety data supporting our application. As described earlier, the sponsor's safety analysis originally included 208 patients in each arm who received any part of study treatment. The FDA has asked us to base the safety on those who received cilta-cel product that met all release specifications. This includes 188 patients in total; 170 out of the 176 patients received a conforming cilta-cel product as study treatment, and 18 out of the

20 patients that received cilta-cel as subsequent treatment received a conforming product.

The overall safety profiles between the original safety analysis with 208 patients and the FDA's requested safety analysis with 188 patients is very similar; therefore, for simplicity, we will present only these data for the FDA safety analysis set. Overall, the safety profile was similar between the arms and consistent with the approved cilta-cel label, as well as the known mechanism of action of CAR T cell therapy. All patients in both arms experienced one or more adverse events and most experienced one or more grade 3 or 4 adverse events. Thirty-five percent and 38 percent of patients reported a non-fatal serious adverse event in cilta-cel and standard of care, respectively.

As of the November 2022 data cutoff, adverse events leading to death were reported in 11 percent of patients in the cilta-cel arm and 8 percent of patients in standard of care, but using the most recent data cut in December of 2023, deaths due to adverse events were reported in 12 percent versus

13 percent of patients. This helps address part of the FDA's concern regarding the imbalance of AEs leading to death.

Of those AEs leading to death, most were due to infections in either arm, the most common infection being COVID-19 in the cilta-cel arm. Hemorrhage and AML/MDS were also seen in 2 percent of cilta-cel patients. The adverse events in the cilta-cel arm were consistent with the known safety of approved cilta-cel and the known mechanism of action of CAR T cell therapy.

Adverse events that occurred at a rate of greater than or equal to 30 percent in either arm are presented here. All of these events observed are already described in the current label for cilta-cel. The most common grade 3 to 4 adverse events were cytopenias. This was to be expected based on the mechanism of action of CAR T cell therapy and easily managed with supportive care by the treating physician. Serious adverse events were reported for 38 percent of patients in cilta-cel and 39 percent of patients in the

standard of care arm. The most commonly reported SAEs were pneumonia and viral infection across both arms.

Now, let me briefly share the adverse events of special interest for cilta-cel. We see that CAR T-specific AEs were largely as expected. Most cases of cytokine release syndrome were low grade and resolved in about 3 days after onset. Rates of neurologic toxicity, including ICANS, cranial nerve palsies, peripheral neuropathy, and movement and neurocognitive toxicity, or MNT, were all relatively low, and most had resolved by the data cutoff.

We also investigated secondary primary malignancies. The overall incidence of secondary primary malignancies during the study was similar across both arms. In both, the most common malignancies were cutaneous and non-invasive cancers. Three percent of patients in the cilta-cel arm had a hematologic secondary malignancy, including myelodysplastic syndrome, acute myeloid leukemia, and one patient who

developed CAR T positive peripheral T cell lymphoma. The non-cutaneous and invasive solid organ malignancies were balanced between the two arms.

We also investigated the safety data for patients who received cilta-cel as subsequent therapy after progression relative to those who had successful bridging therapy. You see that all patients reported an adverse event, and patients who received cilta-cel post-progression, which is denoted in the light blue column, were more likely to experience a serious adverse event. More of these patients also died to adverse events.

In contrast, patients that received cilta-cel as study treatment, which is in the dark blue column, had a similar risk for fatal AEs compared to the standard of care arm, and it's understandable that patients with early progression of the disease would experience more serious adverse events and more adverse events leading to death. The deaths due to adverse events in patients who received cilta-cel as subsequent

treatment were mainly driven by infections and bleeding events, and this was at a higher percentage than those who received cilta-cel as study treatment.

We compared CAR T-specific adverse events for the patients who received cilta-cel as subsequent therapy versus patients who received cilta-cel as study treatment. As you can see in this table, there are more AESIs overall and more severe AEs reported for patients who received cilta-cel as subsequent therapy post-progression. This further highlights the importance of controlling disease prior to lymphodepletion and CAR T cell infusion.

In conclusion, safety findings from the pivotal CARTITUDE-4 study were consistent with the previous cilta-cel experience and the known mechanism of action of CAR T cells. Our findings suggest a reduction in the rate and severity of CAR T-specific AEs in an earlier disease setting compared to heavily pretreated relapsed/refractory myeloma as in CARTITUDE-1.

I'd like to thank the committee for their attention. I'd now like to invite Dr. Sundar Jagannath to share his clinical perspective on these data.

Applicant Presentation - Sundar Jagannath

DR. JAGANNATH: Thank you. I'm Sundar Jagannath, the Director of Multiple Myeloma at Tisch Cancer Institute and Professor of Medicine at Icahn School of Medicine at Mount Sinai, New York. I'm happy to be here today to share my clinical perspective on the data I just reviewed and the importance of having cilta-cel as an option for our patients with lenalidomide refractory multiple myeloma.

Overall, the data observed in CARTITUDE-4 were outstanding. The progression-free survival improvements observed were clinically meaningful with strong trends towards improved overall survival. The minimum residual disease negativity, or MRT negativity, of 88 percent for evaluable patients further supports the potential for improved long-term outcomes and data were

consistent across all the subgroups. The data do not support exclusion of any subset of patients and all patients have the potential to experience meaningful benefit from cilta-cel. As discussed, the imbalance in early progressions occurred mostly in patients who did not receive cilta-cel, speaking to the need for disease control prior to cilta-cel infusion.

For patients who relapsed after 1 to 3 prior lines of therapy, several triplet regimens have been approved; however, these regimens have largely been tested in variable lenalidomide naive or lenalidomide sensitive patients. Among patients with the triplet regimen, median progression-free survival is around 12 months, with longer median progression-free survival noted for the CANDOR and IKEMA studies, which were largely not lenalidomide refractory patients. Additionally, the response shown in these studies relies on ongoing therapy until progression of disease, potentially resulting in cumulative toxicity and significant treatment burden.

The MRD negativity rates for cilta-cel are impressive, as MRD is an important marker for depth and durability of remission. With a one-time administration, cilta-cel produces responses unattainable with other modalities. Of course, we must consider the safety in our determination of benefit-risk. There are risks with cilta-cel, as with any therapy; however, these are well understood by physicians and are manageable. CRS and ICANS, for example, were mostly mild in CARTITUDE-4 and all resolved. There is also my experience in clinical practice, as we know how to manage these events.

Infections are a known risk and well-established management protocols are already in place. Most of the fatal infections observed in CARTITUDE-4 were due to COVID-19, which has now been minimized through less prevalence of serious COVID, vaccinations, and our understanding of the disease. It is also important to consider that the safety profile appears to be even better when used in the earlier line setting.

There is less incidence and severity of CRS and neurotoxicities, including MNT, movement and neurocognitive toxicity being reported in CARTITUDE-4 than in the prior CARTITUDE-1 study. This continues to support the positive benefit-risk for patients with 1 to 3 prior lines of therapy. Not only are there receiving all the benefits of CAR T therapy before T cell exhaustion, but their safety profile tends to be more favorable.

To contextualize the safety profile, here again I show cilta-cel compared to other available treatments of relapses and refractory multiple myeloma. You can see that cilta-cel has fewer serious adverse events versus its counterparts. Cilta-cel is a one-time infusion; however, the other triplet regimens are given continuously until disease progression, imparting additive toxicity and treatment burden.

Cilta-cel brings significant clinical benefit compared to other approved therapies, based on improved efficacy, and has changed the treatment landscape for late-stage patient care. Being able

to provide these deep and durable responses and the chance for improved progression-free survival and overall survival to patients with lenalidomide refractory myeloma would be invaluable. Saving the best therapy for last would not be good, particularly in lenalidomide refractory myeloma, as these patients tend to have worse outcomes.

While scientifically we want to understand the imbalance in early progression observed in the cilta-cel arm, we know from the data this was prior to cilta-cel infusion. Regardless of the reason for the imbalance of the overall benefit-risk, it remains overwhelmingly positive. Based on the data and my experience with the drug, cilta-cel would be an appropriate treatment option for all patients who meet the criteria consistent with CARTITUDE-4 enrollment. I hope to see this transformative treatment option available to early align patients. I appreciate your time and consideration. This concludes our presentation. Thank you.

DR. MADAN: We will now proceed with FDA's presentations, starting with Dr. Helkha

Peredo-Pinto.

FDA Presentation - Helkha Peredo-Pinto

DR. PEREDO-PINTO: Good morning. I'm Helkha Peredo-Pinto, a pediatric hematologist/ oncologist in the Division of Clinical Evaluation Hematology in the Office of Clinical Evaluation in CBER, and the primary reviewer for the supplemental biological license application 125746/74 for Carvykti, or ciltacabtagene autoleucel, which I will refer to as cilta-cel during my presentation.

Cilta-cel is an autologous CAR T cell therapy approved for the treatment of relapsed/refractory multiple myeloma. The applicant seeks expansion of the indication, as I will discuss in my presentation. Listed on the slide are the members of the FDA review team who contributed to my presentation.

The applicant submitted the results of the phase 3 CARTITUDE-4 trial to demonstrate the safety and efficacy of cilta-cel for the proposed indication. CARTITUDE-4 compares cilta-cel to standard therapy in patients with relapsed/

refractory multiple myeloma who have received a proteasome inhibitor and an immunomodulator drug and who are refractory to lenalidomide. The trial met its primary endpoint, demonstrating a statistically significant improvement in progression-free survival for patients randomized to the cilta-cel arm compared to the standard therapy arm.

During the review of the application, we identified an increased rate of early deaths in the cilta-cel arm compared to the standard therapy arm. As a key issue, this issue is the main topic of discussion at this Oncologic Drug Advisory Committee meeting.

During my presentation, I will provide a very brief overview of the treatment of relapsed/refractory multiple myeloma and provide a brief regulatory background. I will then summarize the key efficacy and safety results from CARTITUDE-4 and present the main topic for discussion. My colleague, Dr. Wang, will then provide an overview of the statistical

considerations pertaining to the main topic of discussion. I will conclude my presentation by briefly discussing FDA's consideration of the PRO data submitted in the application and presented in the discussion and voting question.

As discussed by Dr. Mailankody in the detailed overview of multiple myeloma treatment, shown here is the current treatment landscape for treatment of relapsed/refractory multiple myeloma. Please note, and as discussed by Dr. Mailankody, the treatment landscape has changed drastically over the last decade with multiple approvals. Combination regimens typically include patients that fall within the three main classes. This includes immunomodulator drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies.

For patients who have received 1 to 3 prior lines of therapy, including a PI and an IMiD, several treatment options exist, as shown in the slide. Highlighted regimens on the slide were used in the CARTITUDE-4 trial. Also available as options for treatment in the relapsed/refractory

setting are cytotoxic polychemotherapy, cell-based therapies by specific T-cell engagers, and also two CAR T therapies.

Cilta-cel is an autologous CAR T therapy that targets B-cell maturation antigen, which is expressed on the surface of normal and malignant plasma cells. Cilta-cel was approved in 2022 for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of systemic therapy, including an IMiD, a PI, and an anti-CD38 monoclonal antibody. Approval was based on CARTITUDE-1, a single-arm, open-label trial in 97 efficacy available patients with relapsed/refractory multiple myeloma, with a median of 6 prior lines of therapy.

The overall rate response was 97.9. Median duration was not reached. The ORR and the durability were considered a clinical benefit in this patient population. The approved dose is 0.5 to 1 million viable CAR positive cells per kilogram of body weight. The cilta-cel product labels include a boxed warning for cytokine release

syndrome; neurological toxicities; hemophagocytic lymphohistiocytosis macrophage activation syndrome, HLH/MAS; prolonged and recurrent cytopenia; and secondary hematological malignancies.

With the current submission, the applicant is seeking an indication for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least one prior line of therapy, including an IMiD and an PI, and who are lenalidomide refractory. The proposed dose is the same as the approved dose of 0.5 to 1 million viable CAR positivity cells per kilogram of body weight. The data to support the indication is based on the results from CARTITUDE-4, which I will now discuss.

CARTITUDE-4 is an ongoing, open-label, randomized-controlled trial that enrolled patients with relapsed/refractory multiple myeloma who had received 1 to 3 prior lines of therapy, including a PI and an IMiD, and who were refractory to lenalidomide. Patients were randomized 1 to 1, either to standard therapy arm or cilta-cel arm.

The standard therapy arm included either the PVD or the DPD regimens, which were continued until disease progression or toxicity. The cilta-cel arm included leukapheresis; bridging therapy; which is administered to stabilize the disease during the product manufacture; lymphodepleting chemotherapy; followed by the cilta-cel infusion.

Patients could receive one or more cycles of bridging therapy during the product manufacture. Of note, the investigator selected the standard therapy and bridging therapy prior to randomization, based on prior therapies. The primary endpoint was progression-free survival per an independent review committee assessment. The key secondary endpoints were overall response rate, overall survival, and patient-reported outcomes. Patients from the standard therapy arm were not allowed to cross over the cilta-cel arm.

The primary efficacy and safety results presented today are based on the clinical cutoff date of November 1, 2022, corresponding a median duration of follow-up of 15.9 months and represents

the protocol-specified interim analysis of PFS, where approximately 75 percent of the total progression-free survival events have occurred.

I will summarize the efficacy analysis plan for CARTITUDE-4. The statistical analysis plan prespecified three interim overall survival analyses. The first interim OS analysis occurred at the time of the primary PFS, and the second OS analysis will occur at the time of the final PFS analysis. The third interim analysis for OS is explained when approximately 200 deaths have occurred. A final OS analysis powered at 80 percent will occur when 250 deaths have occurred. The overall type 1 error rate is controlled at two-sided 0.05. Currently, the first interim analysis for overall survival has already occurred. The second, third, and the final OS analysis results are awaited.

In the next few slides, I will briefly review the study results. Shown here are the baseline demographics of the study population. The median age of the study population was 61 years,

which is younger than the median age of 69 years at diagnosis in the United States. The older population, racial and ethnic minorities, were underrepresented in the study. Only 15 percent of the subjects were enrolled from the North America region. Most subjects enrolled had an equal performance status of 0 or 1. It is important to mention that baseline disease factors that are indicative of poor prognosis, such as high-risk cytogenetics, presence of extramedullary plasmacytoma, and ESS [indiscernible - 2:14:04/ISS] stage 3 were balanced across arms.

The majority of the subjects received one or two prior lines of therapy. Only 26 percent of the subjects received a prior anti-CD38 monoclonal antibody and 15 percent of the subjects were triple-class refractory. Only 40 percent of the patients had a high-risk cytogenetic feature. None of the subjects received four or more lines of therapy, the population currently approved to receive cilta-cel. Overall, the study population enrolled in CARTITUDE-4 was not heavily pretreated.

I will now describe the primary efficacy analysis. Treatment with cilta-cel is associated with a statistically significant improvement in the PFS per IRC assessment compared to the standard therapy arm, as noted by the applicant. The median PFS was 12 months for the standard therapy arm and it was not reached for the cilta-cel arm at the time of the data cutoff date.

I would like to draw your attention to the early part of the Kaplan-Meier curve, which indicates inferior PFS in the cilta-cel arm compared to the standard therapy arm and to the data in the table highlighted by the red box, which indicates that a greater proportion of PFS events in the cilta-cel arm are due to deaths compared to the standard therapy arm. I will discuss this issue in a subsequent part of my presentation.

Overall survival was a key secondary endpoint. The first interim OS analysis done at the time of the primary PFS analysis is shown in the slide. Twenty percent of the study population had died at the time of the primary PFS analysis.

The results show a lower overall survival in the cilta-cel arm compared to the standard therapy arm that appears to extend to 10 months, with the curves crossing after that. The crossing pattern of the Kaplan-Meier curves for overall survival renders the average hazard ratio not interpretable. There's a significant censoring after the curves cross, indicating that the data are immature. I will discuss the FDA's concerns with the OS-related results in detail later in my presentation.

In summary, a statistically significant improvement in median PFS with cilta-cel is observed compared to standard therapy. Median PFS was not reached for cilta-cel compared to 12 months for the standard therapy. We observe a higher proportion of PFS events in the cilta-cel arm are due to deaths compared to the standard therapy arm. There were 17 deaths in the cilta-cel arm versus only 4 deaths in the standard therapy arm, and immature overall survival with 30 percent information fraction, we observe an early OS that remained in the cilta-cel arm with a pattern of

crossing of the curves.

I will now present a brief overview of safety. Safety was assessed in all subjects who received conforming cilta-cel in the investigation arm, including subjects randomized and treated under the study and those randomized and treated after disease progression. Overall, the rate of grade 4 adverse event was higher in the cilta-cel arm compared to the standard therapy arm. In the safety population, deaths due to adverse events were higher in the cilta-cel arm compared to the standard therapy arm, 11 percent in the cilta-cel arm compared to 8 percent in the standard therapy arm, as is shown in the last row of the table.

Cytokine release syndrome, neurotoxicity, HLH/MAS, and secondary malignancies are known safety concerns for cilta-cel. Overall, the rate of grade 3 or higher CRS, neurotoxicity, and HLH/MAS was higher in the cilta-cel arm, as was the rate of grade 3 or higher neutropenia and thrombocytopenia.

The overall rate of hematological neoplasm

was higher in the cilta-cel arm. At the time of the 120-day safety update, two new cases of myelodysplastic syndrome in the cilta-cel arm were also reported, bringing the number of patients with secondary hematological malignancies to five, with 2.6 percent in the cilta-cel arm versus none in the standard therapy arm. The major issue we would like to focus on today is the increased rate of early deaths in the cilta-cel arm compared to the standard therapy arm noted in the CARTITUDE-4 trial.

Before I review the FDA assessment of the major issue, I would like to briefly highlight the multiple steps between randomization and CAR T cell infusion, although, traditionally, the safety risks due to the treatment are considered in subjects who actually received the treatment. For CAR T cell therapy, the risk associated with administration of CAR T cell therapy is a process. It starts with the risk of leukapheresis, bridging therapy -- which in CARTITUDE-4 consisted of the same choice of regimens as the control arm, either

PVD or DPD -- delays in manufacture resulting in adverse clinical outcomes, and toxicity from lymphodepleting regimen. All these risks should be considered integral to the benefit-risk assessment of CAR T cell therapy.

Since randomization balances for known and unknown prognostic factors, an assessment of overall survival and safety of randomized patient informs the benefit-risk assessment of any investigational therapy in a randomized clinical trial. Although PFS has been accepted as a primary endpoint and has supported traditional approval in multiple myeloma trials, it's always evaluated at the time of the primary PFS assessment. Particularly for therapies with significant toxicity, assessment of overall survival is important to ensure that there is a favorable benefit-risk assessment.

As I mentioned before, the data in CARTITUDE-4 indicated that a greater proportion of PFS events in the cilta-cel arm were due to deaths compared to the standard therapy arm, as shown in

the table highlighted by the blue box. The progression-free survival plot shows a crossing hazard pattern as well. FDA conducted additional analyses to evaluate the increased rate of early deaths observed in CARTITUDE-4. FDA analysis indicated an increased rate of death in the cilta-cel arm in the first 10 months post-randomization. As shown in the table, 14 percent of the patients in the cilta-cel arm died in the first 10 months compared to 12 percent in the standard arm of therapy. This includes an increased rate of death primarily for adverse events.

Due to the increased rate of death in the cilta-cel arm, FDA further analyzed deaths occurring in the first 10 months post-randomization. It is notable that almost 5 percent of the patients randomized to the cilta-cel arm died without receiving the intended CAR T cell infusion within 10 months compared to almost none of the standard therapy arm.

Although we note the difference in early

deaths in patients who did not go on to receive cilta-cel, as I stated previously, these patients started the process to cilta-cel therapy and had received leukapheresis and bridging therapy. These are still relevant in the assessment of the benefit-risk of cilta-cel. Within the treated patients, the rate of deaths from adverse events is higher in the cilta-cel arm in the ITT population, as is highlighted in the last row of this table.

Analysis of the patients who died within 10 months post-randomization demonstrated that patient attrition occurred at different steps in the process of receiving CAR T cell therapy. This includes patients who were randomized to proceed with leukapheresis and did not receive lymphodepletion; therefore could not proceed to receive cilta-cel infusion.

Thirty-two subjects in the cilta-cel arm experienced progressive disease or death prior to receiving the study treatment; however, there is no clear reason for these 32 early progression of disease or deaths. Twelve patients never received

cilta-cel, and 10 out of those died within 10 months of randomization. Twenty subjects went on to receive cilta-cel as a subsequent therapy after progression and eight died within 10 months of randomization.

Since the role of bridging therapy is to stabilize the disease while awaiting product manufacture, we conducted an exploratory analysis of the recipients of bridging therapy in the patients who progressed or died early and compared it to the patients that received cilta-cel. I would like to point out that while the protocol allowed one cycle of bridging therapy, additional cycles could be administered based on patient risk status and cilta-cel availability. Cycle 2 and following cycles of bridging therapy could be truncated to allow for adequate washout [indiscernible - 2:24:14] for the patient.

In CARTITUDE-4, investigators selected the optimal bridging therapy from the two protocol-specified regimens based on clinical considerations similar to the standard therapy arm.

All the subjects received, and while there were minor differences, the overall bridging therapies in both groups were similar. There are limitations to this analysis, including a small number, and post hoc analysis

To further analyze the early dates in CARTITUDE-4, FDA conducted exploratory analysis to assess whether any particular prognostic subgroup was associated with the higher early mortality in the cilta-cel arm. This slide demonstrates that the increased early mortality with cilta-cel was observed across prognostic subgroup and was observed even in the absence of individual poor prognostic factors. The study was not designed to characterize a heterogeneous study population, which may have contributed to a higher early mortality in the cilta-cel arm.

Since most of the CAR T cell therapy-related toxicities have onset within 90 days of product infusion, and given the higher early death rate in the cilta-cel arm, we analyzed deaths within 90 days of treatment start in the safety population

for patients that received conforming cilta-cel or any treatment in the standard therapy arm. The overall death rate for adverse events in the safety population was higher in the cilta-cel arm compared to the standard therapy arm, 11 percent versus 8 percent. Similarly, deaths due to adverse events within 90 days of treatment start was higher in the cilta-cel arm compared to the standard therapy arm, 4 percent in the cilta-cel arm versus zero in the standard therapy arm.

This table shows the cause of death from treatment-emergent adverse events in the safety population in CARTITUDE-4. Overall, the most common cause of death in both arms was infection. In summary, we observe a higher rate of deaths in the first 10 months after randomization in the intent-to-treat population, 14 percent in the cilta-cel arm versus 12 percent in the standard therapy arm.

Additionally, there is a higher rate of deaths in the safety population due to adverse events. Similarly, a major difference is observed

between the two arms when analyzing death from adverse events within 90 days of treatment start, which was 4 percent in the cilta-cel arm versus zero in the standard therapy arm.

Overall survival is the ultimate clinical benefit endpoint because it is not subject to biased assessment and because prolongation of life in the setting of life-threatening and fatal disease is a clinical benefit. OS not only provides an estimate of efficacy but also a safety. Particularly for therapies with significant toxicity, evaluation of overall survival is important to ensure that there is a favorable benefit-risk assessment.

During the FDA review period, the applicant provided updated Kaplan-Meier curves based on the clinical cutoff of April 17, 2023 for the 120-day safety update, the figure on the left with the information fraction of 44 percent. Most recently, the applicant provided another overall survival update with a cutoff of December 13, 2023, as shown in the figure on the right with information

fraction of 50 percent. Of note, both OS analyses were unplanned and no statistical testing was performed.

While there is a further separation of the curves, the OS data is still immature with only 50 percent information fraction at the latest unplanned data cutoff. In addition, as we can see from the two Kaplan-Meier curves, for OS in this slide, our major concern regarding the early OS detriment is still evident with longer follow-up of OS data.

While CARTITUDE-4 demonstrated a statistical significant effect on PFS and overall response rate in the relapsed/refractory multiple myeloma population enrolled, an increased rate of early deaths was observed as described. Given the higher rate of early deaths in the cilta-cel arm, there is uncertainty if the overall benefit-risk assessment is favorable.

I will now invite the statistical reviewer, Dr. Wang, to provide the biostatistical considerations on the OS analysis for CARTITUDE-4.

FDA Presentation - Cong Wang

DR. WANG: Thank you, Dr. Peredo-Pinto.

Good morning, everyone. I'm Cong Wang, the biostatistical reviewer for the Carvykti application. I'm from the Division of Biostatistics, CBER, FDA. In the next few slides, I will present FDA's biostatistical considerations regarding OS analysis on the CARTITUDE-4 study.

This slide shows FDA's efficacy result on the primary endpoint, PFS, and key secondary endpoint, OS, as discussed earlier in the presentation. The figure on the left shows the Kaplan-Meier curves for PFS per IRC, based on the ITT population. As mentioned by my colleague, Dr. Peredo-Pinto, it shows a statistically significant result with a hazard ratio of 0.41 and p-value less than 0.0001. The figure on the right shows the Kaplan-Meier curves for OS, based on the ITT population, with a data cutoff date of November 1, 2022.

In the presence of a crossing hazards pattern, survival curves occurred at approximately

10 months after randomization. A single average hazard ratio across the entire cause of a study is not able to accurately capture its overall treatment effects profile at different time points; therefore, it is difficult to interpret, and it can be misleading.

We calculated the piecewise hazard ratio of overall survival. The piecewise hazard ratio is 1.04 before the crossing time point. There is heavy censoring afterwards, indicating that OS data is immature. Of note, there was a similar crossing hazards pattern in PFS as in OS; however, the crossing occurred much earlier and was followed by a large and sustained PFS benefit.

The observed early OS detriment is FDA's major concern. We evaluated the potential causes for the early deaths in the cilta-cel arm. One concern with subjects' specific cell therapy is that subjects may suffer morbidity or mortality while waiting for the product to be available. This may have contributed to the early mortality in the CARTITUDE-4 study in the subjects randomized to

the cilta-cel arm. It is also possible that there were product-specific toxicities leading to early deaths. As discussed earlier in the presentation, these subjects started the cilta-cel regimen and had received leukapheresis, bridging therapy, and lymphodepletion.

As mentioned by my clinical colleague, Dr. Peredo-Pinto, there were 32 subjects who experienced progressive disease or died prior to receiving the cilta-cel infusion. Among those 32 subjects, 20 subjects went on to receive cilta-cel as subsequent therapy after progression. Of those 20 subjects, 10 died as of the data cutoff date. It is difficult to determine which death had cilta-cel toxicity as a contribution factor or for which the delayed administration of cilta-cel was the main cause.

Another key question for this application is the duration of the period of increased risk of early death in the cilta-cel arm compared to the standard therapy arm. Because the Kaplan-Meier survival curves cross, a single average hazard

ratio does not provide an interpretable estimate of the entire time dependent [indiscernible - 2:33:36] in the effects profile of cilta-cel of overall survival.

There was a statistical analysis, such as piecewise hazard ratio assessment, conducted based on selected landmark time points that may provide alternative ways to estimate the treatment effect. For example, presented in this slide is FDA's additional analysis on piecewise hazard ratio assessment based on different time cutoffs. On the top, you can see the piecewise hazard ratio for overall survival was 3 months cutoff, while on the bottom, you can see the piecewise hazard ratio with cutoffs of 5 or 10 months.

Based on this assessment, the increased risk of death on the cilta-cel arm goes beyond 3 months after randomization. It appears to persist until at least 5 months and possibly up to 10 months. While an analysis such as this piecewise hazard ratio assessment may provide information to support a benefit-risk assessment, such analysis has

limitations. For example, choosing the cutoffs for such approaches retrospectively, based on observed outcomes, limits generalizability of the findings and lacks the clinical or biological rationale, leading to an unreliable estimate that is unlikely to be replicated in future studies.

Now, I will turn it back to my clinical colleague, Dr. Peredo-Pinto, for the rest of the presentation. Thank you.

FDA Presentation - Helkha Peredo-Pinto

DR. PEREDO-PINTO: Thank you, Dr. Wang.

I will now briefly mention the PRO data presented by the applicant. Because the purpose of a PRO measure is to capture the patient's experience, FDA welcomes the inclusion of PRO data in regulatory submissions. PRO endpoint time to worsening of symptoms in the MySIm-Q Total Symptom Score was not formally tested since it follows OS in the statistical hierarchy; therefore, no conclusion can be made. Some of the limitations are infrequent assessment of PROs early in the trial during acute CAR T toxicity, and the

longitudinal PRO data does not include the experience of patients with early mortality.

In conclusion, the overall survival result from the CARTITUDE-4 study demonstrated a benefit in the PFS and overall response rate in a relapsed/refractory multiple myeloma population who had received 1 to 3 prior lines of therapy and was lenalidomide refractory. An increased rate of early deaths was observed in the cilta-cel arm compared to those randomized to the standard therapy arm. The study was not designed to identify predictive factors for early mortality observed with cilta-cel. The higher rate of early deaths appears to be an inherent risk of autologous CAR T cell therapy. Overall, there is an uncertain benefit-risk of cilta-cel in the proposed proposed population.

Please, discuss whether the results of CARTITUDE-4 are sufficient to support a positive risk-benefit assessment of ciltacabtagene autoleucel for the proposed indication. Is the risk of early death associated with ciltacabtagene

autoleucel acceptable in the context of the PFS benefit?

Displayed on this slide is the voting question. This concludes my presentation. Thank you for your attention.

Clarifying Questions

DR. MADAN: Thank you.

We will now take clarifying questions for Janssen Biotech and the FDA. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon after you have asked your question. When acknowledged, please state your name for the record before you speak and direct your question to a specific speaker. If you wish for a specific slide to be displayed, please let the slide number be known, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you or, "That is all for my question," so we can move on to the next panel member.

If I could use maybe the chair's

prerogative, if one exists, and maybe ask the first question of the FDA, and this is in reference to slide 15 and slide 20. You highlight that the primary concern here is early deaths, and I think you display a lot of numbers on slide 15 and 20, and maybe 26 as well, but the statistical focus is really on survival, which isn't necessarily what the FDA has said is their primary interest here.

Well, I'll just ask you. Are there statistics that can show us if the numbers of deaths that you guys displayed on slides 15 and 20 are indeed statistically significant, or is it just numerical?

DR. VERDUN: Hello. This is Nicole Verdun. I'm the CBER Office Director in the Office of Therapeutic Products. I'm going to turn it over to Dr. Peredo-Pinto.

DR. PEREDO-PINTO: Thank you for the question. What we are going to try to address with our responses is that the overall survival data is immature; therefore, we cannot conclude a statistical value at this point yet. That's why we

mentioned that the maturity of the data is relevant for this situation.

DR. MADAN: Right. So just to clarify, though, the differences, then, in deaths that are displayed on slides 15 and 20 are numerical only; correct?

DR. PEREDO-PINTO: Yes. Those are numerical, and that's the way that we analyze for the safety of the CARTITUDE-4; yes, correct.

DR. MADAN: Okay. Great. Thank you.

I think Dr. Spratt will be next.

DR. VERDUN: Sorry; one more point of clarification on that. Thank you.

DR. FASHOYIN-AJE: Yes. Hi. Good morning. It's Lola Fashoyin-Aje, clinical. I'd also like to add that when we evaluate progression-free survival, we consider the overall survival when it is immature as an endpoint that can contribute to our assessment of safety, and in the context of a safety evaluation, we're not looking for statistical significance. Analysis of safety is typically descriptive. So I just wanted to add

that for context. Thank you.

DR. MADAN: Thank you.

Okay. For our next question, Dr. Spratt.

DR. SPRATT: Thank you. Dan Spratt, University Hospitals Seidman Cancer Center and Case Western Reserve University. This is for the FDA.

Because you have done this recently for various -- and I won't mention the drugs, but in prostate cancer. There was one in kidney cancer. There are things outside of the oncology space where supplemental sensitivity analysis or restricted mean survival times have been calculated, which usually are never prespecified in studies but has been used when especially non-proportional hazard is met. And I'm somewhat surprised that neither the sponsor or especially the FDA's analysis can show us the RMST difference at 24 to 36 months.

Again, I think that's probably a more appropriate way to understand, over that time period, what's the gain or loss in survival time given the focus here. Do you have that calculated?

If so, can you please show it? I don't feel I need to hear from the sponsor unless the FDA doesn't have it.

DR. VERDUN: Thank you for the question.

DR. KANAPURU: Yes. Hi. This is Dr. Kanapuru. I'm the oncology review team lead. No, we did not conduct those analyses, and I would just like to reiterate, as pointed out by Dr. Fashoyin-Aje, a safety analysis, the overall survival is an important safety metric, and all of these analyses are just restricted mean survival. Again, they're generally used when there is a crossover, and they're all considered sensitivity analyses. Here in our analysis, we were looking at the safety based on the observed early overall survival detriment as noted in the KM curves.

DR. SPRATT: Then to follow up, again, following up on the chair's comment, because there's numerically superior outcomes, after where the Kaplan-Meier curves cross, it just seems that this would be appropriate, as the FDA has done previously, to show that data so we can better

understand because there may be statistical significance -- although I realize this is a sensitivity analysis -- to understand the total restricted mean survival time gain or loss in that duration of follow-up we have, but thank you.

DR. SOKOLIC: Thank you, Doctor. It's Rob Sokolic. You're correct, analyses are sensitivity analyses. They're post hoc. They could be the basis of hypotheses, but they're not something upon which we would be able to make a regulatory decision; and that goes with what we're saying, that the data are yet somewhat immature.

DR. MADAN: Okay. Thank you.

Dr. Spratt, does that address your question?

DR. SPRATT: Yes, partially. I wish the analysis was done. The FDA has done that for many other products, so it'd be great if that could be done prior to the decision, but I appreciate their responses. Thank you.

DR. MADAN: Thank you, Dr. Spratt.

DR. SCHECTER: Sorry. Hi. Jordan Schecter with the sponsor.

Dr. Spratt, if you wish us to show the analysis, that's something that the sponsor has prepared, so we are able to show should that be helpful for the committee.

DR. SPRATT: If you have that analysis, I would greatly appreciate it, just to be brief. Thank you.

DR. SCHECTER: Sure. Let me turn it over to my statistical colleague, Tzu-Min Yeh, to bring us through this data. Thank you.

MS. YEH: Hi. It's Tzu-Min Yeh, statistical lead for cilta-cel, Johnson & Johnson. We do have the RMST analysis that I would like to show you. As you said, this is the RMST on the PFS, and the difference in the restricted mean survival time is a gain of 4.7 months in the period up to 22.4 months. We also have the restricting mean survival analysis for the overall survival. As said, this is a post hoc sensitivity, and after a follow-up of three years, the difference in the restricting mean survival is a gain of approximately 2.3 months with a confidence interval

of 0.1 to 4.5.

DR. SPRATT: Thank you. Appreciate it. That addresses my comment.

DR. MADAN: Thank you, Dr. Spratt.

FDA? Okay, you guys are good.

Dr. Vasan, you're next.

DR. VASAN: Hi. Neil Vasan, Columbia. I had two broad questions. The first is on the question of is there a subset of patients who are not benefiting? The FDA presented in their analysis, as did the sponsor, that it didn't really seem like there was, but in the FDA briefing document, on page 31, figure 10, where there's a stratification by the prior line of therapy, I wanted to ask the FDA if they had point estimates for the hazard ratio for the patients who had gotten one prior line of therapy versus two or three. It just looks like, on visual inspection, that this is a higher hazard ratio for the patients who had received only one prior line of therapy.

DR. VERDUN: Dr. Wang?

DR. WANG: Hi. This is Cong Wang,

biostatistical reviewer. Thank you for the question. The answer is no, we don't have such hazard ratio estimates because all the subgroup analyses are post hoc and only can be considered as exploratory and post hoc hypothesis generating. Thank you.

DR. MADAN: Dr. Vasan?

DR. VASAN: The second question has to do with post-progression therapies. This is the FDA briefing document, page 14, table 5. I'm just trying to understand both the balances and the heterogeneities in these post-progression therapies as it impinges on OS. I think there are several issues here.

The first is that it seems that more patients on the cilta-cel arm who progressed received post-progression therapies, so I'd like a little bit of guidance on that from both the FDA and the sponsor. And the second, I think this points to the heterogeneity in treatments that Dr. Mailankody described. It's very hard to interpret these different post-progression

therapies, given the heterogeneity, and also given the fact that 20 patients in the cilta-cel arm got subsequent cilta-cel who didn't actually receive the drug but they were on the variable arm; and then also noting that the study did not have crossover. I'd like a little more clarity on how to interpret these post-progression data since it impinges on OS.

DR. VERDUN: I would like to invite Janssen to answer that question.

DR. SCHECTER: Great. Thank you for the question and for the opportunity to present our perspective. I think we first need to look at the overall OS data, which is contained on sponsor slide number 27, which is our most recent data cutoff and shows the hazard ratio for OS of 0.57.

Our perspective is that this data, while not fully mature, should be easier to interpret since there was no crossover as part of study design. You asked specifically what the patients got after disease progression. I do have a backup slide, which is PF-29 on the screen here. The 32 subjects

who had early progression, 20 of them in the cilta-cel arm, which you could see there, cellular therapy, received cilta-cel.

In the standard of care arm at the interim analysis for PFS, there were zero who received cilta-cel, but there were some patients who received other cellular therapies, including ide-cell or investigational CAR Ts with additional data follow-up. As of the 4-month safety update, there were additionally 2 subjects who had cilta-cel in the control arm. But in total, the data for the OS we think is strong and shows a strong hazard ratio for OS at the most recent data cut, December 2023.

DR. VASAN: Can you comment also on -- this is FDA briefing document, page 13 in table 4. There were 30 patients in the cilta-cel arm who had progression of disease, and then 117 who got standard therapy, and then of those patients -- this is table 5 -- 43 received one or more subsequent anti-myeloma therapies and 112 received the standard therapy, and if you could

comment on those ratios.

DR. SCHECTER: For table 4?

DR. VASAN: I want to make sure I'm interpreting these data correctly. So table 4 says that 30 patients on the cilta-cel arm had progressive disease and 117 on the standard arm. So of those patients, it says 43 subjects received one or more subsequent anti-myeloma therapies, and then 112 subjects received anti-myeloma therapies in the standard therapy arm of those 117. So I'd like a little clarity on what exactly that means.

DR. SCHECTER: I could bring up the list of the subsequent therapies that were offered to the patients who had disease progression on the standard of care arm. In addition to cellular therapies, which I mentioned, some patients received novel therapy; patients received standard of care therapy; and patients sometimes went on clinical protocols.

So I'm not sure exactly if I'm answering your question, but the subsequent therapy, obviously there were more patients who went on to

subsequent therapy in the control group because there's more progression in the control group, as evidenced by the progression-free survival curves.

DR. VASAN: I guess the question is, if there are 30 patients who had progressive disease, but then it says 43 subjects with one or more subsequent anti-myeloma therapies in the cilta-cel arm.

DR. SCHECTER: Right. I think I could explain this by going back to the CONSORT diagram, which is on slide 21 in the sponsor deck. I think where possible confusion lies is that when patients started bridging therapy, there were 32 patients who developed progression or death before cilta-cel, and 20 of those went on to subsequently receive cilta-cel as kind of a compassionate care and 12 never retreated with cilta-cel. Of the patients who received cilta-cel as study treatment, those 176, there were patients that progressed. They may have progressed a year later, 2 years later, and they may have gone on to subsequent therapy.

So there are two separate populations. There are those early progressors who progressed on bridging therapy, and then there are progressors who had cilta-cel as study treatment and progressed well into the future.

DR. FASHOYIN-AJE: Permission from the chair to comment, from the FDA?

DR. MADAN: Yes. Go ahead

DR. FASHOYIN-AJE: Yes. Thank you for all the questions. I think I want to re-emphasize that the purpose of today's meeting isn't really to evaluate the benefit as described by the overall survival as an efficacy endpoint. We're convening this meeting because we have concerns about the rate of early deaths. So in this context, we're evaluating and assessing overall survival as a safety endpoint and as supportive to the main concern around the early deaths in the cilta-cel arm compared to the standard of care arm.

That is really the main concern. And while all these additional analyses around post-progression therapies may be interesting, I

would like to reorient us back to the main purpose of today's meeting, which is to discuss the high rate of early deaths in the context of the PFS benefit, which is the efficacy endpoint that would support the efficacy assessment in this application. Thank you.

DR. VASAN: Thank you. No further questions.

DR. MADAN: Okay. Thank you for that guidance.

Dr. Nieva is next. Dr. Kwok, you will come thereafter.

DR. NIEVA: Hi. Jorge Nieva, University of Southern California. I find the data here very clear that this drug has a great deal of front-loaded risk relative to late benefit, and that's not something new to medicine. We see that in allogeneic transplantations, thoracic surgery; we see it in coronary artery bypass grafting.

Has either the FDA or the sponsor done any kind of comparison of the front-loaded risk seen with this product relative to other procedures that

are commonly used in medicine that are associated with front-loaded risk? Thank you. That concludes my question.

DR. SOKOLIC: I can answer that for FDA. This is Dr. Sokolic. I'm a bone marrow transplant physician, and that's exactly what I said when I saw these curves. This looks like an allogeneic transplant curve. So in allogeneic transplant, we counsel patients. We ask them to accept an upfront burden of increased mortality because we know that, down the line, overall, there's a benefit in survival. So in this setting, we know there's a benefit in PFS. We know there's a safety concern in overall survival upfront. That's not balanced by overall survival balance on the tail end. It may be when the data are more mature, but it's not there yet.

Did that help?

DR. NIEVA: Yes.

DR. MADAN: The sponsor would like to --

DR. SCHECTER: Thank you. Thank you for the recognition. I'd like to call up the slide, CO-30,

which presents our analysis, and it perhaps presents a counter discussion and a counterargument with the comments that we just heard from Dr. Sokolic.

The sponsor and the data show that it's not cilta-cel toxicity. When we looked at different time periods, the only period in time where we see more deaths, those early deaths, are between 0 and 3 months with 7 deaths in the experimental arm and one death in the standard of care arm, and six out of seven patients never received cilta-cel. The one last patient received cilta-cel as a subsequent therapy.

Every period thereafter, the deaths are either balanced as in the months 3 to 6 or more deaths observed in the standard of care arm. And those deaths are really attributable to three causes: number one, patients who progressed because they didn't get cilta-cel and they didn't have effective bridging; patients who received cilta-cel as subsequent therapy; and third, due to COVID-19. And risks one and two could be mitigated

by more effective bridging therapy, and risk number three for COVID-19, we're in a much different period in the pandemic, and the patients that succumb to COVID-19 were not vaccinated, not adequately treated, did not have the supportive care, and of course COVID-19 was much more lethal then. So I would just answer into the record that the data in our assessment do not show that there's a specific cilta-cel toxicity in the early period.

DR. MADAN: Thank you.

DR. VERDUN: From the FDA, can I please call up Dr. Peredo-Pinto? Thank you.

DR. PEREDO-PINTO: Thank you. One might consider that since the subject did not receive cilta-cel, there is no treatment causality; however, it is a consequence of proceeding to receive treatment in the investigation arm. In this case, a CAR T product therefore is relevant to the subject outcome. This brings to light a persistent consideration on the current CAR T treatment pathway in which subjects will die while waiting to receive the product.

As it is clearly shown in this study trial, the early OS detriment in the subjects, in the context of an autologous product that requires the subject to go through multiple steps prior to CAR T, is an important determinant of the overall benefit-risk. Early mortality in subjects who die who did not receive cilta-cel raises issues in the subject selection optimal disease control while awaiting CAR T product and manufacturing issues as well. Thank you.

DR. SCHECTER: If I may be recognized.

DR. MADAN: Yes, this is the heart of issues, so go ahead, but be on point briefly, please.

DR. SCHECTER: Sure. To answer the question, I'd like to ask Dr. Irene Ghobrial to provide her comments, specifically about the optimization of bridging, because I think that really could improve the overall profile.

Dr. Ghobrial?

DR. GHOBRIAL: Absolutely. Thank you so much. So again, I'm not a statistician. I'm a

clinician who sits down with patients and tell them whether they are allowed to get cilta-cel or not. And I can tell you that these days, we are giving very different bridging therapy compared to what we had on the CARTITUDE-4 trial, and this is great because we have now options that we did not have before.

I believe that the current bridging therapy could potentially optimize our patient care, can improve the way that we treat our patients, and make them capable of getting into the cilta-cel. That's a huge difference because the loss of patients early on was truly because we could not have those patients respond well to therapy, and, unfortunately, myeloma is a very aggressive disease. Even when it is first line of therapy, those patients are refractory to lenalidomide, and sometimes even refractory to everything else, even after the first line.

So this is not an indolent disease where we have the option of waiting and giving them other things. This is why they were progressing so fast

why we were trying to rescue them with bridging therapy, but we do have better bridging therapies these days.

DR. MADAN: Thank you.

Okay. I'd like to get to the next question, then, from Dr. Kwok, and, Dr. Gradishar, you're next.

DR. KWOK: Thank you. Mary Kwok from University of Washington. I just have a few clarifying questions. I guess the first one is, how were adjunctive therapies used? Was IVIG and things like that mandated in the protocol?

DR. SCHECTER: I'm happy to take that question. As per protocol, we had supportive care being suggested: IVIG, prophylactic antibiotics, antivirals, growth factor. This was done at the discretion of the treating physician and also subject to local hospital practice or availability, depending on the region.

DR. KWOK: Thank you.

I have just a couple other questions. For the patients that went on to progress and

subsequently receive cilta-cel, did they receive any therapy in between their progression and cilta-cel, or did they go straight to cilta-cel, meaning did they go into cilta-cel refractory already?

DR. SCHECTER: Twenty such patients who received cilta-cel as subsequent therapy, approximately eight received additional therapy between bridging and lymphodepletion cilta-cel.

DR. MADAN: Thank you.

Dr. Kwok, does that answer your question?

DR. KWOK: Yes. Thank you.

DR. MADAN: Okay. Thank you.

Okay. Thank you.

Dr. Gradishar, you're up.

DR. GRADISHAR: Bill Gradishar, Northwestern University. I have a question for Dr. Schechter, and it relates to what you talked about a little bit with respect to dose intensity. Do you have more granular information about the people who either had deaths or were progressing? Do we have a better understanding of what fraction of the

intended dose intensity of the bridging therapy they actually received? Because there was a clustering of a lot of the COVID cases among that group, and I'm just wondering how much have they actually got, and not the entire group, but specifically those who are having the events.

DR. SCHECTER: Yes, absolutely, and this is somewhat of a complicated question, so I'll be brief but hopefully on target. The methodology used, we took all patients who received the bridging therapy. We ranked the patients based on dose intensity, and then we took the lowest 25 percent who received pom or bortez. For pom, there were 104 patients in the lower quartile; for bortez, there were 13 patients in the lowest quartile.

Looking at the 104 patients within the lowest quartile of pomalidomide, 12 out of 104 had an early PFS event. Looking at the patients who were in the lowest quartile for bortezomib, 7 out of 13 had an early PFS event. So the patients who were in the lowest quartile had twice the rate of

early PFS for the pomalidomide, 5 times the rate of early PFS, versus those without this level of dose reduction, and there were twice as many patients in the lower quartile for pom and bortez in the cilta-cel arm.

So we're not saying that this is the obvious smoking gun, so to speak, but we do think that there's an association between that lower dose of pomalidomide and bortezomib and the early progression that was seen.

DR. GRADISHAR: Thank you.

DR. MADAN: Thank you, Dr. Gradishar.

Dr. Hunsberger?

DR. HUNSBERGER: Yes. Sally Hunsberger. In the curves that were shown -- I think slide CO-27, there are four censored observations in the standard of care arm in the first 3 months, but there's no censoring in the treatment arm. So I'm a little bit worried about that censoring pattern because it's all about those early events. So if there are four early events or censoring in the standard of care arm, that's a lot of numbers

compared to the number of deaths. So do we know anything about those events that were censored?

DR. SCHECTER: So there were were 4 patients in the standard of care arm that withdrew consent to study participation. There were also 7 subjects who received subsequent anti-myeloma therapy prior to disease progression; so in total, 11 censoring in the standard of care arm.

DR. HUNSBERGER: And no censoring in the treatment arm.

DR. SCHECTER: That's correct.

DR. HUNSBERGER: Okay. Thank you.

DR. MADAN: Okay. I think, actually, that completes our questions.

Dr. Kwok, I think your hand is up again, so we'll go ahead if you have a question.

DR. KWOK: Sorry. I just have one more clarifying question, and this gets back to the comment from the FDA reviewer about the potential delays that might be built into the cilta-cel arm. My first question is, do we know when the progressions happened? Did it happen on therapy or

during the delays or breaks, washout period?

Then two, I understand the idea of a need for a washout period before leukapheresis in order to preserve T cells and things like that. I don't quite understand the need for a washout period between bridging therapy and initiation of lymphodepletion, so I was just wondering if someone could clarify that. Thank you.

DR. SCHECTER: Sure. Perhaps I could take the first question, and then perhaps turn it over to our clinical experts to comment on the second. You had asked about that potential longer vein-to-vein time. There were a lot of complications treating patients during the pandemic, mostly logistical, so what we've looked at is the receipt-to-release timing, so when we received the product here at Janssen, when it was released, and back to the study site.

We found that the timing was actually very similar between the patients who had early progression events, patients who had later progression events. The average time off of

therapy was essentially zero, so most patients progressed while on bridging therapy. Of those 22 patients who had early progression, the majority, 19 out of 22, had progression events within the first 5 weeks. So it's not like they spent an inordinate time off of therapy and they're waiting around for their product. These are progressing on DPD, and we know DPD should have a PFS of about 12 months. Having a PFS of one and a half months or 1.3 months, that's a very high-risk patient. So our conclusion is that the vein-to-vein time or receipt-to-release time did not inordinately contribute to that early progression events.

Perhaps I'll ask Dr. Yi Lin from Mayo Clinic to help comment on your second question about why a washout period is so common in CAR T studies, specifically that washout between the bridging therapy and then the start of lymphodepletion.

DR. MADAN: That would be great. I just think we should try to keep this brief because we do have to get to a break. We have the OPH session

starting at 11:20, so probably a high-level summary here would be good in a minute or less. Thank you.

DR. LIN: Yi Lin from Mayo Clinic. On clinical trials, there is often a washout period, from the stop of bridging therapy to start of lymphodepletion chemotherapy, to allow patients to potentially recover from any of the side effects of the bridging therapy and any potential effect of the bridging therapy on the CAR T therapy.

We do know in real-world practice that that is certainly not mandatory. We would have more options to consider, patients' overall fitness and status from bridging therapy to the start. So in real-world practice, we do not necessarily mandate a bridging period, and we do have data from real-world practice to show the benefit of the treatment despite the lack of washout period. Thank you.

DR. MADAN: Thank you very much.

DR. PEREDO-PINTO: FDA would like to clarify.

DR. MADAN: A quick point of clarification

would be great. Go ahead.

DR. PEREDO-PINTO: Thank you. It's the applicant's responsibility to demonstrate or prove that a more adequate bridging therapy has the capacity to prevent the early progression of disease or death. Given that the study stands as a single pivotal trial to support the marketing application and likely the scenario with two confirmatory trials, it represents a challenge for the agency to make a conclusive regulatory decision based solely on a speculative assessment of the benefit-risk profile rather than robust scientific evidence. Thank you very much.

DR. MADAN: Okay. Thank you.

With respect to Dr. Advani, who's got a question, we'll try to come back to that after the OPH session. I apologize for not getting to that now.

We will take a quick 9-minute break, as it stands. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break.

We will resume for the open public hearing portion of this session at 11:20. Thank you.

(Whereupon, at 11:11 a.m., a recess was taken, and meeting resumed at 11:20 a.m.)

Open Public Hearing

DR. MADAN: We will now begin the open hearing session.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral comment to advise the committee of any financial relationships that you may have with the applicant. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your participation in the

meeting.

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

The FDA and this committee place a 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 for this open public hearing is for it 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 chair, and we thank you in advance for everyone's participation and staying on time.

We do have 10 speakers, so we'll go ahead and get started with speaker number 1. Go ahead. I see you're already on. Please introduce yourself and state your name and any organization you're representing. You will have 3 minutes. Please go ahead.

MS. DeROME: Great. Thank you. I have no disclosures. Hello. My name is Mary DeRome, and I'm the Senior Director of Medical Communications and Education at the Multiple Myeloma Research Foundation or MMRF. 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.

On behalf of the hundreds of thousands of patients, family members, and friends that the MMRF represents, we would like to express our support for the availability of therapies with a positive risk-benefit ratio to less heavily pretreated

patients, particularly these agents that show efficacy in high-risk populations where there is still considerable unmet need.

Despite decades of progress, the 5-year survival rate for multiple myeloma patients is still only about 60 percent. Myeloma is a disease of remission and relapse, with some patients cycling rapidly through many lines of therapy until their treatment options are exhausted. Due to the increased use of quad therapy in the upfront setting, many patients arrive at their first relapse already refractory to many effective therapies, and the majority of patients, as we have seen in today's presentations, do not survive to receive 4th or 5th line therapy, which is where many of the newer, most effective therapies are now approved.

It is also clear that the more lines of therapy a myeloma patient is exposed to, the more compromised their immune system becomes, making immune therapies less effective. The use of therapies such as CAR T earlier in a patient's

disease journey, as shown in the briefing of today's discussion, can lead to higher response rates and rates of MRD negativity, longer progression-free survival, and improved quality of life, as patients do not resume therapy again until they relapse. These significant benefits, however, must be weighed against the risks for short-term adverse effects such as CRS and ICANS, and long-term effects of cytopenias, serious infections, and second primary malignancies.

It is our hope that the committee will appreciate that despite the significant progress made in myeloma in the last 20 years, more options are urgently needed. In addition, we encourage the FDA to provide guidance on optimizing bridging therapy for patients eligible for CAR T therapy in earlier lines to maximize disease control and enable patients to achieve the best possible outcome.

In conclusion, there remains a significant unmet need for effective therapies for relapsed/refractory myeloma patients, and making

more effective therapies earlier in the disease course will help to address that need. Thank you.

DR. MADAN: Thank you, speaker number 1.

Speaker number 2, please unmute your mic and turn on your webcam. Will speaker number 2 please introduce yourself? Please state your name and any organization for the record. You will also have 3 minutes. Thank you.

MS. CHMIELEWSKI: Hello. Good morning. My name is Cindy Chmielewski, and I'm a multiple myeloma patient and a research advocate. I am on a number of the patient advisory boards and receive honoraria for the work from various pharmaceutical companies, including J&J, but I am not being compensated for speaking at today's meeting.

We all know that myeloma is a disease of relapse and remission. As such, it is a disease of continuous therapy. CAR T is the only treatment now that allows patients to have a break from continuous therapy. I believe it's important to have access to this therapy earlier on in a patient's myeloma journey when they and their

T cells are healthier.

I attend a lot of medical meetings. Doctors are always talking about T cell health, saying that the healthier your T cells are, the more likely you are to have a longer duration of response. Continuous therapy can exhaust your T cells. It makes sense to me to have this therapy available earlier when T cells are healthier. Wouldn't it be nice if someone in a second or a third line could get access to CAR T therapy and have a deep remission so they wouldn't need another therapy for maybe years? And as we heard today, unfortunately, not every patient will make it to the 4th line of treatment, so why wait?

Right now, patients typically have shorter and shorter remissions as they go through successive lines of therapy. These patients live from blood work to blood work. Every lab could be the one that tells them they're out of remission. I know that firsthand, and it makes it hard to live your life and plan for your future. CAR T treatment early on, when T cells are healthier,

could change that. A longer treatment-free interval could help you plan ahead.

In my case, I have not had Carvykti. Now I am on a monthly maintenance therapy. I am very thankful for that treatment option, but to be honest, it's a pain in my neck. I have to figure out where I'm going to be so I can schedule the next shot. I am tied to a treatment center. If I could have a drug-free period, I would be able to travel for business and pleasure freely and to visit my family more easily. My life would be much less complicated. Making Carvykti available earlier could improve patients' lives.

I appreciate this committee's review of this important data, and I want to assure you that whenever I start a new therapy, I always examine the risks and the benefits of the product and how it may affect my future options down the line. I am comfortable doing this with my doctor. What I want are treatment options and the information to be part of that decision-making process over my disease. Thank you very much.

DR. MADAN: Thank you, speaker number 2.

Speaker number 3, please unmute your mic and turn on your webcam. Will speaker number 3 please introduce yourself? Please state your name and any organization you are representing for the record. You will also have 3 minutes.

DR. USMANI: Thank you so much for the opportunity, Mr. Chairperson. My name is Saad Usmani. I'm a myeloma physician who's been treating patients for about 17 years. I have served as an investigator and consultant for Janssen as part of what I do as a researcher, and they are not compensating me for these comments. I'm speaking as a physician taking care of patients every day in clinics.

While we've seen an improvement in myeloma outcomes in the last two decades, we know that myeloma is a very heterogeneous disease, and even in patients who are at their first and second relapses, we see a very aggressive nature of disease. A lot of what I've been hearing in the ODAC so far is a testament to that heterogeneity.

The clinical trial data, as a [indiscernible - 3:28:54] clinician, I see a therapy that is highly effective, clearly demonstrating PFS benefit and meeting its primary endpoint. The early death events, again, as a [indiscernible - 3:29:04] clinician, are included in those PFS events and also demonstrate how quickly the disease can turn and create challenges for both patients and clinicians.

Looking at these data, I do support the notion that this option needs to be there for my patients. Our patients can have discussions with their physicians about the pros and cons of the therapies that they have at hand. They can be well informed and make their decisions for themselves.

Based on these data, what I take away is that the cilta-cel therapy is effective when compared to standard of care in this early line of treatment. I did not see any data that shows me that the OS is any worse with cilta-cel; if anything, it may appear similar. And as a clinician and patient advocate, I think that is a

discussion that I need to be allowed to have with my patients.

We have seen so many examples in clinics of patients cycling through available treatments within months but benefiting tremendously from these therapies and subsequent lines. I'd like to offer that option to my patients who have that aggressive relapse in early lines, who otherwise won't be able to get this therapy. Thank you so much.

DR. MADAN: Thank you, speaker number 3.

Speaker number 4, please unmute and turn on your webcam. Will speaker number 4 go ahead and introduce yourself? Please state your name and any organization you're possibly representing for the record. You will also have 3 minutes. Thank you.

MS. PURI: Hi. Good morning. My name is Aparajita Puri, and I'm going to share the story that me and my father, Ajai Puri, have been through in the past few years with myeloma. Ajai is a patient of myeloma. He was diagnosed in 2021. We speak purely as patients. We're not associated

with any organization. Ajai has gone through the Carvykti treatment in May 2022, and we're here to just share our experience.

As a family member and as a daughter, we went through a torrid time when Ajai was diagnosed in 2021. He went through a bone marrow transplant, and within a few months of the transplant, the disease had recurred again. He also went through a second-line treatment of KPd, but only to see that the disease had come back once again. And within 18 months of diagnosis, we were tearing it apart, which had very few options, and that's when Janssen, and MSK, and Dr. Usmani allowed us a chance at the Carvykti trial, and for us that was a life changer.

Ajai went through the treatment in 2022 of May, and almost 2 years down with the Almighty's blessings and all the care that we received, he's doing very, very well. The treatment process was relatively easier than the transplant. I was with him through the process. The only adverse side effect that he continues to live with is the risk

of infections, but within a few months, we were able to get him back to his normal life, including getting to work, spending time with family, and honestly going on as he would before he was diagnosed.

As a family member and as a daughter, I would only say that this treatment for us has been a blessing, and if we're able to make that choice available for more and more patients for this disease, that is most unpredictable and sometimes in the cases of high-risk patients very quickly takes a dangerous path, this treatment option can give patients another chance at life like it's given us. I'll just let Ajai quickly share his thoughts.

MR. PURI: Thank you very much for letting us in for sharing our experience. I had a successful corporate life. I was a COO for Bharti Airtel, the leading telecom operator in India, and in January '21, as Aparajita said, I figured out that I had myeloma, and as Aparajita said, we went through the treatment phase 1, then a bone marrow

transplant, and then the third treatment, and then we were fortunate enough to be coming in contact with Dr. Usmani, who's been like a godsend figure for us, and went through the the CAR T transplant.

I must say that during the transplant and post-transplant, the experience has been extremely smooth. I would rather risk myself by saying it was better than the stem-cell transplant experience in terms of after effects and in terms of during the treatment effects. I just had one impact, which was a little low blood count and all that, but I think it was very, very well managed in the U.S., and we were there for 3 months post-treatment.

Since then, we've come back to India, and I'm completely drug free. That's a blessing. For the last 19 months, I'm completely drug free. I don't take any drugs at all and live a normal life. I'm on boards of a few companies. I --

DR. MADAN: That's wonderful. That's really --

MR. PURI: Yes. I support some of the

government initiatives. I support some of the philanthropic initiatives, so it's been wonderful. I would only urge that a treatment like this, which can be a lifesaver and a game changer, be brought to many more people at a state when it has lesser impact and immunity is strong in the human body, rather than depleting the immunity first by other treatments, and then giving them this life-saving treatment, which could only risk the life a little more. So I would urge that it should be --

DR. MADAN: Thank you.

MR. PURI: -- opened up globally and across the economic strata. Thank you very much.

DR. MADAN: Thank you very much for sharing your story. We have to move on to our next speaker, but we do appreciate your perspectives as a patient. Thank you very much.

Our next speaker will be speaker number 5. Will speaker number 5 unmute your mic and turn on your webcam? Please introduce yourself and state the name of any organization you may be representing. You'll have 3 minutes. Speaker

number 5, go ahead.

DR. SIDANA: Thank you very much for giving me the opportunity to present. I'm Surbhi Sidana. I'm a myeloma physician and researcher at Stanford University. I am an investigator on J&J sponsored trials and do work with them as a consultant, but I'm not being paid for this testimony.

I would like to share my experience of treating myeloma patients every day, trying to get them to CAR T, and per the current label, I cannot emphasize how challenging it is to get patients to CAR T from when we think about CAR T to CAR T because our options for bridging therapy by the time the patients are at 5th line are very limited. Given the manufacturing time, patients are often progressing and never make it to CAR T or start CAR T with very high disease burden, which we know is associated with increased risk of side effects.

In contrast, I was an investigator on CARTITUDE-4, and I have to say the experience of treating patients early line was completely different. I know there were some patients

progressing on bridging therapy on CARTITUDE-4, but when I see my real clinical practice, that is a stark contrast, and I would like to share with you an example of one such patient I had on CARTITUDE-4.

He's a young man in his 40s. I saw him for a transplant consult, but he progressed within 2 months of starting frontline therapy with bortezomib, lenalidomide, and dexamethasone. We know historically these patients do very poorly. He was randomized to the cilta-cel arm and is in a stringent complete response 3 years later. He's back to work full time, which for him was very important, as he has a young family to support, and he's enjoying an excellent quality of life.

So given that we have many more effective bridging options earlier line, there are lots of logistical issues with CAR T where we need more effective bridging options. I would like to urge the panel to consider allowing earlier line use of CAR T given the progression-free survival benefit and improved quality of life with this limited

duration treatment. The option whether to use it as 2nd line, 3rd line, or 4th line should be a discussion between the patient and the physician, considering the side effects and the logistics, and the circumstances of each patient. Thank you.

DR. MADAN: Thank you, speaker number 5.

Speaker number 6, please unmute your mic and turn on your webcam. Please introduce yourself and state your name and any organization you're representing for the record. You will have 3 minutes. Thank you.

MR. AIELLO: Good morning. My name is Jack Aiello. Regarding any conflict of interest and honoraria, I sit on several pharma myeloma patient advisory councils, including Janssen, BMS, Karyopharm, Genentech, and GSK, but I'm not being compensated for my testimony here, and I'm also on the International Myeloma Foundation's Board of Directors.

I was diagnosed with multiple myeloma in early 1995 and given 2 to 3 years to live. As such, I've been fortunate to participate in

multiple clinical trials, and I've seen the FDA approve 19 new drugs in the last 21 years for myeloma treatment, resulting in tripling survival rates. Thank you, FDA, investigators, pharma companies, NCI, and patients who have made this happen. However, we still have no cure, and nearly all of these treatments are given until progression, and when a treatment stops working, patients hopefully are immediately moved to another available treatment option. Unfortunately, studies have also shown that responses are typically shorter with each new line of therapy.

For the last 20 years, I have facilitated our large San Francisco Bay Area myeloma support group. Last year, I convened a panel of six of our CAR T patients, a mix of folks who received Carvykti or Abecma within trials or commercially. They shared a mix of responses, ranging from 4 months and relapsed to 4 years and counting. They experienced different side effects, including CRS and neurotoxicities. But when I asked each of them if they would go through a CAR T again,

everyone said yes; and the one reason they all strongly indicated was the opportunity to be off treatment for months or years. Patients get so physically tired from treatment after treatment, that a treatment holiday was incredibly beneficial to feeling better.

In so many cases, Carvykti has been shown to work well, resulting in excellent responses. I hope you'll consider giving patients a chance to feel better sooner by approving Carvykti usage rather than waiting until after 4 lines of therapy. This is a difficult disease to battle, and giving patients a chance to stop treatment sooner rather than later would mean a better quality of life. Until you've experienced myeloma treatments, you can't believe how the side effects can wear you down. The benefit of a treatment holiday means so much to patients. Thank you for listening and your consideration of this request.

DR. MADAN: Thank you, sir. I appreciate your perspective.

I think that brings us to speaker number 7.

Will speaker number 7 please unmute and turn on your webcam? Please introduce yourself and state your name, and for the record any organization you are representing. You will also have 3 minutes. Thank you.

MR. BIRU: Good morning. My name is Yelak Biru. I serve as President and CEO of the International Myeloma Foundation. I sit before you today as a myeloma patient, a survivor, and an advocate. I was diagnosed at the tender age of 25 in 1995, a few months after the previous speaker 28 years ago. My journey with multiple myeloma has really been one of ups and downs, requiring resilience, and treatment, and treatment, and retreatment.

The International Myeloma Foundation, where I serve as president and CEO, receives funding from various sources, including industry partners like Janssen Biotech. I have not been compensated for expressing my opinion today. My sole motivation is to champion a treatment that can change patients' lives like mine.

My role at IMF allows me to hear the voice of hundreds of patients from across the U.S. and global. They yearn for more treatment options at different stages of their journey. They are all aware that no treatment is a magic bullet. Every option comes with its own set of challenges and a potential side effect. Their goal: to find the best outcome with the least side effect, allowing for a better quality of life and bridging the gap to the next treatment until a cure is finally found.

Myeloma is really a formidable adversary. It infiltrates our bones, disrupts our immune system, and threatens our very existence. As a patient, I have witnessed firsthand the devastating toll it takes on individuals, families, and communities. We need more treatment options, innovative solutions that can offer a lifeline to those who face this relentless opponent.

I'm not just an advocate, I am a beneficiary of Carvykti. Close to 18 months ago, I underwent this transformative therapy. The results were

nothing short of remarkable, MRD negative, mass spec negative, M-spike negative, with a clean PET CT sustained over 15 months, approaching 18 months. Carvykti allowed me to break free from the cycle of treatment, experience the deepest remission I have known in years, and reclaim my life. It was a second chance, a lifeline that renewed my determination to live fully. The CARTITUDE-4 approach mirrors how autologous stem-cell transplants are used, administered early for maximum impact. Early use of Carvykti had the potential to prevent T-cell function, a crucial element of the immune system for future treatments.

In closing, I stand here not just as Yelak Biru, but as a collective voice of patients, caregivers, and advocates. We implore you to consider the evidence, the science, and the human stories behind Carvykti. Approving this therapy is not a mere decision; it is a lifeline, an opportunity to change the trajectory of myeloma. Thank you for your attention, your dedication, and your commitment to advancing medicine.

DR. MADAN: Thank you, sir, for sharing your perspective.

This brings us to speaker 8. Please unmute and turn on your webcam. Please begin and introduce yourself. Please state your name into the record and any organization you may be representing. You will also have 3 minutes. Thank you.

MS. HAUSTEIN: Good morning. My name is Deb Haustein, and I'm actually a retired oncology nurse. I live in a beautiful little town along the St. Croix River in Hudson, Wisconsin. I'm thankful for the time to share my story with Carvykti. I'm speaking on my own behalf, and I'm not being compensated for my testimony.

I was diagnosed with multiple myeloma in 2014 and went through the usual Revlimid/ dexamethasone regimen, followed by an autologous stem-cell transplant. I had a poor response to this transplant, and after only a few months was back on treatment. It was then 2015, and I was on one treatment after another, from then until May of

2020, when I was offered a CAR T therapy with Carvykti. In total, I received seven different lines of treatment in six years.

I feel strongly that it is important to approve Carvykti sooner instead of later, waiting for patients to go through 4, 5, or 6 lines of treatment, or even seven, as in my case. I received my CAR T therapy with Carvykti 2 years ago. It was successful, and I am still in remission today. This is the longest I have been in remission since being diagnosed. It is the longest I have gone without needing some type of treatment, without being totally impacted by constant fatigue, frequent treatments, numerous daily medications, constant medical appointments and tests, and side effects. I am in remission because of Carvykti.

But it is more than that. It has given me a normal life again. I'm not wearing rose-colored glasses by any means. I know there might be a day in the future when myeloma will come back, but that day is not today, and hasn't been for 2 years of

today, and counting. It feels really good to not wake up every morning knowing that I have cancer. I feel like I can take a deep breath again. I can now make plans with my husband, children, and grandchildren.

I can actually plan vacations. I can even book a European river cruise without having to look at my calendar for appointments and treatment dates that might interfere with these plans. I can plan things. What a great way to celebrate. I feel normal and have a normal life again. Cancer patients will understand how important that is to feel normal.

Thank you for your time and for letting me share my story and why I believe the benefits of this treatment outweigh the risks.

DR. MADAN: Thank you for your story and sharing that with us.

Speaker number 9, please unmute and turn on your webcam. Please begin and introduce yourself and any organization you are representing into the record. You will have 3 minutes. Thank you.

MS. AHLSTROM: My name is Jenny Ahlstrom, and I'm the founder and CEO of HealthTree Foundation, a patient advocacy organization supporting multiple myeloma. More importantly, I'm a multiple myeloma patient who was diagnosed in 2010. As a disclosure, I participate on many former patient ad boards, including Johnson & Johnson's, and Health Tree receives funding support from many companies, including Johnson & Johnson, but I'm not being paid for my testimony today.

When I started therapy at the age of 43, I looked for something that was a one-and-done approach that would allow me to take care of my six young children without constantly being on therapy over many years. I chose tandem transplants, and it turned out to be one of my best decisions. For almost 10 years, I was off all therapy and able to be an advocate for others. About six years after that treatment, however, my myeloma did begin relapsing, but it was slow growing, and I had sufficient time to make a decision about my next

major therapy while doing what was needed to manage my disease. This time my strategy was, once again, to look for a one-and-done approach.

I've spent the last many years understanding the science of myeloma in order to serve my myeloma peers. After a decade of study, consults with experts, and careful consideration, I decided I wanted to receive CAR T therapy, and Carvykti in particular because of the impressive data. What I consider miraculous is that I qualified for and was able to join the CARTITUDE-4 study testing this CAR T in earlier lines of therapy with the help of my doctor, Doug Sborov.

The trial was opened in my hometown, and I was fortunately randomized into the treatment arm. In November 2021, I received Carvykti in that trial. I had grade 1 CRS and no ICANS. I'm still MRD negative after 2 and a half years and hope that will continue for many more. For me, it was a fabulous, effective, and safe approach. The timing of this strategy was important in my decision. I chose it because it would be more effective when my

immune system was stronger. I chose it because my disease is not yet highly aggressive. I chose it because I believe it is one critical step on a curative path for my multiple myeloma.

Like other myeloma patients, I'm not comparing it equally against standard of care options; I'm looking at it strategically. When is a patient's immune system stronger so its immunotherapy has more utility? It's in earlier lines. When is a patient's disease less aggressive and lower risk? It's in earlier lines. Our standard of care options today are not curing patients and they place wear and tear on the immune system, making immunotherapies weaker in later lines of treatment. New approaches are critically needed.

To sit in last year's spring ASCO session in person to hear the data readout for CARTITUDE-4 was a memory I won't forget. May other patients be so fortunate. I highly recommend you approve this therapy for patients in earlier lines to open new doors of hope to myeloma patients in the United

States. Thank you for your consideration.

DR. MADAN: Thank you for sharing your story.

Speaker number 10, please unmute and turn on your webcam. Please begin and introduce yourself, and state into the record your name and any organization you may be representing. You will have 3 minutes. Thank you.

MR. KELLER: Hello. My name is Doug Keller, and I've been a multiple myeloma patient for 12 years. I'm representing myself and have not been compensated in any form for speaking today. My main message today is that, currently, multiple myeloma patients must go through years of debilitating treatments before they can get Carvykti.

As is the case for many myeloma patients, I had a bone lesion that caused a broken bone when I fell. After surgery and radiation, I had induction therapy, a stem-cell transplant, and lenalidomide maintenance. Over the next 8 years, I was on a series of treatments that included elotuzumab,

daratumumab, lenalidomide, pomalidomide, carfilzomib, dexamethasone, and various combinations thereof, a clinical trial and a second stem-cell transplant, all without achieving remission.

I had constant trips to the clinic for blood work and never more than 2 weeks between treatments. My quality of life during this time was only fair. I suffered from sleep disturbances; rashes; cardiac abnormalities; peripheral neuropathy; fatigue; neutropenia; and the anxiety of the cancer burden. My condition also affected the lives of my caregiver and family.

In early 2022, I was able to get a slot for Carvykti. At that point, my serum light chain level was very high at 10,500 milligrams per liter. I had Carvykti at the end of May, and one month later, my serum light chains were 3 milligrams per liter. I've been in remission ever since, with few of the side effects of previous treatments, and my quality of life is excellent.

I think what is not well recognized by FDA

and the medical community is the often debilitating nature of the standard of care treatments that are available to myeloma patients. According to a 2022 HealthTree Cure Hub study, even the successful quad induction therapy comes with a high level of side effects, including fatigue, neuropathy, neutropenia, anemia, bone pain, and GI effects. While overall survival is important, myeloma patients don't want to simply survive, they want to live a full life.

The response rates of the standard of care treatments are not as good as Carvykti's. Carvykti can give the patient significant time off without treatments and has a better side effect profile than standard of care. Having Carvykti as a 5th line treatment or later is not in the best interest of patients who suffer from years of debilitating treatments before they can get their potential for relief. Carvykti can cause serious AEs, but they're usually temporary in contrast to the standard of care. Patients deserve to have the opportunity to make an informed choice about the

use of Carvykti early in the course of a disease that has no cure. Thank you for your time.

Clarifying Questions (continued)

DR. MADAN: Thank you for your perspective, sir.

So with that, the open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. What I'd like to do now, I know we're right at schedule, maybe a little bit behind, but I did promise Dr. Advani that she may ask her question that was a holdover from our earlier session of clarifying questions. I'd like that to be the final question, and then we can move on to our discussion questions.

Dr. Advani, I see you up there. Please go ahead with your question.

DR. ADVANI: Thank you. Ranjana Advani from Stanford. Since most of the deaths were people who didn't get to the product, you've clumped patients -- this is for the sponsor -- one prior line, and then two, and three have been clumped

together. Was there any difference between those who had one, versus two, versus three? Then the second question is, was the PFS different between one, versus two, versus three?

DR. SCHECTER: Okay. Thank you for the question. To paraphrase, you're interested in the the aspect of the patients who had one prior line of therapy. Before we take a look at the subgroup, I would like to review again slide 22, which has the overall patient population of patients with 1 to 3 prior lines, showing that the primary endpoint was met with a statistically significant hazard ratio of either 0.4 for the unweighted or the 0.26 for the weighted.

The subgroups were analyzed. We did look at this in slide 23, if we could bring it up. In the one prior line subset, you can see there on the left-hand side of the screen, sort of two-thirds of the way down, a statistically significant hazard ratio for PFS, which does not cross 1, which is significant. If we look at the similar data for OS, we could see the same performance of that one

prior line setting. If we could look at the OS across subgroups on slide 28, you can see in the one prior line subgroup, again, the hazard ratio for OS in favor of the cilta-cel arm versus standard of care.

Our study was not powered specifically to look at that one prior line subgroup. We had about a third of patients who received exactly one prior line, so any differences between the performance of the one prior line, two to three prior line, is hypothesis generating at best, and therefore is not something we could base firm conclusions on whether there's better effect on the one prior line versus two to three.

What I can say, though, is if we look at the 1 to 3 prior line in totality, the CART-4 study, compared to the CARTITUDE-1 study, we do get a hint at a better response rate, better durability, perhaps, but also equally important, if not more so, better safety. So the adverse events of special interests that are attributable to cilta-cel are better.

This was a slide that was shown previously -- sorry; the adverse event slide. Well, I'll just speak to it in the interest of time. The incidence of cytokine release syndrome, the incidence of ICANS, the incidence of MNT, the the Parkinsonism syndrome, all better tolerated in the 1 to 3 prior line setting as in CARTITUDE-4 than the later line setting in CARTITUDE-1.

DR. ADVANI: Also, people who didn't make it to the product, were they mainly those who had one prior, two prior, or three prior?

DR. SCHECTER: Right. So I think you're specifically asking about the -- is it the 32 patients --

DR. ADVANI: Yes.

DR. SCHECTER: -- who had disease progression? Certainly.

DR. ADVANI: Prior to starting cilta-cel.

DR. SCHECTER: Right. I could bring this up. This is PF-34. On the light blue column all the way on the right, you can see the demographic factors of those patients, those 32 who had early

disease progression, and it's not as if they're only in stage 3 or only in stage 2. You can see that the demographic factors are very similar to the entire patient population, which is the dark blue column, the 208. So we actually agree with the FDA assessment that was discussed in their slide deck, that there are not demographic factors or other variables that we could identify at study baseline that would identify those patients for early risk of progression.

DR. ADVANI: Thank you.

DR. VERDUN: I would like to request the chair if FDA can also respond?

DR. MADAN: Yes, that would be fine.

DR. VERDUN: Thank you.

Dr. Wang?

DR. WANG: Thank you. This is Cong Wang, biostats reviewer. I just would like to highlight that there are important limitations for the forest plot for both the OS and PFS. First, the hazard ratio assessment within each subgroup was calculated based on unstratified log rank test,

ignoring all the stratification factors, and second, based on FDA's exploratory subgroup analysis, in the presence of a crossing hazard pattern or a prolonged overlapping hazard pattern, in the Kaplan-Meier curves for most subgroups, the average hazard ratio reported within each subgroup is unreliable and uninterpretable. So we would like to please ask the committee to interpret the first plot for both PFS and OS for subgroup analysis with caution. Thank you.

Questions to the Committee and Discussion

DR. MADAN: Okay. Thank you. That will end the clarifying question portion of our discussion, and the committee will now turn its attention to the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while the 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 will pause for any questions or comments concerning wording. We will proceed with our first question, which is a discussion question, and we see it displayed here, and I will read this.

Discuss whether the results of CARTITUDE-4 are sufficient to support a positive risk-benefit assessment of cilta-cel for the proposed indication. I will ask the committee now, the panel, as we embark on our discussion, if there are any questions concerning the wording of the question or requests for clarity from the FDA before we proceed with our discussion.

(No response.)

DR. MADAN: Okay. I'm not really seeing any requests for clarification, so I think we understand. I would just like to say that oftentimes during the discussions, we start talking about endpoints or conversations with the FDA, other approved agents, FDA approval. I think we just have to remember that the focus of this discussion is actually the questions before us.

The question here is clearly asking about the risk-benefit assessment of cilta-cel, so if we can keep it on point with that, that would be great.

I would like to open the floor for any comments, or in the absence of any lead-off comments, I would like to lead into the expertise of our invited panel members, who probably deal more with multiple myeloma than many of us on this panel. That would be Dr. Kwok and Dr. Lattimore, so if one of you would like to volunteer to give us your thoughts on this specific question at hand.

Dr. Kwok, I saw your camera come on, so by all means.

DR. KWOK: Thank you. I'm happy to weigh in. Actually, a lot of the testimony that we heard from people who treat myeloma and the patients of myeloma echo also my personal --

DR. MADAN: Dr. Kwok, just for procedure, just state your name and your institution.

DR. KWOK: Sorry. My name is Mary Kwok. I'm from the University of Washington. I actually also had very similar thoughts as -- I forgot his

name, but the person who said he was a BMT physician; that the curves really remind me a lot of transplant-associated toxicities and things like that are high early on, and a lot of the thoughts on disease heterogeneity, rapid relapse of disease, and things like that, really, really echo what I also see in my practice.

I think that the treatment option, bringing Carvykti or CAR T cell cell early on is an important consideration for a variety of reasons that were already stated; one, that it's an effective therapy. Sometimes it takes a lot of creativity to get to 4 lines of therapy and sometimes giving therapies that you think might not be very effective.

I also recognize the importance of a one-and-done treatment. I practice in Washington State, where I see patients who come to us from outlying states where they might not have access to clinical trials or more intensive myeloma therapies. They come to us from Alaska, or Montana, or Idaho, or wherever, and to be able to

give a one-time treatment without requiring them to come back and forth is a really important treatment option.

I think it's interesting -- and I'm just trying to reconcile in my head why there would be a difference in the initial overall survival when the patients were given the same treatments. I wonder if it's just kind of bad luck or if there's a more scientific explanation, but I think that beyond that, the separation of the survival curves is really striking and impressive to me.

DR. MADAN: Dr. Kwok, I think you brought up an interesting point, and it's not been probably touched on a lot. But is it true that multiple myeloma patients who face autologous transplant early on also face a mortality risk, and how would you characterize that risk in the context of what we're seeing here?

DR. KWOK: I would say the risk associated with autologous stem-cell transplant, it's very, very low, like probably close to 1 percent, but it's not zero. Then we know from studies, like the

DETERMINATION study, that there's a significant quality-of-life decrease that goes on during a period of stem-cell transplant because of toxicities related to intensity of therapy, cytopenias, et cetera. So conceptually, I think toxicities that go into a cell therapy, like receiving CAR T cell, where you're getting lymphodepletion, we know that you're going to have cytopenias and infections, and it seems inherent in the design of the study that that would happen, but if you can get past that, the long-term benefit pays off.

DR. MADAN: Thank you.

Dr. Lattimore -- and Dr. Advani -- is also a hematology expert here on this panel. Would either of you like to weigh in specifically on this question, of the CARTITUDE data and how it is able to support, or not, a risk-benefit assessment?

MS. LATTIMORE: Yes. I'm Susan Lattimore. I just want to be clear that I'm here as a consumer representative on this panel.

DR. MADAN: Oh, okay. My apology.

MS. LATTIMORE: That's my role on this committee. But I do want to say, in lifting Dr. Kwok's comments, I think we can't understate the ability of individuals who have this period of non-treatment that allows them higher quality of life, which the data did support, and moving into more of a disease-free state. I think that, certainly, there's some confounding data around outcomes, but I think there is some disclosure from a patient perspective that allows those discussions to really be lifted in a treating physician and a patient realm. That also allows the opportunity for people to have more ability to have choice in treatment, and then certainly have that choice earlier on where quality of life may be overwhelmingly improved, but also the opportunity for a higher quality of life to be available to begin with. I don't think that that could be understated.

I do think it's difficult supporting a positive risk-benefit assessment. Some of the data, again, from a patient perspective, might be

very challenging to understand and interpret. So we think that if the committee can come to -- or if some labeling could come to the opportunity to be overtly transparent about what that risk-benefit looks like and entails in more lay terms, I think it would allow for more opportunity of choice on a patient perspective.

DR. MADAN: The chair recognizes Dr. Vasan.

DR. VASAN: Neil Vasan, Columbia. I think that this comparison to transplant, I think, metaphorically is powerful and relevant for this patient population. I guess I would just add, and wanted to get Dr. Kwok's thoughts on this, that, obviously, with transplant, we do have risk stratification factors as to who is a better candidate than others, age, and other molecular factors and whatnot. Here, the discussion has really focused on the fact that there really isn't a stratification factor we can point to, to identify the patients who would not benefit.

So I wanted to ask if you could comment on, given the heavy censoring, if this longer term

follow-up may sway that decision also.

DR. KWOK: Thanks for the question, but I'm not sure that I'm the best person to answer this. I will just say that, in general, when we think of stem-cell transplant, we use age and performance status probably as our biggest cutoffs in determining eligibility. That doesn't exactly exist for CAR T. I mean, yes, you consider performance status, but the oldest patient I think on this study was 78, and in other types of CAR T cell therapies, we've heard of people getting it in their 80s and things like that. I would wonder if there's more data in this setting, but I don't know that I would take it off the table necessarily for someone purely based on an age cutoff or something like that.

If I could say something about age, people are living longer and longer with myeloma these days. If there is a consideration that things like maybe age or other comorbidities will play a role into whether or not they can get CAR T cell, it makes me wonder if somebody is diagnosed, say, at

age 69, the average age, and then they get 6 years out of their initial therapy, and then they get another 2 years or 3 years out of the next subsequent lines of therapy, by the time they are 4th line therapy, currently FDA approved, they're quite elderly and may have more comorbidities and things like that. And I wonder if things like that contribute to whether or not somebody can tolerate something like CAR T.

So I think thinking about bringing it earlier on certainly makes these types of options available to people, although to answer your question directly, I'm not sure that there are strong cutoffs in terms of who we would necessarily give it to or not. We think about things like kidney and what's appropriate for someone with chronic kidney disease, or maybe end-stage renal disease, which is not uncommon in myeloma, and whether or not somebody can tolerate the cytokine release syndrome that comes on early on. I think these are interesting questions; I just don't exactly have the answer to them.

DR. MADAN: Just to follow up a little bit on your answer -- this is Ravi Madan, NCI -- would you say that age is a harder cutoff for a transplant than it would be for this type of agent? Is that what I heard you say?

DR. KWOK: I think so. We draw a line in the sand. I think because there are a lot of clinical trials looking at autologous stem-cell transplant, in Europe it tends to be a little bit on the younger side, like 65 or 70, and in the U.S., we push it a little bit more, 70-75. It's like a physiologic age, but usually it corresponds well because the risk for transplant-related mortality and stuff like that increases.

I don't know if that kind of data exactly exists with CAR T cell. Clearly, they were not excluded from this clinical trial for age, so I think it's an important option, regardless of age, if somebody's able to receive the treatment.

DR. MADAN: Okay. Great.

DR. VASAN: Neil Vasan, Columbia. The point I was trying to make was that it's an interesting

metaphor, and I think that there are a lot of similarities, but it does seem like one difference is the fact that, with transplant, we have decades and decades of experience. We have very mature stratification factors for whom may or may not be a great candidate, and I think with CAR T cells, we have less of that, just given that these are new therapies. Thank you.

DR. MADAN: Thank you.

Dr. Frenkl, I see your hand's up.

DR. FRENKL: Yes. I have a question maybe back to Dr. Vasan, just to understand his perspective a little bit more on this, because when I am interpreting the data, for me, for the patients who receive it, to me, they have a very clear benefit based on the PFS and the trending OS.

So I'm wondering when you're thinking about stratification, are you thinking about people who can make it to the therapy or are you actually thinking about it for the patients on therapy? Because for me, when I look at this study, it's really the maintenance of the patients during

bridging that is critically important and maybe something that requires more transparency in education, or that we need to allow the physician and patient to decide what's best for them, based on the heterogeneity of the population and also the emerging treatment landscape.

So my question is, are you talking about up until bridging or after with this specific drug?

DR. VASAN: Yes, I guess both, and also if longer follow-up, given that the information fraction was lower -- I think it was about a third on this interim analysis. That was my question to Dr. Kwok, so I guess I'm answering your question with a question as well; if longer term follow-up would shed light on these separations.

I guess to answer your question, Dr. Frenkl, I think that for those patients who are not receiving therapy, I guess the question is just to what extent does that confound the data, and I think we've seen a lot of subanalyses, sensitivity analyses, that have pointed to what that is.

DR. FRENKL: Thank you.

DR. MADAN: Great.

DR. FRENKL: May I make one more comment?

DR. MADAN: Go ahead, Dr. Frenkl.

DR. FRENKL: I'm sorry. Thank you.

I'll just say that I think with the OS curve, the crossing of the OS curves is not going to change; that has long passed. But we could continue to see further separation or lowering of that with continued follow-up, but the crossing's done, based on the timing of the study.

DR. MADAN: Yes. It does seem in the early stages.

DR. FRENKL: Yes. Thank you.

DR. MADAN: Dr. Advani, I wanted to give you an opportunity to weigh in as more of a heme malignancy specialist. Did you have any thoughts you want to add to this question, specifically?

DR. ADVANI: I think it's a difficult comparison because we have a lot of experience with transplant --

DR. MADAN: I mean, you can answer that question if you like, but I just meant the FDA

question about the data and how it supports a positive risk-benefit assessment, not necessarily -- if you want to talk about the transplant, you can as well, but I meant more the -- either one, quite frankly. Go ahead.

DR. ADVANI: I don't have questions on this right now. I'd just like to clarify better. It's a little gray area because we're referring to those 32 patients who didn't make it, predominantly, because otherwise, there looks great, and there's no stratification factor, which came across as helping us understand who those patients were compared to the rest of the population. So I don't know how to think of it any differently.

DR. MADAN: Okay. Yes, and we'll get to the early events with the second question that we have for discussion here today.

Does anybody else have any additional comments? I think Dr. Frenkl did bring up the point that it probably isn't said, but the curves have crossed, and that was in the past, and we have seen that with immunotherapy trials sometimes in

the past.

Dr. Nieva?

DR. NIEVA. Yes. I just want to add that part of this issue of the start-up time is somewhat going to be ameliorated when it leaves the clinical trial setting because we have consent processes and an authorization process. We've looked at how long it takes to get people started up on clinical trials, and it does add about 30 days. And for these patients, that 30 days may actually have been --

DR. MADAN: Dr. Nieva, I'll just ask you to hold this thought, and you'll be the first one to talk in the second question because the second question actually focuses on the risk of early death; so that's actually a great way to kick off that.

But do we have any other discussion points specifically on discussion question number 1 here?

(No response.)

DR. MADAN: I think just to summarize this discussion, there is a sense that there is benefit.

There are risks here to this population, but in some ways, somewhat modulated, their risks are a little bit similar in some ways to the risks of transplant that this population has faced before.

Something that's lost in the curves but really came out in the discussion, not just amongst the panel but also the patients, is the progression-free survival is really also like a freedom of treatment, and these patients are liberated from therapy as well, and I think that was something that resonated with the panel discussion here, that some of the benefit here is indeed being able to get a therapy, and then kind of coast for a while.

I do think that the risk component will take on another discussion component here as we get to the second discussion question, which we will now move on to that, which talks about the early deaths, and I think that's kind of where the risk has been highlighted.

So here is the discussion question that's now displayed. I think at this time, we will not

be taking any comments from the sponsor. This is the discussion point for the panel here, again, and the question is, is the risk of early death associated with cilta-cel treatment acceptable in the context of the PFS benefit?

Before we move on to this, are there any requests for clarifications from the FDA on this question? And again, the discussion here is really to focus on the early deaths that were seen on this, as the question is asking us to focus on, in in the context of what was seen later in the trial. So any questions for clarifications from the FDA?

Okay. I think those two hands that I see were up before my request for questions, so please let me know if that's incorrect. No? Okay.

So with respect to Dr. Nieva, who I somewhat rudely cut off earlier, and I apologize, sir, but I will allow you to kick off this discussion with the points that you were making, which I think are very relevant to this question, so please go ahead.

DR. NIEVA: Thank you. Jorge Nieva, USC. So I was saying that in the clinical trial context,

there's going to be more delays than there will be in actual practice because of the consent process and everything else associated with trial enrollment, so we expect that problem of delays to go down. Now, I think we've heard some comments from the FDA that you can't analyze the OS curves because we don't have, a priori, rules and formal testing at this level of events, but those curves are pretty wide, and they don't look like they're going to cross again, and I think the MRD data that we have also supports they're not going to cross again.

So I really think this is a case of front-loaded risk, much like we see with many other things in medicine, and I think as long as the patients understand the magnitude of the front-loaded risk, then I think these risks are acceptable. Thank you.

DR. MADAN: Thank you, Dr. Nieva. I appreciate you holding those comments for this section.

I believe, Dr. Spratt, your hand was up

next.

DR. SPRATT: Thank you. Dan Spratt, UH Seidman Cancer Center and Case Western Reserve University. When I look at this, it's very interesting, the early deaths, because with a PFS benefit, there's also a worse or inferior PFS early on as well. So you have to look at this in the context globally and both, as the FDA appropriately stated, will say a flawed assuming proportional hazards analysis. But even in their analysis, which, of course, would never be prespecified, looking only at 0 to 3 months, their statistically was not statistically significant, and looking over the whole curves, it is, and as the sponsor showed, the restricted mean survival time is a benefit at various cutpoints.

Still very much, I don't think any trial will ever be able to prespecify for non-proportional hazards because you would not know that necessarily a priori. So given it's widely accepted in the statistical community that that is probably a more appropriate way of looking at this,

I think that for patients treated, there is a non-significant increase in early deaths and there is a significant improvement in survival and PFS. So I'm not overall concerned, and I think Dr. Nieva hit the nail on the head, as I think these are delays related, and we've talked about COVID, and we talked about real world versus clinical trials.

DR. MADAN: Yes. Thank you, Dr. Spratt.

Dr. Lieu?

DR. LIEU: Yes. I'll keep my comments short because I totally agree with Dr. Nieva and Dr. Spratt. I'll just make mention, when you look at the context of the progression-free survival benefit and the sheer number of patients that you see on the tail of that curve, along with the duration of durable response, you put that in the context of what could be harm, for sure, in the first 3 to 6 months.

But I keep going back to the sheer number of events that we see, and it's a really small number. That's why, to Dr. Spratt's point, when you look at the confidence intervals -- and I know safety is

descriptive, and we shouldn't rely on statistical analyses here, but those confidence intervals are unbelievably high when you look at the hazard ratio, and that really just reflects the small number of events in that period of time.

So to answer this question, when you look at the context of the harm in a handful of events in the early months compared to the tail of the curves that we're seeing, I think it's a pretty clear signal of benefit.

DR. MADAN: Thank you, Dr. Lieu.

Dr. Hunsberger?

DR. HUNSBERGER: Sally Hunsberger. I just want to emphasize again, the censoring only in the control arm is problematic to me, especially, again, the fact that there are just so few in the first 3 months and there are four censored events that could totally make up -- those could be the people that would have died going off treatment to get something else. So again, the imbalance in the censoring is also a problem to me, so I think I also feel that the risk is probably acceptable.

DR. VERDUN: Hi. This is FDA. We would like to respond as well. Is that ok?

DR. MADAN: Yes, briefly.

DR. VERDUN: Thank you. I'd like to bring Dr. Scott from statistics. Thank you.

DR. SCOTT: Thank you. John Scott, statistics. We appreciate the committee's discussion of the RMST. We just wanted to point out that the interpretation of RMST does very much depend on, when you're looking at it, what the cutpoints are, and that we're not yet fully convinced of a long-term advantage on overall survival, although, certainly, there is separation visually in the curves after the crossing point. Thanks.

DR. MADAN: Yes. Thanks for clarifying that.

I think the committee accepts the uncertainty of the data as it stands, but we're doing our best, I think -- if I'm not speaking for everybody, go ahead, but I think we're doing our best to wrap our heads around it. But I think

Dr. Spratt can maybe go ahead and say something more eloquent than what I just said.

Go ahead Dr. Spratt.

DR. SPRATT: Yes. Just for a discussion point to the FDA, I mean, there's obviously the clinical -- sorry, Dr. Spratt, Dan Spratt from UH Seidman Cancer Center. I think that statistical tests, while none of them are perfect, there is conventional statistical significance using both a log rank, a hazard ratio, and I assume they use some type of Cox proportional hazard, as well as the sponsor presents -- it wasn't in the packet provided -- it was statistical significance. I realize, for honesty, you have to pick a time point, so picking something around 20 some odd months was decent follow-up, or the 36 months, I believe.

So I think by any standard statistical test, realizing most of all of this is not prespecified, they all are directionally consistent and reach statistical significance. So it just seems that we're digging really, really hard to focus on

non-statistically significant, very, very few events early on, and I would just state that, are we looking in contrast at survival curves that separate early on in favor of, let's say, the investigational agent, but come back together or maybe cross later, and how do we handle that?

I don't want to be tangential here, but they often come back together, and we often don't follow patients long enough to see if they end up flipping. So it just seems there may be some inconsistencies here to be putting so much weight on a couple events early on.

DR. SCOTT: Thanks. John Scott, FDA, biostatistics. Yes. I certainly appreciate your comments. I can't really speak to the second part of that about curves coming together later, but I would say there's a variety of statistical significance tests that can be used, but we always put a very strong premium on the prespecified primary analyses of trials to support regulatory decision making because looking post hoc and choosing cutpoints after all the data have been

observed does tend to inflate the false positive chance of being misled. Having said that, we support the committee using all the evidence they have in front of them to make up their minds. Thank you.

DR. MADAN: Ravi Madan, NCI. I think from my perspective -- this is shared across the committee -- it's almost unsatisfying because we have these 6 or 8 early deaths before treatment, but we really can't pin down exactly what happened. We can chalk it up to bridging therapy, or COVID, and both of those things leave the door open for things to get better in the future, which we hope, but I think we're used to having more of a direct tie.

Depending on how you see this, a little bit, it's actually, I think, dictated by the long-term outcomes, and what do you do when you have so much unknown around such a small number of patients in the beginning, and how does that balance with the long-term potential benefits here? That's at least my thoughts on this question.

Any other comments from the panel?

(No response.)

DR. MADAN: So I think in summarizing this, the panel is struck by the fact that there are numerically increased deaths early on. It's hard with descriptive statistics to really understand the implications and the ultimate determinations here, but there is a sense of long-term benefit as well. So I think the the sense of the panel's discussion here has been that there are issues up front, but they are small and perhaps balanced by the long-term benefits.

If anyone wants to clarify that characterization of this discussion further, please let me know. But I also think we have to acknowledge that, statistically, we can't be as certain as maybe we'd like to be with the final polished results of a phase 3 trial or something, and I think that is well understood by the panel as well, and that's part of the reason why it's a discussion point here.

The FDA wants to make a final comment. Go

ahead.

DR. VERDUN: Hi. Yes. Sorry. Thank you. We'd like to make one additional comment. Thank you.

DR. FASHOYIN-AJE: Hi. It's Lola Fashoyin-Aje again from FDA. I guess I just want to emphasize and clarify our view of these data. We may never know why there was this increase of early deaths in the cilta-cel arm compared to the control arm. This trial was not designed in a way that allows us to know with certainty which population is experiencing these increased deaths in the treatment arm. This trial was a randomized trial.

We do see these early deaths, and what we're asking the committee, really, here is to consider whether in light of the clinical benefit shown in this trial, which we agree is clinically meaningful, whether that benefit outweighs these risks, which are risks associated with cilta-cel treatment. Whether it's before the treatment is administered or after the treatment is

administered, it's a risk. When a patient is referred to receive this treatment, they're foregoing other treatments that may not result in deaths, so the totality of the risks associated with the treatment should be considered as part of the benefit-risk assessment.

Now, there was a lot of discussion around the overall survival curves and the data provided for survival, and I think another consideration for the committee may be whether or not, at this time, it is your assessment that those additional data provide more support and reassurance around the clinical benefit in a way that outweighs, again, those risks that we don't completely understand why these early deaths occurred.

So that's ultimately the reason we convened this committee, is for you to say these PFS data, this evidence of effectiveness, how do we consider these early deaths in that context? But this trial is not going to tell us for whom CAR T in this line of treatment is more favorable than another group. Thank you.

DR. MADAN: Right. I think their discussion points -- Ravi Madan, NCI -- have really wrestled with those 6 or 8 patients early on, and we don't know, that are before the therapy. I think that's actually been the crux of a lot of our discussions here, and my sense, generally, is there is a sense of benefit in terms of PFS here, but I welcome anyone from the committee, or the panel I should say, who would like to join in or have any other comments in addition to that context. But I think our discussion has been within that context, and if anyone wants to chime in, go ahead, Dr. Frenkl.

DR. FRENKL: Okay. Thanks. I'll just say when I look at the FDA slide, on slide 21, the rate of death in the first 10 months after randomization, I think is the context of what we're talking about here. But I also appreciate the sponsor's demonstration of the data, where it was really in the first 2 months that accounted for the difference in the death, which, of course, they didn't receive the drug yet.

But if I look at that data that the FDA

showed on slide 21, it's 14 percent versus 12 percent in the rate of death, and that's in the beginning before treatment -- first of all, 14 to 12 percent, it's hard to know if that's really a meaningful difference, and then it's driven by progressive disease prior to treatment, which makes sense, and then after treatment, the rate of death is actually lower in the cilta-cel arm. It's 9.1 percent versus 11.3 percent. So overall, lower, and then the AE rate of 7.7 percent versus -- sorry, I'm just trying to remember.

DR. MADAN: The slide's up. I think they put it up.

DR. FRENKL: Oh, the the slide is up? Okay. Thank you. Yes. So here, after treatment, the higher rate of death is due to AEs, 7.7 percent versus 4.2 percent, but then that's traded with death from PD, and results in the overall. So, to me, it's definitely a positive risk-benefit ratio here when we're looking at it.

DR. MADAN: Okay. Yes. I think you've highlighted the slide that's pinpointed a lot of

what we've been discussing here, Dr. Frenkl, so I thank you for doing that.

Does anybody else want -- Dr. Spratt, go ahead.

DR. SPRATT: Yes. Dan Spratt, Case Western. Again, just trying to make it a discussion here, and again, to respond, I appreciate what the FDA said, that they want for regulatory approval to focus on prespecified endpoints. And just going back to the question here, the discussion point, the PFS benefit prespecified was positive.

I don't know if they can pull up on the FDA presentation, slide 30, which is the OS data with the longer term follow-up data cutoff from December 13, 2023, if that can be shown, but in the context -- perfect; on the right, we're talking about the early deaths. I think, again, they showed -- and I realize the confidence intervals are incredibly wide because there are so few events early on. There is no statistical difference, and I think many of us early on, if you saw curves that just sort of floated around there, we would say

that's probably just negative, no difference, but there's plenty of events happening after that.

So I think in this prespecified secondary endpoint, overall survival was also statistically significant, so I'm still a little bit confused here. The prespecified a priori endpoints were positive.

DR. MADAN: Right, and I think that that factors into a little bit of our discussion here because we have some positive long term with survival and PFS signals, but the short-term focus of this question is really the early risk of death, so we're struggling with that a little bit. But I think that's actually been the heart of the matter this morning, and not something lost on the panel.

I do think that Dr. Spratt, in a lot of ways, summed it up very nicely, that we're seeing those curves, we're seeing the PFS benefit, and the deaths up front are concerning and definitely factoring into our decision, including the deaths before treatment, and that's factored into our discussion here.

My sense, again, from this conversation that we're having about specifically question 2, just as a summary, is that there is an acknowledgement of early risk, some of what may or may not be clearly mitigated in the future. There is optimism that that's possible, but there are no guarantees, but the sense is that it does lead to long-term benefits here, and I think that's the sense of the the panel, although I think we'll have a vote coming up with our third question. That's how I would summarize our discussion point here. I appreciate everyone for contributing, and this was good.

So with that, unless there are any last comments, we will now proceed to question 3, which is a voting question. I don't see any hands, so Dr. Joyce Frimpong will now provide us instructions for the voting question. And again, just pay attention to what the question's asking and make sure that we go ahead.

Dr. Frimpong, you're up.

DR. FRIMPONG: Thank you, Dr. Madan.

This is Joyce Frimpong, DFO. Question 3 is a voting question. Voting members will use the Zoom platform to submit their votes for this meeting. If you are not a voting member, you will be moved to a breakout room while we conduct the vote. After the chairperson reads the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, we will announce that voting will begin.

A voting window will appear where you can submit your vote. There'll be no discussion during the voting session. You should select the button in the window that corresponds to your vote. Please note that once you click the submit button, you will not be able to change your vote. Once all voting members have selected their vote, I will announce that the vote is closed. Please note that there will be a momentary pause as we tally the vote results and return non-voting members into the meeting room.

Next, the vote results will be displayed on

the screen. I'll read the vote results from the screen into the record. Thereafter, the chairperson will go down the list and each voting member will state their name and their vote into the record. Voting members should address any subparts of the vote in question, including the rationale for their vote.

Are there any questions about the voting process before we begin?

(No response.)

DR. FRIMPONG: Since there are no questions, I will hand it back to Dr. Madan so we can begin.

DR. MADAN: Okay. This is the voting question that we are being asked to vote on. Is the risk-benefit assessment of cilta-cel for the proposed indication favorable? And I'll ask the committee or panel if they have any requests for clarification on voting question number 3?

(No response.)

DR. MADAN: Not seeing any hands requesting clarification, I think we will move forward with voting on question 3.

DR. FRIMPONG: We will now move non-voting participants to the breakout room.

(Voting.)

DR. FRIMPONG: Voting has closed and is now complete. The voting results will be displayed.

(Pause.)

DR. MADAN: Thank you. I think I'm not seeing the Excel voting list, but we will now go down the list.

DR. FRIMPONG: Dr. Madan --

DR. MADAN: Go ahead.

DR. FRIMPONG: -- I'll be able to read.

DR. MADAN: Go ahead.

DR. FRIMPONG: There are 11 yeses, 0 noes, and 0 abstentions. I'll hand it over to you.

DR. MADAN: Thank you. Okay. Thank you, Dr. Frimpong.

We will go down the list and have everyone who voted state their name into the record. You may also include the rationale for your vote. It looks like I am up first, so I will go ahead and do that.

I voted yes. The data from the CARTITUDE-4 is still somewhat immature, but it appears to be favorable in its totality at this time. While the risks of early death, often prior to therapy, are not ignored in this discussion or this vote this morning, it does seem to be outweighed by the long-term potential benefits here. Ideally, emphasis in the further development of this therapy could be placed in better understanding of how to optimize bridging therapy and guarding against infection for patients with multiple myeloma to further optimize this therapy.

Our second vote comes from John Deflice.

DR. DEFLICE: Yes. My perspective is from a myeloma perspective. I've had myeloma for 13 years, and I know most of the people that gave testimonials for Carvykti is based on the CARTITUDE-4 study. I've been a facilitator of a support group in New Mexico for greater than 10 years, and we've had attendees at the last meeting from California and New York. We've also started a support group to the IMF, a Spanish

support group, which is mostly international, and I also volunteer for the LLS.

As we witnessed, we were informed that the deaths were not related to Carvykti but were related to other issues, and it was during the pandemic. And we were also informed that there may be variations and options for bridging therapy, so I wholeheartedly voted yes.

DR. MADAN: Thank you, Mr. Deflice.

Dr. Advani?

DR. ADVANI: So I voted yes for very similar reasons. I think the benefit is pretty robust, and there's the small number of patients in the beginning, and largely the deaths are related to not getting the treatment, or inadequate bridging, or delay, or COVID; not completely understood, but I think, overall, it was a very positive trial with significant benefit to most patients.

DR. MADAN: Thank you.

Dr. Lieu?

DR. LIEU: Hi, everybody. This is Chris Lieu from University of Colorado. I voted yes. To

me, I thought that the data that was striking was the tail of the PFS curve and the duration of response. If patients have a chance to get a durable response while being off of therapy, the question is whether or not the patients are willing to undertake the risk that we see in the data so far of early progression or death.

The old adage is, is the run worth the slide? And the run here, it's not trivial. We're talking about potential increased risk of death in the early months. There's no question that these patients are going to experience cytokine relief syndrome, the possibility of ICANS, and other long-term toxicities. If there's only a minimal improvement in PFS, the answer here is always no; it's too short of a, quote, "slide," however, there's a chance for a long durable response.

While not receiving toxic therapy during that response time, the answer may be yes, and I honestly believe the answer will likely be yes for patients who may want just a chance at a long, durable time off treatment for multiple myeloma, so

therefore, I believe the benefit-risk profile is favorable. Thank you.

DR. MADAN: Thank you, Dr. Lieu.

Dr. Gradishar?

DR. GRADISHAR: Yes, much the same. I felt that the long-term PFS was compelling and the survival is going in that direction. Furthermore, the upfront risk, I remain unconvinced that that's directly attributable to the therapy itself. I think there are other factors that are likely contributing rather than the therapy in question. So I think the totality of the data is what motivated me to vote yes.

DR. MADAN: Thank you.

Dr. Vasan?

DR. VASAN: Hi. Neil Vasan, Columbia. I voted yes. So for me, this came down to acknowledging the very real but small risks of early death relative to the large benefits, and I believe that the benefits here do outweigh the risks. I think that the analogy to bone marrow transplant is relevant, and that in further years,

as we obtain more experience with CAR T cells in myeloma, we'll have a better understanding of all of these risks and benefits.

That being said, I do have concerns about the balance in post-progression therapies in this trial, which would directly impinge on OS. I'd like to thank the FDA and the applicant. I think this was a productive discussion today on endpoints. It's clear that there are challenges in getting patients to CAR T therapy in myeloma, and I hope that all stakeholders can further define the subgroups of patients who can and cannot make it to therapy and expedite the timeline to receiving CAR T cells. Thank you.

DR. MADAN: Thank you, Dr. Vasan.

Dr. Nieva?

DR. NIEVA: Jorge Nieva, USC. I voted yes. People want to be cured, and this treatment induces long term eradication of minimal residual disease, but I think it comes at an upfront cost, and I don't think it's entirely the delays. I think it's also the preconditioning regimen. But this is

something that can be individually decided between patients and physicians, and I think each person can decide for themselves if the run is worth the slide, as Dr. Lieu said. Thank you.

DR. MADAN: Thank you, Dr. Nieva.

Dr. Spratt?

DR. SPRATT: Yes. Dan Spratt, UH Seidman Cancer Center and Case Western Reserve University. I voted yes. I think the FDA was very appropriate to focus on these early deaths; however, seeing the totality of the data, I think both the prespecified primary and at least all the presented secondary endpoints -- so PFS, CRs, minimal residual disease just mentioned, and even including overall survival -- clearly favor this agent.

I think the benefit outweighs the risk, and I think there's a lot of learning lessons to continue to optimize this, as well as I think the discussion today is worth further discussion also on design of endpoints and prespecification analyses, and how to actually embed these in a realistic way.

DR. MADAN: Thank you, Dr. Spratt.

Dr. Lattimore?

MS. LATTIMORE: Thank you. Susan Lattimore. I also voted yes. I just want to lift the comments of others on this committee in that the opportunity for off-treatment time is incredibly compelling for patients and families. Certainly improving access to this treatment will improve overall outcomes for all individuals, so I appreciate the conversation and a second look at this data.

DR. MADAN: Thank you, Dr. Lattimore.

Dr. Hunsberger?

DR. HUNSBERGER: Sally Hunsberger. I voted yes. I agree that the PFS data is very strong. I think it was appropriate for the FDA to want to explore the early deaths and ask this question, so I do applaud that, and so I affirm Dr. Spratt's comments. But I do think the long-term survival curves that are looking to separate are really important and outweigh the early deaths, but I think we do need to explore what's going on early. Thank you.

DR. MADAN: Thank you. Dr. Hunsberger.

Dr. Kwok?

DR. KWOK: Mary Kwok, University of Washington, Fred Hutch Cancer Center. I also voted yes. I think the separation of the curves showing improvement of PFS with this regimen early on is impressive. It's an important therapy, and I just echo other comments from this panel.

I also agree that treating oncologists will have to have a serious conversation with the patient when it comes time to choose this option to explore the increased risk of death, and then I also look forward to future data to help us understand what's going on and what we can do to improve.

DR. MADAN: Thank you, Dr. Kwok.

So I think, just to summarize, we see that the votes were 11 for yes and zero for no. I think the committee in this discussion today clearly recognized that the early deaths are a concern and something that really needs to be worked on to be mitigated in the future, but I also think that the

committee recognized that despite our best efforts, we probably don't have one clear cause for that. And on top of that, the PFS data is encouraging, and then the added dimension of the fact that those aren't just curves, but are patients free of therapy, I think really resonated with the committee today.

I think there was some optimism that these survival curves are giving us a glimpse into truly longer duration of flattening of the curves, or tails on the curves as we like to say, which maybe indicates much more longer disease-free survival. But I think that everybody agrees that we need to pay attention to these upfront deaths and also optimize this, and continue to follow this data.

Taking a step back, though, I agree with the committee here. This was an important question to ask, and I appreciate the FDA for their balanced discussion and helping us understand the data in an added dimension as well. I appreciate the openness of Janssen Biotech in sharing their data, and the presentations I thought were very good on both the

FDA and the sponsor side.

We had 10 open public hearing speakers, and they shared their stories, and I do think that, again, it resonated with the committee. So I just want to say thank you to everybody for joining this morning session. We still have an afternoon session to come, which we'll talk about in a moment. But before we do adjourn this morning session, I just want to make sure that there are no last comments from the FDA.

DR. VERDUN: Thank you. I would just like to, on behalf of the FDA, really thank the committee for the robust conversation and discussion this morning. It was extremely helpful to us, and we appreciate your time and the thought that you put into that discussion. Thank you very much.

Adjournment

DR. MADAN: Thank you.

So we are now going to adjourn this morning's session. We went a little long, so I would like to reconvene at 1:30 instead of 1:25.

The FDA has given us an opportunity to do that, so we can reconvene, then, at 1:30. Panel members, please remember that there's no discussion or chatting of the meeting topics with other panel members during this break or lunch. Additionally, panel members should plan to join back at 1:20 p.m. Eastern Time to ensure that we are connected before we reconvene to start the afternoon session at 1:30 p.m. Eastern Time.

Thank you, everybody, for a productive morning session.

(Whereupon, at 1:00 p.m., the morning session was adjourned.)