FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

(ODAC)

Virtual Meeting

Afternoon Session

Friday, March 15, 2024

1:30 p.m. to 5:08 p.m.

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(1:30 p.m.)

Call to Order

DR. MADAN: Good afternoon, and welcome. I would first like to remind everyone to please mute your line when you are not speaking. My name is Ravi Madan, and I will be chairing this afternoon's session and meeting. I will now call the afternoon 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: Thank you, Dr. Madan.

Good afternoon. 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. I will start with our standing members.

Dr. Advani?

DR. ADVANI: Ranjana Advani. I'm a

hematologist/oncologist at Stanford.

DR. FRIMPONG: Thank you.

Dr. Gradishar?

DR. GRADISHAR: Bill Gradishar, Northwestern University.

DR. FRIMPONG: Thank you.

Dr. Lieu?

DR. LIEU: Hi, everybody. I'm Chris Lieu, GI medical oncologist from University of Colorado.

DR. FRIMPONG: For our chairperson, Dr. Madan.

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

DR. FRIMPONG: Thank you.

Dr. Nieva?

DR. NIEVA: Hello. I'm Jorge Nieva, thoracic medical oncologist, University of Southern California and Norris Comprehensive Cancer Center.

DR. FRIMPONG: Dr. Spratt?

DR. SPRATT: Dan Spratt. I'm the Chair of Radiation Oncology at University Hospitals Seidman Cancer Center and Case Western Reserve University.

Thank you.

DR. FRIMPONG: Thank you.

Dr. Vasan?

DR. VASAN: Hi. Neil Vasan. I'm a breast oncologist and physician scientist at Columbia University Cancer Center.

DR. FRIMPONG: Thank you.

And now for our industry representative, Dr. Frenkl?

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

DR. FRIMPONG: Thank you.

And now for our temporary voting members, first for our patient representative, Dr. Deflice.

DR. DEFLICE: Hello. I'm John Deflice. I'm a gastroenterologist, and I'm a 13-year survivor of myeloma.

DR. FRIMPONG: Thank you.

Dr. Hunsberger?

DR. HUNSBERGER: Sally Hunsberger, biostatistician at NIAID. Thank you.

DR. FRIMPONG: Dr. Kwok?

DR. KWOK: Hi. My name is Mary Kwok. I am at the University of Washington and Fred Hutch Cancer Center.

DR. FRIMPONG: Thank you.

And now for our consumer representative for the meeting, Ms. Lattimore.

MS. LATTIMORE: Hi. I'm Susan Lattimore.

DR. FRIMPONG: Thank you.

And now for our FDA participants, Dr. Pazdur.

DR. PAZDUR: Hi. Dr. Richard Pazdur, Director of the Oncology Center of Excellence.

DR. FRIMPONG: Thank you.

Dr. Theoret?

DR. THEORET: Hi. Good afternoon. Mark Theoret, Deputy Director, Oncology Center of Excellence, FDA.

DR. FRIMPONG: Thank you.

Dr. Verdun?

DR. VERDUN: Good afternoon. Nicole Verdun, the Director of the Office of Therapeutic Products.

Thank you.

DR. FRIMPONG: Dr. Kanapuru?

DR. KANAPURU: Hi. Bindu Kanapuru. I'm a hematologist/oncologist physician at Oncology, Center of Excellence, Medical Oncology Review Team Lead. Thanks.

DR. FRIMPONG: Thank you.

Dr. Sokolic?

DR. SOKOLIC: Hi. Rob Sokolic, Chief of Hematologic Malignancy Branch at CBER.

DR. FRIMPONG: Thank you.

Dr. Sharma?

DR. SHARMA: Good afternoon. I'm Poornima Sharma, a hematologist/oncologist in the office of Clinical Evaluation, CBER, and the primary reviewer for this application.

DR. FRIMPONG: Thank you.

And Dr. Lin.

DR. LIN: Good afternoon. I'm Xue Mary Lin. I'm a mathematical statistician at the Division of Biostatistics at CBER. I'm the primary statistical reviewer of this BLA supplement. Thank you.

DR. FRIMPONG: Thank you.

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 be a fair and open forum for discussion of these issues and that individuals can express their opinions and views without interruption. Thus, a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting this afternoon.

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. Thank you.

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

Conflict of Interest Statement

DR. FRIMPONG: Thank you.

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 the

purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of supplemental biologics license application, sBLA, 125736.218 for Abecma, idecabtagene vicleucel, suspension for intravenous infusion, submitted by Celgene Corporation, a Bristol-Myers Squibb Company. The proposed indication is for the treatment of adult patients with relapsed or refractory multiple myeloma who have received an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

The committee will have a general discussion focused on the overall survival data in Study MM-003, KarMMa-3, and the risk and benefit of idecabtagene vicleucel in the intended population. This is a particular matters meeting during which specific matters related to the supplemental biologic application 125736.218 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 firm.

The waiver also involves 10 of the employer's research contracts for various studies funded by the party to the matter or competing firms. Dr. Kwok's employer receives between $0 to $50,000 per year for each of the four total 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, TeneoOne, and AbbVie; and between $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 reasoning for issuing the waiver are described in the waiver document, which is posted on 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're encouraging 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.

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.

Back to you, Dr. Madan.

DR. MADAN: Thank you, Dr. Frimpong.

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

FDA Opening Remarks - Robert Sokolic

DR. SOKOLIC: Thank you.

My name is Rob Sokolic. I'm the Chief of the Malignant Heme Branch at the Office of Clinical Evaluation in CBER. I will briefly introduce the

purpose of the convening of this Oncology Drugs Advisory Committee meeting. During this meeting, we'll be discussing the clinical development program for idecabtagene vicleucel, also known as ide-cel and Abecma, for the treatment of relapsed multiple myeloma.

Ide-cel is an autologous T-cell immunotherapy for the treatment of myeloma. Cells are engineered to express a chimeric antigen receptor directed against BCMA, a protein expressed by benign and malignant plasma cells. Ide-cel is currently approved for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.

The applicant, Celgene, submitted a supplemental biologics license application, or BLA, seeking expansion of the ide-cel indication to the treatment of adult patients with relapsed or refractory multiple myeloma who have received an immunomodulatory agent, a proteasome inhibitor, and

an anti-CD38 antibody. 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 the questions for which we are requesting the committee's discussion.

The applicant submitted the results of the KarMMa-3 trial to provide evidence of the safety and effectiveness of cilta-cel [?] for the proposed indication. KarMMa-3 demonstrated an improvement in progression-free survival in patients randomized to ide-cel compared to patients randomized to standard for care therapy.

During the review of the application, FDA identified the higher rate of early deaths in the ide-cel arm compared to the standard therapy 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 15 months. As you'll hear from my colleagues in the subsequent FDA presentations, the crossing

hazard 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 KarMMa-3 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 KarMMa-3 trial. KarMMa-3 is an ongoing open-label, randomized, phase 3 clinical trial. A total of 286 participants with relapsed or refractory multiple myeloma after 2 to 4 regimens, including an IMiD, a proteasome inhibitor, and daratumumab, who had disease refractory to the last regimen, were randomized. Participants were randomized to either a single infusion of ide-cel after having undergone lymphopheresis, bespoke product manufacturing, and lymphodepleting chemotherapy, or to standard of care immunochemotherapy until

progression or intolerance. Treatment response is assessed in KarMMa-3 using the 2016 IMWG criteria.

Shown here is the Kaplan-Meier plot for progression-free survival for the intention-to-treat population at the interim analysis. KarMMa-3 demonstrated a statistically significant effect on PFS, with a hazard ratio 0.495, indicating a 50 percent reduction in the hazard rate of progression for patients randomized to ide-cel compared to patients randomized to standard of care. Median PFS was 13.3 months in the ide-cel arm and was 4.4 months in the standard of care arm.

KarMMa-3 demonstrated a numerically increased overall survival in the ide-cel arm, although the crossing hazards pattern makes the hazard ratio uninterpretable. Median OS was 32.8 months in ide-cel and was not reached for the standard of care arm. My colleague, Dr. Sharma, 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 idecabtagene vicleucel led to a significantly improved rate of progression-free survival, but with a decrement in overall survival in the first 15 months of the trial, and that the decrement in overall survival calls into question whether the risk-benefit assessment is favorable.

We ask the members of the committee to discuss whether the results of KarMMa-3 are sufficient to support a positive risk-benefit assessment of ide-cel for the proposed indication, and whether the risk of early death associated with ide-cel treatment is acceptable in the context of the PFS benefit.

Shown here is the voting question, which I'll now read. Is the risk-benefit assessment for idecabtagene vicleucel for the proposed indication favorable? Thank you for your attention. I now invite representatives of Celgene to give their presentation. Thank you.

DR. MADAN: Both the Food and Drug Administration and the public believe in a

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

For this reason, the FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships they may have with the applicant, such as consulting fees, travel expenses, honoraria, and in the interest of the applicant, such as equity, or those that are based on the outcome of this 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 these financial relationships at the beginning of the presentation, it will not preclude you from speaking.

We will now proceed with the Celgene presentation. Thank you.

Applicant Presentation - Anne Kerber

DR. KERBER: Thank you.

My name is Anne Kerber. I lead Late Clinical Development for Hematology, Oncology, and Cell therapy at BMS. I would like to thank FDA and the ODAC members for your time today to review study results of the KarMMa-3. Today, we will first present disease background and unmet need, KarMMa-3 design and results of the primary endpoint of PFS, then overall survival and safety data, and we will close with the clinical perspective.

At the heart of our discussion today is making Abecma available to the many patients who in the current treatment landscape exhaust their therapy options much earlier, as you will hear from Dr. Lonial and Dr. Raje. The current indication for Abecma is in the treatment of patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, which must have included an immunomodulatory agent, a proteasome inhibitor, and anti-CD38 monoclonal antibody. This excludes many patients who by then are too frail to

successfully undergo CAR T therapies.

The indication we are seeking is for patients with relapsed or refractory multiple myeloma who are triple-class exposed, meaning they received an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. This indication allows access to CAR T therapy to patients at any time after they exhaust all three classes of therapy and often when they are more fit to receive and benefit from CAR T treatment.

As you've heard, ide-cel is a genetically modified cell therapy, targeting the BCMA antigen on the surface of the myeloma cells via the chimeric antigen receptor. Upon binding to the target antigen, the CAR T cell is activated and leads to T-cell mediated killing of the tumor cell. Ide-cel is an autologous product that is manufactured individually for each patient from their own T cells.

Now, let me show you the cell therapy treatment journey, as it provides important context for the interpretation of the study results.

Patients identified for CAR T cell therapy first undergo leukapheresis, a process during which white blood cells are collected from the patient's blood. These cells are shipped to a manufacturing facility where CD4- and CD8-positive T cells are first separated, activated, transduced with a lentiviral vector that carries the CAR construct, then expanded and cryopreserved for transport back to the treatment center.

During this time, patients need anti-cancer therapy to control disease progression. We call this treatment bridging therapy. Subsequent to bridging therapy, the patient undergoes a washout period. Once available at the treatment center, patients receive 3 days of lymphodepleting chemotherapy, followed by the CAR T cell infusion. In summary, this is a multistep process that takes about 3 to 4 weeks to complete.

The KarMMa-3 protocol was initially submitted in 2018 and amended in January 2020 to introduce crossover and to add two additional standard of care options. At that time, evolving

data showed unprecedented benefit-risk for CAR T in relapsed/refractory multiple myeloma, and as such, both physicians and patients were not supportive of enrollment into the control arm. As a result, we decided to offer crossover for patients. In addition, also based on the advice from our investigators, we added two standard of care options which reflects the lack of a defined standard of care for this patient population.

We submitted the sBLA for KarMMa-3 in February 2023 after meeting the primary endpoint of PFS at the second interim analysis. Since December last year, ide-cel was approved in Japan, Switzerland, and received a positive CHMP opinion in the European Union based on the KarMMa-3 trial results.

What you will hear today is a detailed analysis of the KarMMa-3 trial, the first and only randomized study of CAR T, in patients with triple-class exposed, relapsed or refractory multiple myeloma, a patient population with very high unmet need. We will review data on the

primary and key secondary endpoints, showing clinically meaningful benefit across all prespecified subgroups. We will take a deep dive into the overall survival data with a focus on the crossover design, as well as the numerical imbalance in early deaths in the trial. These early deaths were driven by patients who never received ide-cel.

I would also like to highlight that at 15 months, when the Kaplan-Meier curves crossed , two-thirds of the patients in the standard of care arm had already crossed over to receive ide-cel. You will also hear from Dr. Lonial and Dr. Raje how KarMMa-3 fulfills a critical unmet need, especially for patients who are exposed to all three classes of anti-myeloma therapy earlier in their treatment course.

Using ide-cel earlier in the treatment course offers patients a better chance to bridge to CAR T therapy and lowers their risk of not receiving ide-cel, as you will hear later today from Dr. Raje. It is important to note that in the

KarMMa-3 study, bridging therapy was restricted to allow us to better isolate the ide-cel treatment effect; however, as our clinicians will discuss, in clinical practice, bridging therapy is individualized and can be optimized beyond what was permitted in the protocol, and time without anti-multiple myeloma control can be minimized.

With that in mind, BMS is committed to making adequate information and support available to both patients and physicians. Data on the potential for early deaths and the need to effectively bridge patients will be included in the USPI to allow for informed decision making.

The administration of ide-cel will continue to be restricted to qualified centers as part of our REMS program, and as such, all treating physicians are specifically trained and have deep expertise with respect to the identification of the right patients and the selection of the best bridging approach. We will continue to monitor commercial patients for 15 years in the context of our registry.

Importantly, we have made significant progress to get product to patients faster and more reliably. Our turnaround time is currently 25 days in the U.S., which is much shorter than the 34 days in the trial, and we have a manufacturing success rate of more than 90 percent in the commercial setting. I would like to conclude that the benefit-risk profile of ide-cel in patients with triple-class exposed relapsed/refractory multiple myeloma is favorable and supports the use in an earlier treatment line setting.

Dr. Lonial will now give a brief overview of multiple myeloma and where we are in treating patients with this incurable cancer.

Applicant Presentation - Sagar Lonial

DR. LONIAL: Thank you, Dr. Kerber.

My name is Sagar Lonial, and I'm the Chief Medical Officer at the Winship Cancer Institute of Emory University, and I'm Professor and Chair of the Department of Hematology and Medical Oncology, also at the Emory University School of Medicine. I appreciate the opportunity to give you the disease

background on myeloma as part of this presentation. While I do serve as a consultant for BMS, I have received no compensation for preparing and participating in today's ODAC, and I have no financial interest in the outcome of the meeting.

Multiple myeloma is a progressive disease that presents with both hematologic and non-hematologic complications. In recent years, there have been great advances in outcomes for patients with multiple myeloma as evidenced by numerous studies and collaborations between academia, industry, the FDA, and patient groups, but despite these advantages, the numbers of patients that need access to novel therapies continues to increase. This is particularly of importance when we look at the prevalence of myeloma increasing dramatically in the last 10 years, because while patients are living longer as a consequence of these advances, their need for additional therapies has become greater.

Here is data from our own center looking at a retrospective analysis of 325 patients, in black,

who received Dara RVd 300 at the top, transplant, and then risk-adapted maintenance, compared to a group of patients who received RVd 1000 in green below, triplet versus quadruplet induction, with much longer follow-up in the triplet induction group.

To really address the question that Dr. Lieu asked in the morning session, progression-free survival is a main driver of treatment choices for myeloma patients in their first 1 to 3 lines of therapy because median overall survival for many patients is in excess of 10 years, and for standard risk myeloma, may be in excess of 15 years. Overall survival is important as we assess toxicity over time, but progression-free survival in myeloma drives time with family, time being productive, and in the context of CAR T cells, time off of therapy.

What you can see from this figure is that there's a significant improvement, again, with the addition of quadruplets in black compared to triplets in green; however, even in frontline, patients are now becoming triple-class exposed,

thus impacting the efficacy of their subsequent therapy. And as we heard from Dr. Mailankody this morning, it's clear that many of our salvage therapies are effective, but being triple-class exposed was not a prerequisite for most of those studies, so that data will be more limited.

What remains a challenge is that there is no true plateau on either the remission or the survival curves, suggesting that what we are doing is perhaps converting myeloma to a chronic disease. That chronicity, however, does not eliminate the need for highly effective therapies later on in the treatment paradigm.

Thinking about the remaining unmet medical need, this slide compares two different groups of patients, standard risk in black and high risk in green, all treated on that RVd 1000 retrospective series that I previously mentioned. On the left, you see a significant drop in overall survival in the first 2 years that is attributable to patients who have unexpected early relapse, also defined as functional high risk. Management of these patients

remains a significant challenge.

We know that the median duration of remission for the average patient is greater than 5 years for their first remission, particularly with the use of high-dose therapy and auto transplant, but as you see, there's about 20 percent of patients that die or relapse despite that aggressive therapy within the first 2 years. On the right side of the graph, the box that shows patients continue to relapse and die of myeloma despite all the treatment advances in the last decade, these deaths are a consequence of either attrition or the development of drug resistance.

A high unmet medical need thus remains for patients with myeloma, and it really boils down to these three categories. The first is resistance, early resistance in the context of functional high risk, as I mentioned before, and the fact that 20 percent of patients die within the first 2 years of their initial induction therapy.

Second are patients who are triple-class exposed earlier in their disease course, as early

as frontline therapy in 2024, which sows the seeds for subsequent drug resistance following induction therapy. And finally, the concept of attrition, which is important from an access and equity perspective, we know that with each line of therapy, 20 to 30 percent of patients do not get the subsequent treatments, limiting the patients that can ultimately benefit from highly effective therapy, including agents such as ide-cel.

At the bottom of this slide is an example of a patient that might be treated at any center around the country, and what you'll often see is Dara RVd, or a quadruplet as induction, followed by transplant, followed by lenalidomide plus or minus daratumumab as maintenance therapy. This was recently published in the New England Journal.

The brown shading starting from the left shows how these patients are already triple-class exposed at the time of their initial frontline therapy, and many of them may become triple-class resistant at the end of their first-line therapy as well. When you get beyond salvage number 2,

available treatments become quite limited and are associated with significant toxicity, which is why moving treatments like ide-cel earlier in the disease course becomes even more important.

In addition, effective bridging is critical to outcomes. As you're going to hear later today, effective bridging therapy increases the fraction of patients who can receive CAR T cells, and yet as patients become more resistant, access to bridging therapy becomes more limited.

The attrition seen here in blue demonstrates that with each line of therapy, one loses 20 to 30 percent of patients. With each line of therapy, you lose the efficacy of treatment, T-cell health, effective bridging, and ultimately more patients die. In order to improve outcomes, highly effective therapies such as CAR T cells need to be brought earlier in the disease course.

So to wrap up, the three unmet medical needs remain. First, there is a significant treatment gap with limited agents available beyond third-line therapy. Many patients are becoming triple-class

exposed as part of frontline therapy, raising the need for more effective therapies earlier. Second, due to significant attrition, many patients don't even get a chance to receive highly effective therapy options. And finally, we know that efficacy of bridging is directly linked to getting more patients to CAR T cell infusion successfully as opposed to, unfortunately, relapse or dying before they get the product.

Moving CAR T access to earlier in the treatment course allows patients to be treated with a broader range of more effective bridging therapies, particularly in the context of refractoriness, and we've seen this in the context of real-world data, where the the frequency of patients going from a collection to infusion is a much greater percentage than in most clinical trials.

Thank you very much for your attention. With that, I will turn it over to Dr. Bleickardt.

Applicant Presentation - Eric Bleickardt

DR. BLEICKARDT: Thank you, Dr. Lonial.

My name is Dr. Eric Bleickardt, and I'm Head of Late Clinical Development, Cell Therapy at Bristol-Myers Squibb. I would like to show you important data demonstrating a clinically relevant benefit of ide-cel in patients with triple-class exposed relapsed/refractory multiple myeloma. First, let me describe the KarMMa-3 trial design and guide you through the primary and key secondary endpoints.

The intent of the KarMMa-3 trial was to evaluate a highly effective and safe therapy in a patient population where a treatment gap exists. KarMMa-3 included patients with relapsed/refractory multiple myeloma, who had 2 to 4 previous regimens, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody, daratumumab. Thus, all patients were exposed to all major classes of myeloma therapy or triple-class exposed.

Patients were also refractory to their last regimen. Stratification factors included age, number of previous regimens, and high-risk

cytogenetics. Patients were randomized 2 to 1 to receive ide-cel versus one of the five standard regimens. The 2 to 1 ratio was included to improve accrual to the trial given emerging data from ide-cel in a later line setting from the previous KarMMa-3 trial. In the ide-cel arm, a single cycle of bridging therapy was allowed during the manufacturing process. A minimum 14 days of washout was required prior to lymphodepleting chemotherapy.

On the standard regimens arm, patients began one of the five selected regimens prior to randomization and continued until disease progression or unacceptable toxicity. Patients in a control arm could crossover to receive ide-cel upon confirmed disease progression.

The primary endpoint in this trial was progression-free survival as assessed by a blinded independent review committee, an endpoint validated for clinical benefit in multiple myeloma. The key secondary endpoints were objective response rate, also by an independent review committee, and

overall survival. Additional secondary endpoints included complete response rate, minimal residual disease, patient-reported outcomes, and safety.

The primary endpoint of progression-free survival and key secondary endpoints of overall response rate and overall survival were evaluated using a group sequential hierarchical testing strategy. It is important to point out that the trial was designed to have a 50 percent power for overall survival; therefore the ability to show a difference in overall survival was limited from the outset. The data we are presenting today is interim progression-free survival efficacy, which is the primary PFS analysis, as well as overall response rates. The information fraction was 84 percent for the primary PFS analysis.

These were the data submitted and reviewed by the FDA. Overall survival data will be based upon an updated cut of the data when the PFS analysis was final. The information fraction for overall survival was 74 percent. Final PFS data were consistent with the interim PFS data cut.

The patient population in the KarMMa-3 trial was reflective of patients with high-risk, triple-class exposed myeloma refractory to most of the available therapeutic options. The majority of patients were enrolled from the United States. The revised international staging system of three, comprising the worst prognosis, were noted in more than 10 percent of patients. About a quarter of the patients had extramedullary plasmacytoma, more than a quarter of patients had high tumor burden, and nearly half the patients had high-risk cytogenetics. Importantly, two-thirds of patients had triple-class refractory multiple myeloma, and the vast majority, 93 to 95 percent, were refractory to daratumumab.

The time without anti-myeloma therapy at the beginning of treatment, shown here with red, was different between the treatment arms. In the standard of care arm below, within 7 days, patients received a standard regimen, which they continued in either 21- or 28-day cycles. Patients randomized to the ide-cel arm above had no therapy

prior to leukapheresis to ensure optimal T cells for manufacturing. The bridging therapy for ide-cel was optional, limited to one cycle and was restricted to one of the five regimens. These were the same 5 regimens used in the control arm.

Importantly, there was a minimum of a 2-week washout period between the end of bridging therapy and the start of lymphodepleting chemotherapy. Patients received fludarabine and cyclophosphamide over 3 days, which is not particularly effective against myeloma; then there were 2 days off before the ide-cel infusion.

The primary endpoint was met with a statistically significant and clinically relevant improvement in progression-free survival and a hazard ratio of 0.49. With a median follow-up on the trial of 18.6 months, the median progression-free survival was 13.3 months on the ide-cel arm and 4.4 months on the control arm.

The table at the bottom highlights the expected median progression-free survival for patients with triple-class exposed

relapsed/refractory multiple myeloma from seven external control series, including contemporary real-world evidence and a subgroup of patients in the recently published CARTITUDE-4 trial. The median progression-free survival is in the range of 4 to 5 months, which is exactly what we saw in the control arm of the KarMMa-3 trial, providing further external validation.

The progression-free survival benefit was consistent across all the prespecified subgroups, including the triple-class refractory patients, those with R-ISS stage 3, high tumor burden, extramedullary plasmacytoma, 2, 3, or 4 prior lines of treatment, as well as high-risk cytogenetics, all favoring ide-cel.

In the key secondary endpoint of objective response rate, there was a significant benefit with an objective response rate of 71.3 percent on the ide-cel arm versus 41.7 percent on the control arm. This key secondary endpoint is one of the highest response rates seen in a randomized trial for this particular patient population. There was a

striking difference in the complete response rates between the two arms favoring ide-cel. The median duration of response also favored ide-cel.

Looking at the very deep responses of minimal residual disease among patients with a complete response, again, there was a dramatic difference between treatments with ide-cel, leading to MRD negativity in 20 percent of patients compared to 1 percent in the standard regimen's arm.

In a trial that met its primary endpoints of progression-free survival and response rates, but overall survival is confounded by crossover, patient-reported outcome data take on a crucial role in understanding the clinical benefit. Ide-cel led to improvements in quality of life according to several validated patient-reported outcome instruments, including the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire C30 and Multiple Myeloma Questionnaire. This analysis looked at overall score change from baseline to month 20 in

the intention-to-treat patient population. In particular, ide-cel led to a meaningful improvement in pain, fatigue, physical and cognitive function, and overall quality of life, and this was seen throughout the time on the trial.

A patient's quality of life is significantly impacted by myeloma and the ongoing chronic therapies. One of the critical features of CAR T cell therapy is that it's a one-time treatment with a long treatment-free interval, and this translates into an important improvement in quality of life.

In summary, the KarMMa-3 trial demonstrated a clinically meaningful benefit of ide-cel. It is the first randomized trial directly comparing a CAR T cell therapy with standard regimens in a triple-class exposed relapsed/refractory myeloma patient population. Ide-cel demonstrated a significant and clinically relevant benefit in the progression-free survival, with a reduction in progression or death of 51 percent. Ide-cel also led to an increase in the objective response rate over the standard regimens. The PFS and ORR

benefits were consistent across all of the preplanned subgroups. Important and meaningful for patients is that a one-time infusion of ide-cel led to an improvement in quality of life with a prolonged respite from myeloma therapy.

Overall survival was a key secondary endpoint in the KarMMa-3 trial. The crossover design confounded the comparison of overall survival. Let's look at the results. In the KarMMa-3 trial, 386 patients were randomized 2 to 1, with 254 assigned to ide-cel therapy and 132 assigned to the standard regimen arm. 225 patients in the ide-cel arm received the treatment, which includes 3 patients that received an out-of-specification product.

Among those in the comparator arm, 126 patients received the standard regimen. On the bottom right, we see of those 126 patients on the standard regimen arm, 74, or more than half, crossed over to receive ide-cel upon IRC confirmed progression. Not surprisingly, this confounds the comparison as reflected in the overall survival

results.

The median overall survival on the ide-cel arm was 41.4 months, and on the standard regimen arm was 37.9 months. Crossover affected the overall survival curve very early in the trial. Recall that 56 percent of the patients on the standard regimen crossed over to receive ide-cel, and that happened as early as 3 months. This is expected with a median progression-free survival on the standard regimen arm of 4.4 months.

The overall survival hazard ratio is 1. There's no perceived benefit or detriment in either treatment arm. Furthermore, to adjust for crossover, we used two prespecified and one post hoc statistical analysis. Acknowledging their limitations, notably, each of these analyses showed a hazard ratio less than 1, which further supports the absence of a detriment in overall survival.

Patients in both arms lived longer than expected. In the intention-to-treat curves, both arms showed a median overall survival close to 40 months. In the table at the bottom of the

slide, the median overall survival among the triple-class exposed patients from six different sources shows the expected survival for this patient population. The median overall survival is 18 months with over 2,600 patients. Since most patients in the KarMMa-3 trial received ide-cel, both arms of the trial exceeded the median overall survival expected for this patient population.

We are often asked how well the standard regimen treated patients do if they cross over to receive ide-cel? We cannot answer that question perfectly, but here is an analysis that endeavors to answer that question.

These overall survival curves show patients who progressed only on the standard regimen control arm of the trial. Patients who crossed over to ide-cel, in green, were required to meet the same criteria for ide-cel infusion as the patients who originally randomized to the ide-cel arm at the beginning of the trial. The patients are re-baselined at the time of their disease progression. Acknowledging this analysis is not

protected by randomization. Patients in the standard regimen arm who cross over with the intent to receive ide-cel have a favorable overall survival. Among the patients who do not crossover, in blue, the median overall survival of 20 months is expected for this patient population.

We saw in the intention-to-treat overall survival analysis that the curves cross at 15 months. Upon careful evaluation of the overall survival curves, it is clear that the perceived difference at the beginning of the curve is driven primarily by the results in the first 6 months.

The bar graph on the left shows the rates of death by different time segments early in the trial. In the first 6 months, the rate of death was numerically higher in the ide-cel arm. The rates become similar in the 6 to 9 month time frame at 7 percent and 5 percent, and after 9 months are higher with the standard regimen arm. A landmark analysis at 6 months further confirms that the difference is driven by the first 6 months, and the curves on the right are similar until month 15,

where they begin to separate. You will see that the FDA focused on the first 9 months from randomization in their briefing book. I will show you the 9-month data demonstrating that the conclusion is similar.

Here is the same figure but with the analysis by 9-month increments on the left and the landmark analysis on the right. The point is that the overall survival curves cross at 15 months. The vast majority of the difference in the curves is driven primarily by patients in the first 6 months after randomization.

Next, we asked which factors drive the overall survival results in the first 6 or 9 months. I will show you in the next few slides there were factors that did not contribute to the results and factors that could have played a role. Specifically, the parameters around bridging therapy and random variation could account for the early overall survival results. Regarding the imbalance in early deaths, we looked closely at these data to understand why there was a

difference.

Here is a very critical difference, and we have displayed this with both cutoffs, the 6 months in the BMS briefing book and the 9 months in the FDA briefing book. While the numbers are different, the trend and interpretation are similar. First, let's focus on the deaths in the first 6 months in the first two columns.

First, we look at the total number of patients who died. Within the first 6 months, the rates were 11.8 percent on the ide-cel arm and 6.8 percent on the standard regimen arm. Among patients who received study treatment, shown in the second row, the early death rates were similar, 5.1 percent for ide-cel versus 6.8 percent for the standard regimens, with progression of myeloma as the leading cause.

Where we see the big difference is among patients who do not receive study treatment. More than half the patients who died early, 6.7 percent of the overall ide-cel arm, never crossed the bridge to receive ide-cel. This is in contrast to

the standard regimen arm where none of the patients were in this category. Looking at the right, at the deaths within 9 months, the difference is 20 patients versus zero patients in the ide-cel arm and standard regimen arm, respectively. This explains the difference in the early death rates. It is not a direct ide-cel-related mortality; it is the patients who do not receive ide-cel.

Protocol restrictions led to more time without anti-myeloma therapy in the first 2 months in the ide-cel arm. The median time off therapy was 26 days in the ide-cel arm versus 6 days in the standard regimen's arm. Patients were randomized to the standard regimen at the bottom, had a median of 5 days until the start of therapy, and continued for 3- or 4-week cycles.

In the ide-cel arm above, let me show you the time off therapy. There was a median of 7 days from randomization to bridging. Bridging was not utilized in 17 percent of the patients. The median time from bridging to ide-cel infusion was 24 days. This could account for the differences in the early

deaths in the ide-cel arm, driven by patients who do not cross the bridge and were not able to receive the ide-cel infusion.

Additionally, we are able to see who these patients are. Patients who died within six months of randomization were not surprisingly enriched for high-risk factors. These include more patients with R-ISS stage 3, high-risk cytogenetics, extramedullary plasmacytoma, and high tumor burden. The conclusions are also the same for patients who died within the first 9 months. Since the difference in early deaths are driven by patients who are unable to bridge to ide-cel infusion, it highlights the importance of bridging therapy, particularly in this subset of patients.

Finally, we looked at the precision around the survival curves. On this graph, the lines represent the point estimates and the shading represents the confidence intervals. As you can see, the confidence intervals considerably overlap, even in the early part of the curve.

Finally, I will summarize the overall

survival results. The KarMMa-3 trial allowed crossover, which confounds the overall survival interpretation. There is no perceived benefit or detriment in either treatment arm. In fact, the early deaths in the ide-cel arm are driven by patients who do not receive ide-cel. There is no increase in early deaths from ide-cel infusion compared to the standard regimen's arm. Most patients in the KarMMa-3 trial from both arms received ide-cel, and the result in overall survival in both arms is better than expected for this patient population.

The KarMMa-3 trial demonstrated that individualized bridging is required to allow patients to receive ide-cel. Ide-cel is prescribed at qualified centers by experts able to apply the insights from KarMMa-3 to bridge and treat patients.

Dr. Mark Cook will now review the clinical safety data from the KarMMa-3 trial.

Applicant Presentation - Mark Cook

DR. COOK: Thank you, Dr. Bleickardt.

My name is Mark Cook, and I'm the Senior Clinical Trial Physician for KarMMa-3 at BMS. I will review the safety profile of ide-cel in the proposed indication. For the KarMMa-3 study, these are some of the key adverse events of special interests, which were immediately reportable as serious adverse events. These AESIs were predefined based on our learnings from KarMMa and other studies. They include an adverse event of greater than or equal to grade 3 of cytokine release syndrome, neurologic toxicity, infection, as well as a new diagnosis of malignancy, including second primary malignancies known as SPMs.

Within the ide-cel population, the rate of cytokine release syndrome, CRS, was just under 90 percent. The vast majority were grade 1 or 2, with much fewer grade 3 or higher. Two grade 5 CRS events were observed, one in a subject who developed multi-organ failure day 6 after ide-cel infusion and one in a subject with concomitant grade 5 *Candida* sepsis on day 21 after ide-cel infusion.

The median time to onset of CRS was one day with a median duration of 3 and a half days. CRS was managed in the majority of patients with tocilizumab, which was given to just over 70 percent of ide-cel recipients, and just over a quarter received steroids as well. The overall incidence, severity, onset, and resolution of CRS was consistent with the previously reported safety profile.

In KarMMa-3, neurotoxicity related to ide-cel was recorded as investigator identified neurotoxicity, iiNT. Neurotoxicity rates were low at 15 percent, and in particular, were mainly grade 1 or 2 with no grade 5 events. The median time to first onset of iiNT was 3 days and the median duration was 2 days. Just under half of subjects with iiNT received steroids as treatment for their neurotoxicity. There was no parkinsonism or Guillain-Barre syndrome reported. Overall, the severity, incidence, onset, and time to recovery for iiNT was consistent with the previously reported safety profile of ide-cel.

Hematologic adverse events were the most common adverse events seen, of which neutropenia was the most common grade 3-4 event in both arms. Whilst the grade 3-4 rate of neutropenia seen in the ide-cel arm is double that seen in the standard regimen's arm, we do not see the same proportionate increase in grade 3-4 infection rates. The rate of grade 5 AEs due to infection are low.

Fifty-eight percent of subjects recovered their neutrophil count to grade 2 or better within one month of infusion and 83 percent within 2 months of infusion. Similarly, 62 percent of subjects recovered their platelet count to grade 2 or better within one month of infusion and 85 percent within 2 months of infusion.

In the treated population, rates of adverse events and serious adverse events were similar between the ide-cel and standard regimen arms. The rate of death due to adverse events was also similar across both arms. In the ITT population, death rates were similar between the two arms. The most common cause of death seen in both was disease

progression. Importantly, very few deaths due to second primary malignancies were reported. They were balanced between the two arms, and there were no second primary malignancies of T cell origin in the ide-cel arm. Overall, the safety profile of ide-cel remained consistent with no new safety signals identified.

Second primary malignancies, or SPMs, are malignancies that develop in patients with myeloma and relate, in part, to the chronic immunodeficiency seen in multiple myeloma and the anti-myeloma treatments used, including alkylating agents and other drug classes such as immunomodulatory agents.

In KarMMa-3, we can see that whilst the crude rate is slightly higher in the ide-cel arm, the rate per hundred person-years, which reflects exposure time on study, is very similar between the two arms and lower than recently reported rates of 19.3 SPMs per hundred person-years in triple-class exposed patients. The rate of hematologic SPMs seen is in line with the literature, where rates of

anywhere between 1 and 8 percent are reported. Of note, no T-cell malignancies have been seen on the study.

In summary, the KarMMa-3 study showed that ide-cel has a consistent safety profile as documented previously, with no new safety signals identified. Death due to adverse events were similar across the ide-cel and standard regimen arms. There were no cases of Guillain-Barre syndrome, parkinsonism, or T-cell malignancies reported. There was no increase in SPMs compared to the expected rate. Rates of both CRS and CAR T associated neurotoxicity were in line with the known safety profile of ide-cel and were generally low grade and manageable.

I will now hand over to Dr. Raje to give her clinical perspective.

Applicant Presentation - Noopur Raje

DR. RAJE: Thank you so much, Dr. Cook.

Good afternoon. My name is Noopur Raje, and I am the Director for the Center for Multiple Myeloma at Mass General, and I'm also a Professor

of Medicine at Harvard Medical School, and I take care of multiple myeloma patients. I'm going to share my perspective on the benefits and risks of ide-cel in the treatment of triple-class exposed multiple myeloma patients. I'm a consultant to the sponsor, but I have no financial interest in the outcome of this meeting.

The KarMMa-3 trial addresses a growing treatment gap in patients with myeloma. An important aspect for me as an investigator for the KarMMa-3 trial was the fact that this was a very patient-centric design which allowed for crossover, but having that crossover does confound the overall survival assessment, specifically when close to 60 percent of patients on the standard of care arm crossed over to receiving ide-cel.

Trial restrictions presented several challenges. For one, this was a pretty relapsed/refractory patient population. Also, bridging therapy was limited to a single cycle and there was also a mandated 14-day washed out period. I want to draw your attention to the fact that

KarMMa-3 patients were triple-class exposed and, importantly, over 65 percent of these patients were triple-class refractory to an IMiD, a PI, and an anti-CD38 monoclonal antibody.

The question posed by the FDA today is whether the benefit-risk of ide-cel is favorable for multiple myeloma patients who are triple-class exposed. KarMMa-3 showed a very significant benefit with ide-cel in this patient population. You'll see a median progression-free survival of 13.3 months compared to 4.4 months, with a hazard ratio of 0.49, essentially tripling the progression-free survival in this patient population.

To me as a clinician, PFS is an established endpoint because it guides treatment decisions. There is significant morbidity associated with progression such as bone disease, renal dysfunction, et cetera, so the goal of treatment is to try and prolong the time to progression in these patients, and ide-cel significantly improved progression-free survival. In addition, ide-cel is

a one-time therapy where patients are otherwise treatment free. In contrast, the standard of care for these patients is basically continuous therapy. Importantly, we saw that the health-related quality-of-life outcomes were in favor of patients who received ide-cel.

So can we manage the safety profile of ide-cel? We've been using CAR T cells now for over five years and, to me, the biggest learning is that the toxicity specifically for ide-cel is predictable and manageable. We know about the cytopenias, about CRS, and we know about ICANS, and in fact, CAR T cell products are given in specialized centers with expertise in managing these adverse events.

It is also especially reassuring that we haven't seen any new safety signals in KarMMa-3, and we know that this imbalance in early death was not due to ide-cel-related toxicity. Even more important for me is that we don't see any new safety signals, even in real-world data, which has been presented in over 821 patients, so to me, a

very reassuring safety profile with ide-cel.

So the next obvious question is why should we be using ide-cel earlier in the course of disease? As Dr. Lonial has presented very nicely, with the national history, you see there's an increasing dropout rate of patients who start developing relapsed/refractory disease. In the context of ide-cel, you see a large drop off even from the start of leukapheresis to the time of infusion.

If you've had two prior lines of treatment, the drop off rate is 5 percent, and if you jump to four prior lines of treatment, it more than doubles. Part of the reason is the increasing disease burden of these patients, and so the bridging therapy in these patients becomes less effective.

I think the greatest PFS benefit is seen when ide-cel is used earlier. These pink lines here highlight patients who've had 2 lines of therapy, and as you can see, the PFS is significantly in favor of ide-cel, looking at the

solid line for ide-cel. Here is the comparison for 3 lines of treatment, and here you see 4 lines of treatment, where you see a PFS benefit in earlier lines with ide-cel, making the case that the earlier we use effective treatments, the better the outcome and benefits for our patients.

So how can we bridge patients through ide-cel effectively? I will tell you that this is something we do in clinical practice all the time. In the real world, we treat lots of patients, and less than 5 percent of them are unable to not bridge to ide-cel. Recall the KarMMa-3.

This was a registration trial and was designed to isolate the treatment effect of ide-cel. The protocol thus put limitations on the types of bridging therapy and number of cycles for bridging therapy. It also mandated that 14 day washout period. These limitations do not exist in clinical practice, and as clinicians, we have a broad range of access to different bridging therapy options, depending on what the patient's individual needs are.

So the answer is absolutely yes. In clinical practice, we can actually successfully bridge the majority of patients to CAR T cells.

To underscore the earlier use of ide-cel, I will share a patient's story with you. This is a patient of mine, a 64-year-old professor who presented acutely with significant bone disease, high-risk cytogenetics, and a borderline creatinine clearance. We started treatment with bortezomib, daratumumab, and dexamethasone right away. As soon as the kidney function improved, we added lenalidomide; unfortunately, she progressed within 3 cycles.

In second line, we continued with the daratumumab, but ended up having to add carfilzomib and pomalidomide. We were able to get her to transplant, but unfortunately that didn't hold her and she progressed. I would have loved to have access to ide-cel at that time, but I couldn't, and therefore she went through 3rd and 4th lines of treatment, wherein we continued to recycle some of these treatments.

After the 4th line, because of the product label, we were able to get ide-cel for this patient. In this context, I was able to bridge her with DCEP chemotherapy. She's now been in a stringent complete remission with no evidence of disease for 18 months post-ide-cel therapy.

This patient illustrates a very difficult situation in getting patients through effective treatments such as CAR T cells. We were fortunate in this case, but given that we've used triplets and quadruplets early on from the get-go, having ide-cel approved earlier would have been ideal in this situation.

To summarize, there's a high unmet medical need specifically in triple-class exposed relapsed/refractory multiple myeloma patients. This is a growing segment because we're using triplets and quadruplets at the outset. Ide-cel extends progression-free survival, and there is no doubt that this represents a clinically meaningful benefit to our patients. The long-term treatment-free interval actually contributes to

improved health-related quality of life for our patients.

The earlier use of effective treatments is exceedingly important for optimizing progression-free survival and to more effectively bridge patients so that they can get these effective treatments in the relapsed setting. What is most reassuring to me is the fact that we haven't seen any new toxicity signals with these treatments, even after close to over 800 patients being treated in the real-world setting.

With respect to the observed early deaths, we know that they were not driven by ide-cel-related toxicity. The overall favorable benefit-risk profile of ide-cel in patients with triple-class exposed multiple myeloma is pretty clear in my mind, and for that reason, I think moving ide-cel earlier on would be a benefit to all our patients. Thank you so much for your attention.

DR. MADAN: Thank you.

We will now proceed with the FDA's

presentations, starting with Dr. Poornima Sharma.

FDA Presentation - Poornima Sharma

DR. SHARMA: Good afternoon, everybody. I'm Poornima Sharma, a hematologist/oncologist in the Office of Clinical Evaluation in CBER and the primary reviewer for the supplemental biologics application 125736-218, for Abecma or idecabtagene vicleucel. I will refer to the product as ide-cel in the presentation.

Ide-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. The members of the FDA review team are listed here, and my presentation represents their collective input.

My presentation will start with a brief overview of the treatment background for relapsed/refractory multiple myeloma and the overview of ide-cel approval. I will then summarize the key efficacy and safety results from KarMMa-3 and present the main topics for

discussion. My colleague, Dr. Lin, will then provide the statistical considerations pertaining to the main topics of discussion. This will be followed by conclusions, discussion, and voting questions.

The applicant submitted results of the phase 3 trial, KarMMa-3, to demonstrate the safety and effectiveness of ide-cel for the proposed indication. KarMMa-3 compared ide-cel to standard myeloma therapy in patients with relapsed/refractory multiple myeloma who had received 2 to 4 prior lines of therapy and who had been exposed to an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. The trial met its primary endpoint, demonstrating a statistically significant improvement in progression-free survival for patients randomized to the ide-cel arm compared to the control arm.

During the review of the application, we identified an increased rate of early deaths in the ide-cel arm compared to the standard of care arm as

a key review issue. This increased rate of early death and the uncertainty of the clinical benefit in the context of PFS improvement are the main topics for discussion at this Oncologic Drugs Advisory Committee meeting.

This slide shows the current treatment landscape for patients who are triple-class exposed and have received 2 to 4 prior lines of therapy, the population treated in KarMMa-3. The treatment landscape has evolved over the last two decades with multiple approvals as described earlier by Dr. Mailankody.

Drugs and combinations within the three main classes of IMiD, PI, and anti-CD38 antibodies can be used in triple-class exposed patients if they are not refractory to these agents. Two BCMA-directed CAR T cell therapies, cilta-cel, and the therapy under discussion in this session, ide-cel, are approved in patients who have received four or more prior lines of therapy and who are triple-class exposed. In addition, several bispecific T cell engagers have been approved in

this population. Other options include selinexor-based regimens, high-dose therapy followed by autologous transplant, and chemotherapy combinations. Highlighted regimens on the slide were used in KarMMa-3.

I will now begin my discussion of ide-cel. Ide-cel is an autologous CAR T cell therapy that targets B-cell maturation antigen, which is expressed on the surface of normal and malignant plasma cells. Ide-cel received traditional approval in 2021 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. The approved dose is 300 to 460 million CAR positive T cells.

The approval was based on KarMMa, a single-arm, open-label trial in 100 efficacy evaluable patients with relapsed/refractory multiple myeloma, with a median of six prior lines of therapy. In the single-arm trial, the clinical benefit was determined based on an overall response

rate of 72 percent with a median duration of response of 11 months. The ide-cel product label includes boxed warning for cytokine release syndrome, neurologic toxicities, hemophagocytic lymphohistiocytosis, or macrophage activation syndrome, and prolonged cytopenia with risk of bleeding and infection.

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 an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. The proposed dose is 300 to 510 million CAR positive T cells. The data to support the indication are based on results from KarMMa-3, which I will discuss now.

KarMMa-3 was an open-label, randomized-controlled trial that enrolled patients with relapsed/refractory multiple myeloma, who had received 2 to 4 prior lines of therapy, including a PI, an IMiD, and daratumumab, and who were refractory to the last line of therapy. While the

trial specified a requirement for receipt of at least two up to four prior lines, the requested indication is broad and not entirely reflective of the study population.

Patients were randomized 2 to 1 to either the ide-cel or standard of care arm. The standard of care arm included 1 of 5 regimens which were continued until disease progression or toxicity. This slide shows the treatment process in the ide-cel arm, which starts with leukapheresis, followed by bridging therapy, which is administered to stabilize the disease during product manufacture, followed by lymphodepleting chemotherapy and ide-cel infusion.

Patients could receive up to one cycle of bridging therapy at investigator discretion. The protocol specified a 14-day washout period between completion of bridging therapy and start of lymphodepleting chemotherapy to allow for recovery from hematotoxicity. I would like to point out that prior to randomization, investigator selected one of the five protocol-specified regimens to be

administered as treatment in the standard of care arm or as bridging therapy in the ide-cel arm using clinical factors.

The primary endpoint was progression-free survival for blinded IRC assessment. The key secondary endpoints were overall response rate and overall survival. Upon IRC confirmed disease progression, at investigator discretion and if eligibility criteria were met, patients from the standard of care arm could cross over to the ide-cel arm. The primary efficacy and safety results presented today are based on the April 18, 2022 data cutoff date, which represents the primary efficacy analysis.

This slide summarizes the efficacy analysis plan for KarMMa-3. The efficacy endpoints were tested in a hierarchical order from progression-free survival to overall response rate, and then to overall survival in order to control the overall type 1 error rate, the two-sided 0.05. The statistical analysis plan prespecified two interim OS analyses. The first interim OS analysis

occurred at the time of the primary PFS analysis for superiority, and the second OS analysis occurred at the time of the final PFS analysis. A final OS analysis powered at 50 percent will occur at 222 deaths. At this time, the second interim analysis for OS has already occurred and the final OS analysis results are awaited.

In the next few slides, I will review the study results. This slide shows the demographic characteristics of the study population. The median age of the study population was 63 years, which is younger than the median age of 69 years at diagnosis in the U.S. Overall, only 9 percent of the study population was black or African American. A lower proportion of black or African American patients were on the ide-cel arm compared to the standard of care arm; otherwise, the demographic characteristics were balanced between the two arms. As noted in the slide, the older population, 75 years and older, and racial and ethnic minorities were underrepresented in the study.

This slide shows the disease and treatment

characteristics of the study population. It is important to note that baseline disease factors that are indicative of poor prognosis, such as high-risk cytogenetics, Revised ISS stage 3, and presence of extramedullary plasmacytoma were balanced between the two arms. In terms of the treatment history, the median number of prior lines of therapy was three; 95 percent were refractory to anti-CD38 monoclonal antibody.

Overall, this was a triple-class exposed population and 66 percent of the patients were triple-class refractory. The baseline treatment history was balanced between the two arms. I would like to point out that one-third of the study population had received four prior lines of therapy, a population for which ide-cel is commercially available.

I will now describe the primary efficacy results. Treatment with ide-cel was associated with a statistically significant improvement in progression-free survival for IRC assessment compared to the standard of care arm. The median

PFS was 13.3 months for ide-cel and 4.4 months for the standard of care arm. As discussed by the applicant, this improvement in PFS was supported with improvement in overall response rate. As noted in the table, a higher proportion of PFS events in the ide-cel arm were attributed to deaths compared to the standard of care arm, 8 percent versus 3 percent.

Although progression-free survival has been accepted as a primary endpoint and has supported traditional approval in multiple myeloma, overall survival is evaluated at the time of primary PFS assessment, given its importance, both as an efficacy and safety metric. Particularly for therapies with significant toxicity, assessment of overall survival is important to ensure that there is a favorable benefit-risk profile.

The first interim OS analysis done at the time of the primary PFS analysis is shown in the slide. The results show a lower overall survival in the ide-cel arm compared to the standard of care arm that extends to 15 months, with curves

demonstrating a crossing pattern after that. Due to the crossing pattern of the Kaplan-Meier curves for overall survival, the average hazard ratio does not capture the entire treatment effect and is considered unreliable.

There is significant censoring at approximately 9 months, indicating that data are immature. Overall, 28 percent of the study population had died at the time of the primary PFS analysis. The number of deaths were higher in the ide-cel arm compared to the standard of care arm, as shown on the table. I will revisit FDA's concerns with the overall survival results in detail later on in my presentation.

In summary, a statistically significant improvement in median PFS was observed with ide-cel compared to the standard of care arm. A higher proportion of deaths as PFS events were observed in the ide-cel arm compared to the standard of care arm, 8 percent versus 3 percent, and an overall survival detriment was observed for up to 15 months in the ide-cel arm with crossing of the curves.

I will now present an overview of safety. All safety events and deaths that occurred after patients had crossed over to receive ide-cel were analyzed under the standard of care arm according to randomization. This table also shows only those adverse events that occurred in the standard of care arm prior to crossover. Overall, the rate of grade 4 adverse events were higher in the ide-cel arm compared to the standard of care arm. If we compare the ide-cel arm to the standard of care arm prior to crossover, the rate of grade 3 and higher adverse events, including fatal adverse events, was higher in the ide-cel arm.

Cytokine release syndrome, cardio cell related neurologic toxicity, and HLH or MAS are known safety concerns for ide-cel. For the standard of care arm, these adverse events reflect the toxicity of ide-cel after crossover in 58 patients who received conformal ide-cel. Overall, the rate of grade 3 or higher CRS, neurologic toxicity, and HLH or MAS was higher in the ide-cel arm. The rate of grade 3 or higher

neutropenia and thrombocytopenia was also higher in the ide-cel arm. At the time of the 90-day safety update, 5 cases of myeloid neoplasms have been reported in the ide-cel arm compared to none in the standard of care arm, a rate of 2.2 percent versus 0, indicating a higher rate in the ide-cel arm.

I will now begin my discussion on the main topics. The major issues we would like to focus on today are the increased rate of early deaths in the ide-cel arm compared to the standard of care arm, as noted in the KarMMa-3 trial, and the uncertainty in the clinical benefit due to observed early deaths in the context of PFS improvement with ide-cel.

Before I review FDA's assessment of major issues, I would like to briefly highlight the process between randomization and CAR T cell infusion, as shown on this slide. In this study, patients underwent leukapheresis, and the apheresis material was sent for product manufacture. During product manufacture, patients underwent bridging therapy if required, followed by lymphodepleting

chemotherapy and ide-cel infusion.

In general, the safety risks due to a treatment are considered in patients who receive an investigational drug. For CAR T cell therapy, the treatment process for a patient starts with leukapheresis; therefore, the risks associated with administration of CAR T cell therapy, such as risks of leukapheresis; bridging therapy, including lack of an adequately defined bridging therapy; delays in manufacture resulting in adverse clinical outcome; and toxicity from lymphodepleting chemotherapy, are all inherent risks of the process, which are integral to the benefit-risk assessment of ide-cel.

As shown previously, the first interim OS analysis at the time of the primary PFS analysis showed a higher rate of early deaths in the ide-cel arm. During the FDA's review of KarMMa-3, the applicant provided results from the second interim OS analysis done at the time of the final PFS analysis and more mature OS data, and an additional one year of follow-up. These results are

consistent with the first interim OS analysis with persistent OS detriment for approximately 15 months after randomization. At the time of this analysis, 42 percent of the study population had died and 56 percent of the patients in the standard of care arm had crossed over and received ide-cel.

I will now present FDA's analysis of deaths to evaluate this early overall survival detriment observed in KarMMa-3. All deaths that are presented today are based on the April 28, 2023 data cutoff date, the date of the second interim OS analysis. I would like to remind the committee that all deaths after crossover to the ide-cel arm were analyzed and are being presented under the standard of care arm as per the initial randomization.

FDA's analysis of deaths that occurred in the first 15 months in the study demonstrated a higher rate of death in the ide-cel arm in the first 9 months post-randomization. As shown in the table, 18 percent of patients in the ide-cel arm died in the first 9 months compared to 11 percent

in the standard of care arm. This includes a higher rate of death from disease progression, any adverse events, and unknown causes. Note that out of the 6 deaths from adverse events in the standard of care arm in the first 9 months, 3 deaths occurred after crossover to the ide-cel arm.

Given the higher rate of death in the ide-cel arm in the first 9 months from randomization, FDA further analyzed these deaths. It is notable that 8 percent of the patients, so 20 patients randomized to the ide-cel arm, died without receiving the intended CAR T cell infusion within 9 months of randomization compared to none such patients in the standard of care arm. The most common cause of death was disease progression followed by adverse events and unknown causes.

Although we note the greater difference in early deaths in patients who did not go on to receive ide-cel, as stated previously, these patients started the process to receive ide-cel and had received leukapheresis and bridging therapy; therefore, these deaths are important to evaluate

the benefit-risk of ide-cel. Within the ide-cel-treated patients and patients who received standard of care therapy, the rate of death and deaths from adverse events was similar between the two arms in the intent-to-treat population.

Analysis of the 20 patients who died prior to ide-cel infusion within 9 months of randomization demonstrates that patient attrition occurred at different steps in the process to CAR T cell infusion. This includes patients who were randomized but were unable to proceed with leukapheresis; patients who underwent leukapheresis but did not proceed further; manufacture failures; patients with need for repeated apheresis resulting in delays and inability to receive ide-cel; and a patient who received lymphodepleting chemotherapy but did not receive ID cell infusion.

As I had discussed previously, the role for bridging therapy is to stabilize the disease while awaiting product manufacture. Since the majority of patients died from disease progression prior to ide-cel infusion, we analyzed the bridging therapy

administration in the subgroup of 20 patients who died prior to ide-cel infusion within 9 months of randomization and compared it to patients who did receive ide-cel.

Overall, the rate of bridging therapy administration was comparable between these two groups. The median time from randomization to start of bridging therapy and the median duration of bridging therapy were also similar between the two groups. There was a higher proportion of patients who received two or more cycles in this group of early mortality prior to ide-cel compared to the treated group. Bridging therapy cycles were truncated and modified in the event of cytopenia or infections, and in some instances, more than one regimen was administered as bridging. Overall, no significant difference was found between the median time from leukapheresis to product release in the two groups.

In all, this analysis indicates that bridging therapy administration was similar between the early mortality subgroup that did not receive

ide-cel and ide-cel-treated patients. In addition, investigators used clinical judgment to tailor bridging therapy, including administering more than one cycle, and non-protocol-specified bridging therapy to meet patients' individual clinical needs in KarMMa-3.

This slide demonstrates the distribution of bridging therapies and how that compares with the standard of care regimens. The most common regimen used as bridging was elotuzumab in combination with pomalidomide and dexamethasone, EPD, followed by daratumumab in combination with pomalidomide and dexamethasone or DPD. In the standard of care arm, DPD was the most frequently selected regimen followed by EPD.

To analyze the early deaths within 9 months in KarMMa-3, FDA conducted exploratory analyses to assess whether any particular prognostic subgroup was associated with a higher early mortality in the ide-cel arm. This slide demonstrates that a higher early mortality with ide-cel was observed across multiple prognostic subgroups and was observed even

in the absence of individual poor prognostic factors.

In summary, no particular prognostic subgroup was associated with or was driving this observed higher early mortality. The study was not designed to characterize the heterogeneous study population, which may have contributed to higher early mortality with ide-cel.

Since most of the CAR T cell-related toxicities have onset within 90 days of product infusion, we analyzed deaths within 90 days of treatment start in the safety population. While the overall death rate from adverse events in the safety population was similar between the two arms, deaths due to adverse events within 90 days of treatment start were numerically higher in the ide-cel arm compared to the standard of care arm, 2.7 percent versus 1.6 percent. This includes death from CRS, HLH, neurologic toxicity, infections, and stroke in the ide-cel arm.

This table shows the cause of death from treatment-emergent AEs in the safety population in

KarMMa-3. Please note that at the time of the second OS interim analysis, 72 patients in the standard of care arm had crossed over and received conformal ide-cel. Six percent of these patients died from an adverse event. Overall, the most common cause of death from adverse events in both arms was infection.

In summary, the rate of early mortality within the first 9 months was higher in the ide-cel arm, 18 percent compared to 11 percent in the standard of care arm. When considering the population that actually received ide-cel, the difference in mortality persisted, although it is smaller in magnitude. A higher proportion of deaths occurred before disease progression in the ide-cel arm compared to the standard of care 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. Overall survival not only provides an estimate of efficacy but also

safety.

Clinical trials in oncology, including multiple myeloma, have demonstrated improvement in tumor-based endpoints such as progression-free survival but with worse overall survival. Therefore, while progression-free survival has been accepted as an endpoint in relapsed/refractory multiple myeloma to expedite drug development, FDA recommends that overall survival should be prioritized as a key secondary endpoint to evaluate benefit-risk.

While KarMMa-3 demonstrated a statistically significant effect on PFS and overall response rate, an increased rate of early deaths was observed as described. While the final analysis of OS was prespecified, the results from a fairly mature OS analysis are included in the BLA. It remains uncertain if additional follow-up of overall survival, even if statistically significant, will overcome the increased risk of early deaths. Overall, findings from KarMMa-3 lead to uncertainties regarding whether the overall

benefit-risk assessment for ide-cel in the indicated population is favorable.

I will now invite our statistical reviewer, Dr. Lin, to review the impact of crossover on the OS analysis and the duration of observed detriment with ide-cel.

FDA Presentation - Xue Mary Lin

DR. LIN: Thank you, Dr. Sharma.

Good afternoon. My name is Xue Mary Lin. I'm a mathematical statistician at the Division of Biostatistics at CBER. I'm the primary statistical reviewer of this BLA supplement, and I will focus on the statistical considerations on the OS detriment.

This figure shows the overall survival Kaplan-Meier curves for the ITT population. The blue line represents the standard of care arm and the red line, the ide-cel arm. The two curves cross at around 15 months after randomization. Before month 15, the standard of care arm had higher survival probability than the ide-cel arm, and then the two curves crossed. After crossing,

there was heavy censoring.

As noted previously, there was treatment crossover from the standard of care arm to the ide-cel arm. Though the ide-cel arm showed substantial benefit on progression-free survival over the standard of care arm, we are concerned about the overall survival results, as shown in this figure.

Here are our two key points. First, the impact of crossover, the KarMMa-3 study allowed crossover from the standard of care arm to the ide-cel arm upon disease progression. While one can perform sensitivity analyses to assess the impact of crossover, we don't think such analysis can provide convincing evidence that ide-cel reduced the risk of death after adjusting for treatment crossover due to their inherent limitations.

Second, the duration of OS detriment, the available data shows that the detrimental effect of ide-cel lasted up to 9 months after randomization. First, in the impact of crossover, according to the

statistical analysis plan, the primary analysis of OS was the ITT analysis. Two models accounting for treatment crossover was specified as sensitivity analysis, the rank preserving structural failure time, RPSFT, model and a two-stage accelerated failure time, AFT model. Another post hoc analysis using the inverse probability of censoring weighting, the IPCW, method was also provided by the applicant.

All three sensitivity analyses rely on unverifiable model assumptions limiting their ability to explain OS detriment. The RPSFT model assumes common treatment effect; that is the treatment effect of ide-cel on OS is the same when administered after disease progression on the standard of care arm, as well as administered after the initial randomization, and AFT and IPCW approaches both assume that there are no unmeasured confounders at the time of treatment crossover; in other words, any systematic differences between subjects who crossover and who do not can be explained by model covariates, and these

assumptions are unverifiable.

This forest plot shows the estimated average hazard ratio from the applicant's sensitivity analysis. Although each point estimate was less than 1 after adjusting for treatment crossover, it is notable that the crossing hazard pattern or delayed effect pattern still persisted after adjusting for crossover. As a result, the average hazard ratio is not interpretable. There's also considerable uncertainty about the point estimates, reflected by the wide confidence intervals.

As an example, this figure shows the overall survival Kaplan-Meier curves adjusting for treatment crossover using the RPSFT model. The early OS detriment persisted. The crossing hazard pattern renders the average hazard ratio uninterpretable and the wide confidence interval indicates there's much uncertainty about the point estimate.

In summary, for the limitations of sensitivity analyses to assess impact of crossover, the sensitivity analyses adjusting for treatment of

crossover rely on testable assumptions and cannot be used to ascertain that ide-cel treatment has OS benefit when the ITT analysis clearly indicates an OS disadvantage. So in conclusion, the sensitivity analyses adjusting for treatment crossover cannot provide convincing evidence that ide-cel reduces the risk of death.

Second, the detrimental effect of ide-cel lasted for up to 9 months, so assuming the first 15 months of OS data, when the death rates are broken down in 3-month intervals, it is clear that the elevated rate of death in the ide-cel arm persisted beyond 6 months into the 6- to 9-month range as highlighted in the table. The piecewise hazard ratio estimate with different cutoff points also show that the treatment effect of ide-cel lasted up to 9 months.

The overall survival data demonstrate clear and persistent increased mortality for the ide-cel arm compared with standard of care arm, with rates of deaths up to 9 months. The overall survival disadvantage persisted to 15 months after

randomization when the curves finally crossed.

This concludes my portion of the presentation, and now I will turn it back to Dr. Sharma.

FDA Presentation - Poornima Sharma

DR. SHARMA: Thank you, Dr. Lin.

In conclusion, KarMMa-3 demonstrated a progression-free survival benefit and an improvement in overall response rate in a triple-class exposed relapsed/refractory multiple myeloma population after 2 to 4 prior lines of therapy; however, an increased rate of early deaths was observed in the ide-cel arm, leading to uncertainties, if the additional follow-up of overall survival, even if statistically significant, will overcome this increased risk of early death.

The study was not designed to identify predictive factors for early mortality observed with ide-cel. This higher rate of early death appears to be an inherent risk of this therapy. Overall, there is uncertain benefit-risk of ide-cel

in the proposed population.

We would like the committee to discuss the following topics. Discuss whether the results of KarMMa-3 are sufficient to support a positive risk-benefit assessment of idecabtagene vicleucel, or ide-cel, for the proposed indication. The second discussion question is, is the risk of early death associated with idecabtagene vicleucel treatment acceptable in the context of the PFS benefit?

The voting question for the committee is the following, is the risk-benefit assessment for idecabtagene vicleucel for the proposed indication favorable? With that I conclude my presentation. Thank you for your attention.

Clarifying Questions

DR. MADAN: Thank you.

We will now take clarifying questions for both Celgene Corporation and the FDA. For the panel, please use the raise-hand icon to indicate that you have a question and please remember to lower it by clicking it again after you've 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 either the sponsor or FDA.

If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be good and helpful to acknowledge the end of your question with a thank you or end of the follow-up of your questions with, "That's all for my questions."

So we can now move on to that portion. Dr. Spratt has, I think, his hand up first, so go ahead, Dr. Spratt.

DR. SPRATT: Thank you. Dan Spratt, UH Seidman Cancer Center, Case Western Reserve University. I appreciate all the time both the FDA and the sponsor put into all this. Not surprising probably, I'll first ask the FDA, did you conduct an RMST analysis, given the non-proportional hazard here?

DR. VERDUN: Thank you. I would like to turn it over to our statistical colleagues.

DR. LIN: No. We didn't conduct this post hoc exploratory analysis.

DR. SPRATT: Thank you. The sponsor, did you?

DR. KERBER: Yes, we did.

Daniel Li, please, from biostatistics.

DR. LI: Daniel Li, biostatistics, BMS. Slide up. We did conduct a post hoc analysis on restricted mean survival time, and at the time of analysis, we selected the time up to month 31, which is the median follow-up overall survival at this data cut. The ide-cel is 23 months and standard regimen arm is 23 months. The difference is 0.06, and there's no difference in terms of the RMSTs, and this is conducted under the ITT analysis adjustment for crossover.

DR. SPRATT: Thank you. That's all.

DR. KERBER: Just to wrap this up, this is, of course, in the context of the crossover design of the study, as we all understand.

DR. MADAN: Okay. I guess I will ask my question next. I guess this is primarily for

Celgene. We've heard a lot today about how getting RTs earlier in the disease course is requisite for better outcomes, yet here we have a trial where patients got it earlier, there's a huge PFS benefit, which is an acceptable endpoint in this disease state, and only half the patients are so crossed over, yet survival -- let's not argue better or worse -- let's just say it's the same for argument's sake.

How am I, as a non-myeloma expert, supposed to reconcile that?

DR. KERBER: It is critically important to move this treatment into an earlier treatment line, and as you've seen, as Dr. Raje has shown, the progression-free survival is best in patients who just received two prior lines versus 3 or 4 prior lines of therapy at the same time.

We do see a higher dropout rate if patients have experienced more prior lines of therapy; in other words, there's a lower likelihood that they make it to ide-cel treatment, and progression-free survival is really the key endpoint in multiple

myeloma, clinically highly relevant, and I'll ask Dr. Raje to comment on this.

DR. RAJE: Thank you so much, Anne, and thank you for that question, Dr. Madan. I think you bring up a critical point. We've shown the data out here wherein earlier lines of treatment, 2 lines of treatment, patients did better with ide-cel, and that was true across the board. The one thing I do want to highlight is the fact that these were actually quite heavily pretreated. They'd been triple-class exposed and refractory to a lot of the treatments, so the earlier we move these, the better the outcomes are going to be with all of these treatments. I've also shown you data of the dropout rates, and as you move from 2 to 4 lines of treatment, there was a doubling of the dropout rate in receiving ide-cel in this patient population.

DR. MADAN: Right. So just to follow up there, this was a heavily pretreated median 3-line population, and the crossover rate was 50 percent, which is higher, I guess, than historical controls.

So again, I think that puts that in the context. Again, I'm just, like I said, trying to understand how to reconcile some of this sentiment of moving it earlier with the actual data I'm seeing, so thank you.

DR. KERBER: Maybe I can add as an additional piece of information -- I just saw that Dr. Lonial wants to comment as well -- that given the very high unmet need in this triple-class exposed population and the fact that they only have a median progression-free survival of 4 months, we see this crossover effect very early. Patients crossed over in this study at 3 months post-randomization, and at the time the Kaplan-Meier curves cross, already two-thirds -- more than two-thirds, actually -- of the patients had crossed over. So the impact of crossover on the survival curves happens very early on.

Dr. Lonial, please, for additional comments from a clinical perspective. Thank you.

DR. LONIAL: YES. Thank you again for the

opportunity to address this. A third of the patients in the trial were in first relapse, a third were in second, and a third were in subsequent relapse. So there is a pretty even mix. And one of the challenges when assessing overall survival in early relapse trials is that you can't control for subsequent therapies, and in trials historically that have showed an overall survival, it's been predominantly enrolled in Europe where access to salvage therapies is not the same as it is in the U.S.

This trial was almost 50 percent enrolled in the U.S., so there were a number of subsequent therapies, and access was not as big an issue for many of these patients. So I think what you're seeing is that if you have access, you can do better, even after relapse. If you don't have access, in trials predominantly enrolled in Europe, that's where you start to see the OS curve separate in the context of early relapse.

DR. KERBER: Thank you, Dr. Lonial.

As the sponsor, we would also like to

comment on a conclusion that the FDA made on their slide 15, which is also related to death and survival. The FDA concluded that there's a higher number of fatal adverse events when we compare the ide-cel versus the standard of care arm, after subtracting patients who died after crossover to ide-cel in the standard of care arm. What the FDA hasn't shown, and what we would like to show, is the number of patients who died after crossing over to subsequent or receiving subsequent treatment in the ide-cel arm.

What you will see is that the number of patients who experienced a fatal adverse event is very similar between the two arms, and the same is true with respect to the number of patients who experienced a fatal event after subsequent therapy.

Eric Bleickardt, please.

DR. BLEICKARDT: Thank you. If we can put the slide up, this shows the deaths within 9 months of randomization, according to how the FDA provided the information. You can see the ide-cel patients on the left and the standard regimen patients on

the right. If you look at column 1 and 3, you can see at randomization, and then column 2 and 4, you can see after the patients progressed and received subsequent anti-myeloma therapy or AMT.

If you look in the first pink row, you can see that the number of patients who died in the first 9 months from an adverse event were 11.4 percent in the ide-cel versus 10.6 percent in the control arm, but you'll notice a third of those patients happened after they had progressed and received anti-myeloma therapy, 5.5 percent in ide-cel that crossed over to receive anti-myeloma therapy versus 5.4 that crossed over on the standard regimen to receive ide-cel.

You can also see it within the first 9 months as well in the second pink row, that whether you look at the randomized patients in column 1, or column 3, or after receiving alternative anti-myeloma therapy in column 2 and 4, it's very similar rates. Thank you.

DR. MADAN: I would like to recognize the FDA who had their hand up as well. I'm not sure

whether it was to the original question, or this, but obviously feel free to respond to both.

DR. VERDUN: Yes. I'd like to invite Dr. Sharma.

DR. SHARMA: Yes. This is Dr. Sharma, the clinical reviewer. I'd like to clarify that the slide 15, where we are demonstrating the differences, we are looking at the safety population. I think the slide that we had up earlier was the ITT population; there are some differences there.

The primary safety analysis that we did, including the analysis of death, was taking into account the crossover within the standard of care arm, but we wanted to display the adverse events and deaths that occurred in the standard of care arm prior to crossover just so there is a comparison just for the benefit of the committee. But our primary safety analysis for the standard of care arm included the adverse events and deaths that occurred after crossover as well.

Again, I think the slide that was pulled up

with the 6- and 9-month data is the ITT population, and here we are focusing on the safety population.

DR. KERBER: If I may, we have the same data for the safety population; it shows the same, the same conclusions. It shows the same balance in terms of adverse events that occur during the initial treatment period and after subsequent therapy, so I don't think it changes anything in terms of the conclusions. Thank you.

DR. SHARMA: Well, I think I would like to, again, just clarify that the primary safety analysis that we did, again, we looked at the ide-cel-treated patients for the duration of the follow-up in the study, as well as the standard of care arm, and it's only in slide 15 that we wanted just -- so the data is available prior to ide-cel crossover, and I think that was the intent of that. But we have taken into account the crossover in the standard of care arm for all of our subsequent analyses and tables. Thank you.

DR. MADAN: Thank you.

We'll just remind everyone of the rules to

request to be recognized so we keep this situation a little more organized and orderly, and have a nice productive conversation.

Dr. Kwok, I think you had your hand up. If you still have a question, please feel free to go ahead.

DR. KWOK: Thank you. I was actually wondering if the FDA could put slide 15 back up again because that's one question that I did have, again, trying to reconcile the data. Then a separate question that I had for the company was, I think 17 percent of patients didn't receive bridging therapy. Did all those patients go on to progress? Do you know why they didn't receive bridging? Was it because they had already progressed on prior therapies?

DR. KERBER: Bridging therapy was not mandatory in the study, so it was at the physician's discretion. Typically, when patients did not receive bridging therapy, physicians didn't feel that that was required. Unfortunately, among those patients who experienced early deaths and did

not receive ide-cel, some of them, actually, didn't even receive bridging therapy.

I'll ask Eric Bleickardt to provide the exact numbers there.

DR. BLEICKARDT: Thank you. If we'd put the slide up, we looked at the patients that did not receive ide-cel in the ide-cel arm. You can see there were 29 patients that did not receive ide-cel, and you can see the 17 patients that died within the first 6 months, and you can see the reasons why they did not go on to receive ide-cel. Mostly it was for reasons of not meeting the treatment criteria either because of cytopenias or renal function. Thank you.

DR. KERBER: Thank you. Maybe we can provide the numbers on how many patients did not receive bridging and did not receive ide-cel in a moment. Thank you.

(Pause.)

DR. KERBER: We can come back to it in a moment. We're pulling up the slide. Maybe we want to look at slide 15 from the FDA in the meantime.

DR. MADAN: Dr. Hunsberger, are you with us?

DR. HUNSBERGER: Yes. Sorry. I didn't hear you. Sally Hunsberger. In the briefing book, it said that the washout period was a minimum of 14 days, but the range was from 12 to 75 days; so that seems like a a very long range. Was there any relationship between the length of washout and death?

DR. KERBER: I will ask Eric Bleickardt to answer the question. There are a few outliers that drive the upper range, but the majority of patients, really, they're within the same range of time from end of bridging to ide-cel infusion.

Eric Bleickardt, please.

DR. BLEICKARDT: Yes, we did have one patient that had a very long time to actually receive the bridging therapy and that was because initially they did not plan on starting bridging therapy, but during the waiting time for manufacturing, they did require additional bridging, so that delayed the time to starting of bridging therapy. We did have one patient also

between the end of bridging and the start of lymphodepletion that was prolonged, and that was because they had a COVID-19 infection, and they received it after that. Thank you.

DR. HUNSBERGER: Can I just follow up? I thought the washout happened after the bridging. I'm a little bit confused because you were talking about the bridging therapy.

DR. KERBER: There were two periods during which patients did not receive anti-multiple myeloma treatment. The one period was from randomization to start of bridging therapy, so that's the time where the leukapheresis happened, and that's what Dr. Bleickardt referred to in one part of his response. And then, of course, there was washout period after the bridging therapy, which was a minimum of 14 days.

I don't believe we have seen a true relationship between the lengths of that treatment gap and the occurrence of early deaths, and the 75 days that you see at the upper limit, that was a one-patient outlier. As Dr. Bleickardt has just

described, there was a patient with COVID-19.

DR. HUNSBERGER: Thank you.

DR. KERBER: We could provide the numbers now on patients who did not receive bridging and died early now, if that is appropriate, or we can continue to discuss slide 15.

DR. MADAN: No. I think we don't have any hands raised, so please go ahead.

DR. KERBER: Okay. Slide up, please. You see that we have split this out by the ITT population, the patients who did not receive ide-cel infusion and died within the first 6 months. That's the first column you see here, and you see that 23 percent, or an N of 4, unfortunately, did not receive bridging therapy and experienced an early death without receiving ide-cel. Thank you.

DR. MADAN: Okay. Do we have any other questions from the the panel, any other clarifying questions?

(No response.)

DR. MADAN: Okay. I think I don't see any

other questions, so with that, I think we can go to break, unless --

DR. VERDUN: Sorry.

DR. MADAN: FDA wants to say something. Go ahead. Yes, we've got the time.

DR. VERDUN: Yes, can we please provide one statement for clarification.

Dr. Sharma?

DR. SHARMA: Yes. Thank you. I'm the primary clinical reviewer for the application. I'd just like to clarify that for bridging therapy, the protocol did specify up to one cycle of bridging therapy; however, if we look at the duration of bridging therapy, there were a proportion of patients that did get non-protocol-specified bridging therapy. In addition, if a clinician felt that a patient was clinically deteriorating while awaiting the product, they could discuss that with the sponsor and administer additional cycles of bridging therapy. I believe that was considered a non-key protocol violation.

So we just wanted to highlight that that

flexibility was there in the study; that if a patient had disease progression and they were clinically deteriorating, they could administer additional cycles or even additional regimens to control the disease for a patient. Thank you.

DR. KERBER: May I respond to that comment?

DR. MADAN: Yes, go ahead.

DR. KERBER: So the investigators were not discussing additional cycles with us as the sponsor, and the additional cycles that were administered were considered protocol deviations; they were not considered important protocol deviations, but they are protocol deviations, and the majority of the sites and the physicians have applied those restrictions and just gave one cycle. So there was no signal to the sites, that they could use more than one cycle, which they might have done if that would have been allowed in the protocol, but it wasn't.

I also would want to ask if we can, as sponsor, comment on slide 38 that the FDA has shown, and show the the missing crossover adjusted

analysis. They just showed one method. I think we should complement that with showing the Kaplan-Meier curve for the two-stage model. Is that possible?

DR. MADAN: Go ahead, yes. Go ahead and put that up. We have a couple extra minutes, but keep it brief.

DR. KERBER: Thank you.

Can we pull up that slide, please?

The FDA rightly said that none of the methods that are applied to adjust for crossover are perfect and they all have limitations. They have just picked one of the methods. I think it's important to complement that with the other method that was prespecified, which was the two-stage model. And that curve, the FDA commented that at the RPSFT model, you don't see a change in the crossing of the curves, but if you look at the two-stage model, you see that; you no longer see a crossing of the curve. And we also do see that we don't have an early imbalance in death in the curve and a favorable hazard ratio favoring the ide-cel

arm. Thank you.

DR. MADAN: Okay. We have a new question, but in fairness, I'll let the FDA comment on the new data.

DR. VERDUN: Yes. Thank you

Dr. Lin?

DR. LIN: Hi. This is Xue Mary Lin. I'm the primary statistical reviewer for this BLA supplement. FDA, please pull up the backup slide number 4. This figure will show the Kaplan-Meier curves of overall survival. This is the backup slide for stats, Kaplan-Meier curves for overall survival for two-stage accelerated failure time model with recensoring.

I'm sorry. This is a previous slide, slide number 3. I think the next slide should show the two-stage accelerated failure time model, the Kaplan-Meier curve. Yes, exactly. That's what I was looking for. A moment ago, the applicant showed the overall survival for the two-stage accelerated failure time model without censoring, so their figure is different from this one in that

they didn't do the recensoring, which is normally recommended by the literature. Now, we can see that with recensoring, there's heavy censoring that renders results uninterpretable. From this figure there's no data beyond month 17, so from this figure I think we cannot really draw any conclusions about the benefit of ide-cel in prolonged overall survival. Thank you.

DR. MADAN: Okay. I think Celgene probably wants to comment, it looks like, but I think that we could get into doing statistical interpretations for probably a long time here, so if you have a comment, quickly; otherwise, we do have a question from the panel, so I'd like to go ahead and get to that, if we could. I thought we did; maybe it's gone.

Dr. Lattimore, you had your hand up, but hopefully we didn't scare you off in putting it down. Do you still have a question or was it answered?

MS. LATTIMORE: No, I do have a question; thank you.

DR. MADAN: Okay.

MS. LATTIMORE: One of the sponsor's slides previously had some notations about early attributions for early death, and one of the causalities was study drug manufacturing failure. I'm hoping that some additional detail could just be provided regarding what this means and context.

DR. KERBER: Yes. So we do not think that the data show that the manufacturing success rate -- or the manufacturing failures, had a major contribution here. We had a very high manufacturing success rate in the study of 97 percent, so there were very few patients for whom we couldn't manufacture either, and Eric Bleickardt can actually show you the exact numbers. I believe it's one of the patients that had experienced an early death, but it certainly didn't significantly contribute at all.

Eric Bleickardt, please?

DR. BLEICKARDT: Yes. As Dr. Kerber pointed out, there were only three manufacturing failures, so 97 percent of the patients did have a successful

manufacturing. There was one patient that did have a manufacturing failure, and that was one of the patients that died early within the first 6 months. Thank you.

DR. KERBER: Thank you, Eric.

DR. MADAN: I think that ends our clarifying questions. I don't see any more from the panel, and we thank the sponsor and the FDA for answering our questions.

So now we'll take a little break. As of now, the open public hearing session will start at 3:55. We're going to move that up a couple minutes since we're breaking a little bit earlier. Panel members, please remember that there should be no chatting or discussion of the meeting topics with each other during the break at all. Again, we will resume at 3:55 for the open public hearing portion, so if the panel members can come back a few minutes early just to make sure we're all here. Thank you very much.

(Whereupon, at 3:39 p.m., a recess was taken, and meeting resumed at 3:55 p.m.)

Open Public Hearing

DR. MADAN: We will now begin the open public 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 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 today.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial

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

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

One of our goals 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 only speak when recognized by the chairperson. Thank you in advance for your cooperation.

With that, I believe we have four speakers, and we'll start with speaker number 1. Speaker number 1, please unmute your mic and turn on your webcam. Speaker number 1, please go ahead and introduce yourself. Please state your name and

any organization you are representing for the record. You will have 5 minutes to speak.

MS. DeROME: Thank you.

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. I have no financial relationships to disclose.

The MMRF is a national 501(c)(3) nonprofit organization, and our mission is to accelerate a cure for each and every multiple myeloma patient. We are the number one private funder of multiple myeloma research in the world and have raised over $600 million in support of this mission over the past 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 those patients 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 effective therapies, and the majority of patients do not survive to receive 4th- or 5th-line therapy, which is where many of the newer more 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 may 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 must be weighed against the risk for short-term adverse effects, such as CRS and ICANS, and the long-term adverse effects of cytopenias, serious infections, and secondary 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 outcomes.

In conclusion, there remains a significant unmet need for effective therapies for relapsed/refractory myeloma patients. Making more effective therapies available earlier in the disease will help to address that need. Thank you.

DR. MADAN: Thank you very much for sharing that perspective.

Speaker number 2, please unmute and turn on

your webcam. Speaker number 2, will you please introduce yourself? Please state your name and any organization you're representing into the record. You will also have 5 minutes.

MR. SINGH: Thank you. My name is Sanjay Singh, and I am speaking as a patient. I do not have any financial interests to disclose. I live in Philadelphia, and I'm a financial consultant, and I want to speak today and share my experience receiving CAR T cell therapy and its results and side effects now that I am anniversarying my CAR T cell treatment.

I was diagnosed in September 2021 when I was 57 years old. I presented with IgG lambda multiple myeloma, characterized by serum and urine monoclonal gammopathy, elevated free lambda light chains, and moderate anemia and acute renal failure. My initial presentation was in the context of COVID-19, which could have at least partially accounted for the renal injury and anemia, but there was no other evidence of organ or tissue injury, such as hypercalcemia or lytic bone

lesions.

My first line of treatment started in September 2021 with bortezomib, and lenalidomide, and dexamethasone, and that led to a very good partial response. The second line of treatment I received was an autologous stem-cell transplant in February 2022, along with high-dose melphalan, and this was followed by lenalidomide maintenance, after which I had no evidence of progression.

My first two lines of treatment had significant side effects, especially the dexamethasone in the first line of treatment and the high-dose melphalan as part of the stem-cell treatment. The dexamethasone treatment that went on for 4 months inhibited sleep and induced significant fatigue and severe mood swings because of sleep deprivation.

In the stem-cell transplant, I had to be in the hospital for 2 weeks, and after release, I experienced extreme fatigue, loss of hair, appetite, and had to be isolated for 3 months because of lower immunity. The physical toll of

these treatments was such that I had to leave my full-time job, and I could not take up a new job because of the fatigue and weakness, and the loss of hair and appearance of being very sick.

At the recommendation of my oncologist, I signed up for a CAR T cell clinical trial, Abecma, for patients like me who had been through an autologous BMT within a year and had not achieved complete response. My T cells were harvested, followed by an infusion of lymphodepleting chemotherapy with fludarabine and cyclophosphamide, and then ide-cel BCMA-directed CAR T cells. This was in February of 2023, and this was an outpatient procedure, so I did not have to be in the hospital for 2 weeks like in the BMT.

Following the infusion, I did develop grade 1 CRS, which was treated with toci, tocilizimab and [indiscernible - 8:02:13], again an outpatient procedure the following day, which stopped the side effects almost immediately. And since my CAR T cell infusion, I have had 4 bone marrow biopsies, which show stringent complete

response. I am now on lenalidomide maintenance and have had no evidence of relapse. Along with maintenance dose Revlimid, I'm also on high-dose acyclovir oral and bimonthly IVIG infusions at home that take about 2 hours to finish.

My overall condition is very good. I have resumed most physical activity, and I would say all physical activities prediagnosis. While in its early days, I'm very encouraged by the deep response the CAR T cell therapy has had on my myeloma, I understand there is a risk of recurrence and progression, but the deeper the response in eliminating myeloma, in my case, at an earlier stage, the longer I can expect to live progression-free, and lead a healthy normal quality of life.

I would like to share my treatment history and results publicly to bring this treatment to early-stage myeloma patients, which significantly improves the chances of a complete and deep response and gives the patient a quality of life that has to be taken into consideration in any

approval. I am grateful that I was accepted in the CAR T cell clinical trial. I'm living proof that it improved my quality of life. It changed the way myeloma is affecting my body.

As a myeloma patient, to have this option and opportunity of CAR T cell therapy available to me means hope for a long remission while waiting for a cure. I encourage members of this esteemed ODAC meeting to consider voting to recommend to the FDA to approve this therapy, to be available to other patients earlier in their treatment, before their bodies are beat up by myeloma itself and with other therapies. Thank you.

DR. MADAN: Thank you, sir, for sharing your journey with us.

We will now move on to speaker number 3. Please go ahead and turn on your webcam and unmute your mic. Please begin and introduce yourself. Please state your name and any organization you're representing into the record here, and you will also have 5 minutes. Thank you.

MR. BURGMAN: My name is Carl Burgman. I

live in Tulsa, Oklahoma with my wife of 40 years, Jenny. I am a patient for multiple myeloma. I represent patients and I have no financial association with any of the CAR T companies, and I am also a retired drilling engineer, currently 64 years old.

In February of 2018, after being followed 10 years with an MGUS, my local hematologist in Tulsa diagnosed me with high-risk multiple myeloma. My high-risk multiple myeloma was characterized by high-risk cytogenetics. These were a 1q duplication, a 4;14 translocation, and a 17p deletion, which is where the T53 tumor suppressor gene resides. With these chromosome abnormalities, my hematologist recommended that I go to MD Anderson for treatment. Those chromosomal abnormalities, usually patients relapse a lot faster than normal myeloma patients without those, about every 9 months or so.

So I went to MD Anderson. They administered and/or directed my treatment plan, which was an induction of Kyprolis, Revlimid, and dexamethasone,

followed by an autologous stem-cell transplant. In August of 2018, I had my stem-cell transplant at MD Anderson, and this was followed by Revlimid maintenance. By May of 2019, 9 months after stem cell, I had relapsed again. At the time of relapse, I still had the same chromosome abnormalities. My healthcare team then proposed I participate in the phase 2, BD2121, which became ide-cel, or Abecma, CAR T cell clinical trial.

My wife and I thoroughly reviewed the results of the phase 1 trial, along with the potential side effects. Even though one of the complications of such a trial was listed as death, which really concerned and bothered my wife, the published results of good safety with longer remission for relapsed/refractory patients convinced us that I should participate in the trial.

In September of 2019, I went back to MD Anderson to begin the process of the CAR T cell therapy, and as stated by OPH number 2, went through all the same stages and the lymphodepleting

chemo, and at that time, I became MD Anderson's first myeloma patient to receive CAR T cell treatment.

When I was discharged, I was not prescribed any maintenance therapy, no Revlimid and no chemo. Other than following clinical trial protocols for labs and doctor appointments, along with occasional IVIG and immune boosters, I was able to live life just about the same as I did prior to the myeloma diagnosis.

After 26 months of remission, which is 3 times longer than what was expected for a high-risk cytogenetic patient, I underwent another bone marrow biopsy that revealed that I no longer had the 1q duplication or the 17p deletion, so the CAR T cell therapy proved to be efficacious, providing me with a long remission, with a high quality of life, and it has successfully changed the biology of myeloma for the better.

Due to the success of this CAR T clinical cell trial, for me, I highly recommend this treatment be made available in very early lines of

therapy. If I had not undergone the CAR T cell therapy, an alternative would have been an allogeneic transplant, which often causes graft versus host disease or a multiple of other types of treatment.

So I was grateful to be accepted into that trial. I'm living proof that the quality of life changed back to where it was originally, and I just appreciate the fact of having that, and as the previous speaker said, I would highly recommend that the panel approve this therapy, early lines for patients, because the myeloma can tear up your T cells, along with all the other therapies, so thank you for your time.

DR. MADAN: Thank you, sir, for sharing your story with us.

We will now move to speaker number 4. Speaker number 4, please unmute your mic and turn on your webcam. Speaker number 4, please begin and please introduce yourself, and state your name and any organization you are representing into the record. You will also have 5 minutes. Thank you.

DR. DURIE: Thank you so much. I really appreciate this opportunity. I'm Dr. Brian Durie, and I don't have any compensated relationship for this testimony. I've got no financial conflicts of interest to report.

I'm a physician who has taken care of myeloma patients for decades now, but I'm representing today the International Myeloma Foundation, which I co-founded. I'm currently the Chief Scientific Officer for the International Myeloma Foundation, so what I can convey to you is the perspective from the myeloma patient community, as well as the myeloma community more broadly.

I'd like to just touch on these five points here just to emphasize what has been discussed in great detail already in presentation to the committee. The first two points are pretty clear, and I don't think there's any controversy. The Abecma therapy in the KarMMa-3 trial, clearly a very decisive therapy with a high response rate, 71 percent, 20 percent MRD negative; so high, deep responses, and there is clear PFS benefit, a

tripling of the PFS, 13.3 months versus 4.4 months. So in the traditional assessment of a therapy, this CAR T therapy in this earlier disease setting, triple-class refractory, is clearly beneficial.

As emphasized by the FDA, the early deaths are clearly something that need to be explained. A key aspect to that is the difficulties with the bridging therapy. So as a treating physician, I can comment very clearly that this is a very, very difficult time to manage with patients. They have frequently rapidly progressive myeloma and they need to have their disease controlled sufficiently during this period of time until the CAR T cells are manufactured and ready for infusion.

So clearly, there were a number of issues related to the bridging therapy in this particular trial that have been commented on, the use of one cycle, and then the 14-day washout period, just making it particularly stressful to get patients through that period of time and move on to the CAR T infusion therapy. The key point for me is that the increased death rate was not associated

with the CAR T infusion therapy itself, but it was occurring related to this preparative period.

The final point, which was discussed in quite some detail at the end of the presentations, was the overall survival, and clearly, the overall survival interpretation was very much complicated by the crossover, which was part of the study, including the fact that 56 percent of the patients actually crossed over. One point I'd like to emphasize -- well, two points actually -- is that this crossover started to occur rather early. After 3 or 4 months, patients were starting to crossover because of disease progression, so impacting the survival curve relatively early.

The other point is that if you look at the outcomes for the patients from the standard of care arm who received the ide-cel, their outcome was good and actually similar to the patients who received the ide-cel as a primary goal of the therapy in the treatment arm, very different than the patients who never received ide-cel.

Obviously, I appreciate the difficulties in

the various mathematical models and different ways to analyze these outcomes, truly difficult, and I empathize with that difficulty from a statistical standpoint, but from a pragmatic, patient-oriented, clinician standpoint, it's so tremendously important for these types of therapies, specifically the Abecma, to be made available in an earlier disease setting with a sufficient understanding of what has impacted these statistics. I come down strongly on the side of the fact that there is, indeed, a favorable benefit-risk profile for the ide-cel in this earlier relapsed setting. Thank you for this opportunity.

Questions to the Committee and Discussion

DR. MADAN: You're welcome, sir. Thank you for your comments.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand -- because we don't have any further

clarifying questions -- which will be the careful consideration of all the data before the committee, as well as the public comments.

We will now proceed with the questions to the committee and panel discussion, and I would like to remind 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 its wording. This will be just for discussion by the panel.

Discuss whether the results of KarMMa-3 are sufficient to support a positive risk-benefit assessment of ide-cel for the proposed indication. So again, let's start to ensure that there are no questions that the panel has for clarification on the wording of this question to the FDA before we start our discussion on question 1, for discussion and not voting.

(No response.)

DR. MADAN: I don't see any questions or

requests for clarification.

Again, I think we will try to look at the overall risk-benefit, here, assessment. Is there anybody who wants to start off with their thoughts on this discussion? I'm happy to, again, probably lean into those with expertise in this area, but I've got volunteers for discussion, so, Dr. Spratt, you're up.

Oh, and one thing -- sorry -- please state your name for the record before you start talking.

DR. SPRATT: Actually, I'll give my time. It looks like Dr. Kwok raised her hand, and just would love to hear from her expertise, and then happy to go.

DR. MADAN: Okay, very reasonable.

Dr. Kwok, please go ahead.

DR. KWOK: Thanks so much. When I think of this trial, and I think of access to CAR T, similar to conversations that we had earlier today, I think it's a really important treatment. I wonder if a lot of the increased number of deaths that occurred early could be related to the bridging therapy, for

instance, limiting it to one cycle or something that might not be effective for what the patient needs for treatment. I tend to agree with the comments that were made by some of the testimonies of the other myeloma physicians today, that these are things that we're gaining more experience with and can probably improve on.

DR. MADAN: I think it's worth noting that this question is really focused on KarMMa-3 and this data.

DR. KWOK: Yes.

DR. MADAN: But I think you bring up a good point for discussion, which is the bridging regimen. There was a lot of room for, I think, flexibility, if you will, on this, and on some level, that's kind of the optimism, is that, well, it could have been done a couple different ways, and we'll know better for later.

But on the other hand, that's the flexibility that's going to be potentially down the road, but it's kind of hard for me to just separate out that as a non-factor. I think the bridging

therapy, if it's an issue -- and we don't necessarily have the data that says it's not -- this hope that it will all get worked out down the line, how do people feel about that on the committee? You can raise your hand.

Dr. Kwok, I'll let you start since you're already speaking, and you brought it up.

DR. KWOK: Oh. Well, I think probably that bridging therapy was probably not aggressive enough or was not long enough. I mean, sure, there are probably a lot of different factors, but that's all speculation right now.

Can I say a separate comment or should I come back to it?

DR. MADAN: Yes. No, go ahead. You can go.

DR. KWOK: The other thing I wanted to say is I think the statistics are hard to interpret because of the crossover, but on the other hand, I don't blame the company for making it a crossover study. In fact, for a patient who has been triple-class refractory, or at least triple-class exposed, enrolling them to a study where it's

either something that they might have received or maybe not as good, versus a CAR T cell, which we are hopeful is effective, allowing them to cross over I think is a good thing. I think as a treating physician, I would enroll them on the trial, but it makes the statistics a little bit hard to interpret. I completely agree.

DR. MADAN: Yes, I agree with that, but there are trials with crossovers that are pretty high, in prostate cancer, for example, where you still have a survival advantage. In this one, their numbers ranged from like 46 to 56 percent but any way you slice it, as many as 4, or 5, ad 10 did get the crossover, and without all the statistical permutations, it did seem like survival was similar, whether or not we get into the detriment or not.

So that's something that I also think the committee can discuss in the context of this question, because I'm struggling with that as well. I feel like probably about half the patients crossed over, and we kept hearing how earlier

treatment is better, but that's not necessarily what this data is showing us based on the data readout, so something that I'm sure Dr. Spratt has some comments on, and I think he's next.

Dr. Kwok, did that finish your comments on this?

DR. KWOK: Yes. Thank you.

DR. MADAN: And again, if someone else wants to talk about the crossover, we can do that as discussion before we move on to the next discussion point. But go ahead, Dr. Spratt. I'm sure you have some thoughts on this.

DR. SPRATT: Thank you. Dan Spratt, UH Seidman Cancer Center and Case Western Reserve University. Yes. So when I look at both -- and if the FDA could show slide 12, which is the PFS curves here -- similarly, as you just said, Ravi, the PFS curves come all the way back together, and with that understanding -- I mean, clearly there's a PFS benefit; it's not sustained. There's absolutely no signal here of any tail to the curve or flattening of the curve; they fully come back

together.

What I haven't heard brought up and concerns me a lot about the overall survival results -- if the FDA can show their slide 13 -- is that, ok, we're giving -- and again, no one knows exactly why that potential survival detriment is there early on, but we keep saying, "Oh, crossover explains this." Well, if anything, if we're saying that when you crossover there's potentially a reason that you could have worse outcomes similar to what you see early on in these curves, and that crossover is occurring, if you look at the PFS, and those recurrences are happening at 3, 6, 9 months, you see the standard regimen arm start -- and again, I'm not trying to overinterpret this, but you start seeing the slope drop down.

So, to me, if we say that when you crossover, when you start this therapy, you may have a worsening of survival due to the time to start this regimen, if anything, I'm very concerned that in the standard arm when crossover happens, could that actually be some early events that are

contributing to when these curves actually meet up?

So again, I don't --

DR. MADAN: Yes --

DR. SPRATT: Yes, Ravi?

DR. MADAN: No, it's a challenge, and I hate to open a new can of worms in the discussion, but maybe we can take a step back and just say, at the very least, detriment or not, there's not a clear separation despite earlier therapy. Maybe we can at least agree on that. I think it does get to the question at hand without having to try --

DR. SPRATT: I guess to just say this, if I may -- the sponsor showed this, and not to harp on these RMST analyses -- but, basically, at 31 months, you cannot tell your patients that they will live more than a day longer for whatever the cost of this, a CAR T, is, $500,000 plus whatever dollars. I had never seen any NDF from the FDA or others that this is a surrogate endpoint, formally PFS, and in this case it's not clear earlier is better than later. Thanks.

DR. MADAN: Thanks, Dr. Spratt.

I think that this is an important thing, and I'm happy to move on to other points, but does anybody else want to comment with their perspective on this particular component of the survival after the crossover, any of those components?

Dr. Vasan, your camera's on, so go ahead.

DR. VASAN: Yes. I agree with everything that's been said so far. I don't know if we necessarily need to invoke an OS decrement in this conversation and, indeed, I think the FDA analyses, in their sensitivity analyses of overall survival, the models can't account for that either. But I guess the question is, really, with the crossover design, really the question is, is it better to get the therapy now or later; and with this hazard ratio hovering around 1, it seems that the answer is, it doesn't matter, and I think that's the question we're trying to wrestle with. This is obviously different from a non-crossover design, where the question is more, is it better to get the drug at all?

DR. MADAN: Yes. I think you're right. And

again, the question we're focused on right now is more of the risk-benefit assessment; it's not a detriment here, for this particular question, even though that was a focus for the conversation, so very good.

Anybody else want to chime in on this concept of crossover, or the overall survival, or even PFS as it relates to overall survival?

Dr. Frenkl, I see you're trying to turn your camera on, so go ahead.

DR. FRENKL: Yes. Thank you. Tara Frenkl, industry rep. I remembered to say it this time. Crossovers I think are always complex and controversial, but when you have a drug where early data really suggests a substantial treatment benefit, as they had here, including the crossover, I think it's, really, a very patient-centered approach because it maximizes the number of patients who are going to have access to the investigational drug.

But from an industry perspective, it's a risk, and we know that because it's going to reduce

the treatment differences between the randomized arms, especially for the long-term trial endpoints, and then influence our ability to answer the clinical question that we're trying to do, especially when the crossover rate is more than 50 percent.

When I look at this data, actually, I thought the treatment effect of ide-cel was actually very evident with the PFS, 13 months versus 4 months, and then the early crossover that's happening in those patients and the dramatic increase in the median OS from what was the expected SOC in that arm; they showed the historical expectation was 18 months, and now it's 38 months. So, for me, the efficacy is really actually robust. The trial wasn't trying to answer a question of whether it was sequential or which is the best sequential treatment of it. So I just wanted to add that.

DR. MADAN: Yes. I think that's a good point. That echoes a little bit of what Dr. Vasan was saying, which is it's not clear that earlier is

better. I think we can say the sequencing is probably beyond the scope a little bit.

DR. FRENKL: Yes.

DR. MADAN: But there are trials, and prostate cancer being one of them, with earlier treatments with inevitable crossovers -- and some of them are over 80 percent -- and survival is still shown, and that was shown with PARP inhibitors a few years ago in prostate cancer. So you can see it, and everyone brings their frame of reference, and that's one of mine.

But your point is taken. It may be viewed as a risk from industry, but if the data is supportive of earlier treatment, it should, to some degree, come out. And again, I think we're not debating magnitudes here. Those curves speak for themselves a little bit to us.

Dr. Nieva?

Sorry. Dr. Frenkl, I spoke a little bit after you commented. Did you want to say anything before you closed out? I want to give you a chance to --

(No audible response.)

DR. MADAN: Okay.

Dr. Nieva?

DR. NIEVA: Jorge Nieva, USC. I would have felt much better about these data if I'd seen some kind of plateau on the PFS curve, but we're not really seeing that, and it raises a question of, really, how long term is the benefit that you're getting from this therapy? But I agree with the previous panel members and the industry rep that we really can't evaluate OS with this much crossover.

So I think the benefit here really has to be looked at as a PFS benefit, it's clear, it's there, and it looks somewhat better. And again, in order to get that benefit, you're going to have challenges that are logistical that are frontloaded with this, although there isn't a rapid drop in OS early on, and that's at least good to see. Thank you.

DR. MADAN: Thank you, Dr. Nieva.

Dr. Spratt, I believe you have an additional comment?

DR. SPRATT: Yes. Dan Spratt, UH Seidman Cancer Center. Just to state it slightly differently, if getting the drug when the patients start out, I'm going to presume they're the healthiest and fittest they're going to be when they start this trial. There is some amount of patients who are dying at a numerically higher rate. I don't understand why crossover would affect this because what we're saying is that the patients in the standard regimen arm are crossing over and should be subject to some amount -- not necessarily the full amount because maybe the timing, it was faster, or the bridging, but some amount of this, whatever the cause is, of unknown early cause of death when they go crossover to this drug.

Usually, when we talk about crossover, it's because the therapy you give -- I'll use your example, Ravi, of a PARP inhibitor -- early on gives a very clear signal of benefit, there's no inversion of the curves, and then when the other group gets it, they catch back up. But in this

case, the early effect of the therapy is a potential -- that' why we're having this; it's not clear -- worse survival, so crossover, I don't understand how it confounds this analysis.

DR. MADAN: Any additional comments on that?

(No response.)

DR. MADAN: Okay. Any additional other comments -- Dr. Nieva, you want to follow up?

DR. NIEVA: Yes. I'd just point out that if you imagined a world where this therapy was not available at all, you wouldn't have that lift of OS that may be going on in the population. I think that's really where the crossover matters. It's not so much about the early toxicity; it's about the fact that when we look at this population, who really shouldn't be doing all that well, 18 and 24 months out, that actually both arms are doing ok 18 to 24 months out. And if there wasn't crossover, you'd expect that standard arm to perhaps be crashing a bit more.

DR. MADAN: Yes, but just for context, this is more of a KarMMa-3 specific question, so the

broader availability of this agent, which is available I think currently, is less germane to the point, but your second point is, I think, very clear and very valid. We just want to try to focus on the KarMMa-3-related component of this conversation and this question.

So I think in the interest of time, we'll move on to our second question, but before we do that, I'll summarize. I think the committee is a little bit torn, I think, based on this conversation about how to interpret the very profound PFS benefit that's seen, and then this detriment -- not detriment. I shouldn't say that; strike that from the record -- the relative similar survival time lines.

I think we're all kind of struggling with our lens that we bring to the table to try to understand what that really means, and I think for all of us, that helps us better understand the answer to question 1, which is the overall risk-benefit, and depending on how we see that, I think colors how we answer that question, and I

think I'm hearing that the panel is a little split on that.

Okay. We will now move on to question 2. Here's question 2, and I will read this, and if there are any questions afterwards, we can ask the FDA for clarification, but I think it's clear.

Is the risk of early death associated with ide-cel treatment acceptable in the context of the PFS benefit? I will, again, stick to my -- first of all, clarifications from anybody on the panel to the FDA?

(No response.)

DR. MADAN: I think, again, while I seem to struggle with the OS component here, it is interesting that this question is specifically asking the PFS benefit, but it still brings up some of this early death question.

Dr. Lieu, you have your your hand up, and I'll let you watch [indiscernible - 8:34:39] the conversation here.

DR. LIEU: Yes. I'll really be interested to see what other people think. The issue here is

that, obviously, there seems to be an issue with the bridging therapy. I think that that's pretty clear. You look at the amount of deaths that we're seeing during that time period, that bridging therapy is problematic, and I think we've seen that now across a couple different studies.

Whether it's related to the drug or not, it almost doesn't matter. I mean, this is just part of the treatment paradigm, and people are essentially accruing this risk, whether it's due to the drug itself or whether it's due to the bridging therapy. So that's obviously going to be one of the big takeaways here, is optimization of that time period, which appears to be really critical because we are seeing an increase of deaths in that time.

I think what makes this really difficult is that when you look at the progression-free survival -- and this point has been made multiple times -- that these curves come together in terms of PFS benefit. So there isn't that long, durable benefit that we'd like to see for people to assume

this risk of early death, or at least this trend. So this is where I think it's narrow in regards to the risk that people are assuming for this PFS, that is clearly there. I mean, these are wide curves, but the simple fact is that they come together at the end, and it isn't as durable as maybe one might hope.

DR. MADAN: So durability is your concern and perspective on the PFS. This is also part of what Dr. Kwok was mentioning about the optimization of the bridging regimen, and that really is tied to this early death event.

Any other thoughts from the panel on this?

Dr. Kwok?

DR. KWOK: I want to clarify, duration of response, I think when we think of the current FDA approval of ide-cel, I think, generally, the duration of response that we expect is roughly about a year; it's about that. And I think the duration of response that was seen in this study was about 14 months, if I remember correctly, something like that.

So I think that when the curves come together, it's not a huge surprise; I mean, it's not a cure, and how to interpret that, again, in the context of crossover is a little bit difficult, but I guess that doesn't surprise me. I think of it just as another line of therapy for patients with myeloma.

DR. MADAN: Okay. I think the question is do they have to take that jump? Dr. Lieu kind of highlighted that you can't buy the therapy without the bridging component, and there's risk, obviously, in that, even if it's not tied directly to the therapy, and that's kind of the question here.

Dr. Hunsberger, I think you had your hand up next.

DR. HUNSBERGER: Yes. Sally Hunsberger. I do agree that the bridging does seem to be problematic. I'm a little bit worried about saying that the PFS curves come together in that there's still quite a bit of censoring in the ide-cel arm, so we don't exactly know what's going on. The

tails are coming together, but still, if you look in the middle of the curve, there's a lot of censoring, so we don't really know what the PFS curve looks like for that. The standard regimen, there's not that much censoring, but for the ide-cel arm, there is still a lot of censoring, so I don't know that that we know exactly what's going on in the tails yet.

DR. MADAN: Okay. I think that's a good point, and we appreciate that.

Dr. Frenkl, you're up again.

DR. FRENKL: Yes. Thanks. I was going to make a similar point, so thank you, Dr. Hunsberger. It may be a question for our experts on the panel, our clinical experts on the panel. How does that interpretation of the curves also tie into time off therapy? These patients are not getting any therapy during it, and we know that that increased their quality of life, as well. So how are people thinking about that?

DR. MADAN: Go ahead, Dr. Kwok.

DR. KWOK: Sorry. I keep forgetting to

introduce myself. Mary Kwok, University of Washington, Fred Hutch Cancer Center. I don't know the specifics in this study, but when I think of sending patients for clinical trials, especially something like a CAR T clinical trial, they have to be progressing while they're going on trial. So it's not like they have indolent-controlled disease; usually you have to be progressing and have measurable disease. It's like a time where there's somewhat of an urgency to start treatment.

So when I think of that, and I think of inadequate bridging therapy, it makes me worry that it's hard to get the disease under control, and especially if there are lots of breaks built in because you have to have the break off of therapy for screening purposes, for leukapheresis, to get your bridging approved or whatever, and then another washout before you have your lymphodepletion.

That's a lot of breaks, and for somebody that might have disease that's not super well controlled, and here you're only giving one cycle

of bridging therapy, it's not a huge surprise that there could be disease progression during that time. But I think that myeloma is also very heterogeneous, so you'll have patients that have more of an indolent relapse versus patients that have a more aggressive relapse. So I suspect that the patients that are progressing before they're getting their ide-cel maybe fall into the more aggressive type category.

DR. MADAN: Okay. I see a couple more hands, and then we'll probably get to our voting question.

Dr. Gradishar, you were next.

DR. GRADISHAR: Yes. Bill Gradishar, Northwestern. I would echo what others have said. I think the theme has been that the bridging therapy is problematic, and this came up in an earlier discussion as well. I think the survival curves are a little bit uninterpretable at this point -- and maybe that's being unfair -- because of, obviously, the crossover, but I am still struck by the PFS.

The question that had been raised earlier is whether or not a duration of time of that length, in the absence of ongoing therapy, has value, and I certainly think it does for any patient. So although there are some things that we can't control here, or we can't interpret completely, I think, still, the PFS, as well as the time off a new therapy, is not insignificant to patients who would receive this.

DR. MADAN: Okay. We've heard that before.

Dr. Vasan, you had your hand raised.

DR. VASAN: Neil Vasan. My point was made.

DR. MADAN: Okay. Great.

I see there's a hand from Celgene, but we'd like to probably focus on the panel discussion at this point, unless you have a brief comment you'd like to make; and probably not get into a big discussion. But if you have a brief point, we can go ahead and let you say that.

DR. RAJE: Thank you so much, Dr. Madan. A few points to make, and one is I don't think we can --

DR. MADAN: Let's try to keep it to a minimum because this is panel discussion time.

DR. RAJE: Absolutely. You cannot underestimate the time off treatment for our patients. The second thing, which you brought up, is 56 percent crossed over. It is actually more than 70 percent because only those who progressed crossed over, so that is something important to recognize as well. And the last point, which I think you brought up in your discussion, is the control arm was treated and crossed over when they had a biochemical progression, and that's why you don't see that deficit of survival at the crossover, but earlier on. These are heavily pretreated patients with aggressive disease. I just wanted to make sure the panel understood that. Thank you.

DR. MADAN: Yes. I think those were all incorporated in our conversation.

The FDA now would like to to follow up, so go ahead, and I think that'll be the end of our discussion. Go ahead.

DR. VERDUN: Yes. Thank you.

Dr. Sharma. Yes. Thank you. I'm the clinical reviewer for the application. I think we'd just like to clarify that, as stated earlier, the poor prognostic clinical factors were balanced in the two arms, so the randomization does take care of the unknown and unknown prognostic factors. Both the arms had the same therapy assigned to them based on clinical factors. So I think we are sort of struggling to understand that despite these balances, we are seeing this early overall survival detriment and how that would not also translate into the real-world setting. So we just wanted to bring up that issue. Thank you.

DR. MADAN: Thank you.

I think the panel is somewhat seeing this uniformly in the sense that there is a PFS benefit; it's clear. There's increased toxicity or death that happens likely from bridging and not from the therapy itself. I think, as you heard from different individuals seeing it differently, the crossover and, to some degree, the survival

readouts color that interpretation further.

I do think the panel is a little split on the ultimate answer to this question, but I think that we are in agreement that PFS benefits are clear and the early deaths are an issue and possibly related to the conditioning regimen, which is not optimized at this time.

So I think with that, unless somebody wanted to add clarity from the panel -- Dr. Frenkl?

DR. FRENKL: Thank you. Dr. Frankel, industry rep. Yes. To your point, we're talking about toxicity, and maybe we're saying the same thing, but on slide 22 of the FDA -- and again, a similar point as to earlier -- prior to treatment, the increased rate of death is driven by progression. If I remember correctly, six out of eight patients was from progression.

So again, it is kind of inadequacy, I think, of the bridging therapy but not attributed to toxicity from the therapy. And after treatment, the numbers are quite even from death from adverse events, and then less from progression; so same.

DR. MADAN: No, I think that's correct, and there's the slide for us to reference, if we'd like.

DR. FRENKL: Thank you.

DR. MADAN: Okay.

So now, we will proceed to question 3, which is a voting question, so I'll ask Dr. Joyce Frimpong to go ahead and provide us instructions for voting.

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 will 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 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 also address any subparts of the voting 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, and we can begin.

DR. MADAN: Okay.

I will go ahead and read the question that we will be voting on. Is the risk-benefit assessment of ide-cel for the proposed indication favorable?

I just want to make sure that the question is clear and offer opportunities for anyone on the panel to request clarification on the question.

(No response.)

DR. MADAN: Okay. I'm not seeing any hands. So if there are no further questions or comments concerning the wording of the question, we'll now begin voting on question number 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. There are 8 yeses, 3 noes, and 0 abstentions.

I hand it to you, Dr. Madan.

DR. MADAN: Okay. Thank you.

We'll now go down the list and have everyone

who voted state their name and vote into the record. You may also include the rationale for your vote as well. We'll start with me, I guess. I'm listed first.

Ravi Madan, National Cancer Institute. I know there's a lot of optimism about moving these therapies earlier in the disease states of multiple myeloma but, for me, this data at this level of maturity really didn't provide convincing evidence that ide-cel earlier had a favorable risk-benefit assessment in the proposed indication as the question asked.

There are relatively higher grade 3 and 4 toxicities with this treatment. It seems like the bridging therapy strategies really need to be optimized further. And finally, while the PFS is quite remarkable, the ultimate readouts of similar overall survival, again, question whether earlier is truly better in this setting. So I think that at this level of analysis, this data, for me, left a little bit more to provide clarity to answer in the affirmative for this question, so thank you.

We'll move to number 2 on the list.

Mr. Deflice?

DR. DEFLICE: John Deflice, myeloma survivor. I voted yes. I'm impressed with the prolonged PFS in this very refractory group of patients, so I voted yes.

DR. MADAN: Thank you, Mr. Deflice.

Dr. Advani?

DR. ADVANI: Ranjana Advani, Stanford. I voted yes because I think the PFS is very convincing. We have problems with bridging. We don't know what the ideal bridging is across almost any indication with start and, actually, once it's available, physicians know how to manipulate bridging better than when it's on a trial, where you're restricted to one versus the other.

I do think the crossover suggests that the standard of care arm, survival is better, and that's why the curves came together, not because there's a hint that it's worse. And we do know that on most of the progressions, the early deaths were related to patients who had rapidly

progressive disease and didn't get the product. So I think, overall, I was quite impressed by the PFS curves, and I voted yes for that reason.

DR. MADAN: Thank you, Dr. Advani.

Dr. Lieu?

DR. LIEU: This is Chris Lieu. I'm from the University of Colorado, and I voted yes. I'll be honest, I struggled with this decision given what I feel are data that are concerning for two reasons, the prolonged trend towards overall survival detriment in that 15 months, as well as a lack of durable PFS tail, suggesting a response that's not quite as durable as one might hope, given what we're asking our patients to go through.

Of course, patients have to be aware of the risks associated with the treatment in the early months, whether it's related to ide-cel or just the risk burden that patients are going to carry with them during the bridging period, which is still part of this overall treatment paradigm. But having said that, the PFS difference is prolonged, it's significant, and it offers our patients a

chance of significant time off therapy with associated quality-of-life improvement. And given this, I do believe that the risk-benefit profile is favorable for this population as a whole, but it's a closer margin than I think we would like, and patients will need to have in-depth discussions about the risks and benefits, and balance that with the the possible benefits with their provider. Thanks.

DR. MADAN: Thank you, Dr. Lieu.

Dr. Gradishar?

DR. GRADISHAR: Bill Gradishar, Northwestern, and I voted yes. I think the PFS data is compelling. I think for all the discussion revolving around survival and the crossover, that becomes more problematic to interpret, but I do put a lot of weight on time off from therapy that would come to our patients. So I think that is compelling in light of the PFS. And I think there's still things that need to be worked out better, generally, with respect to bridging therapies and the whole process, but the PFS data

drove it for me.

DR. MADAN: Thank you.

Dr. Vasan?

DR. VASAN: Neil Vasan, Columbia. I voted no. I felt that the lack of the tail of the curve for PFS and the lack of effects on OS outweighed the benefits, and led me to conclude that it is not better to get ide-cel now versus later. I would like to commend the applicant for designing a crossover trial. I think these are the types of trials we want to see. They're very patient centered, they're ethical, and as CAR T cells move into earlier settings, we need more trial designs that can capture the benefits of not only if the treatment is given, but when the treatment is given. Thank you.

DR. MADAN: Thank you, Dr. Vasan.

Dr. Nieva?

DR. NIEVA: Jorge Nieva, USC. I voted yes, though I'm concerned about the lack of a plateau on the PFS curve. There is certainly a benefit there that's prolonged. The quality-of-life benefit made

it convincing to me that patients actually do benefit from this therapy.

I do think that much of the issue around bridging, which I think is a reason for some of the problems here, is, in a way, an artifact of the clinical trial process. I think in the real world, where collection and manufacturing could occur early in the course of disease, it may be less of an issue for patients, which, of course, is very difficult to test in the absence of a clinical trial. So I think that's something where real-world evidence may help us in the future. Thank you.

DR. MADAN: Thank you, Nieva.

Dr. Spratt?

DR. SPRATT: Thank you. Dan Spratt, UH Seidman Cancer Center and Case Western Reserve University. I voted no. This was a challenging one. I want to be clear that our goal is to help patients experience life better, usually quality or quantity of life. The question is the risk-benefit ratio, so the benefits, as everyone said, is

clearly that PFS has improved.

What are the risks right now? Well, the risks are PFS, and the data we have now, it appears transient, and there's no clear benefit that earlier is better than later. Those that do progress and crossover had favorable OS, as they showed, so there's not a clear benefit of earlier intervention.

There is numerically greater early deaths. I still believe there's still uncertain potential of worse OS that crossover doesn't explain, but we don't have all the events matured. And speaking to real-world data, I think there's a whole other side of real-world data, is that providers would need to tell their patient, based on this data, that there's potentially an over half a million dollar expense for a zero day, on average, life gained over a 31-month period.

So I think that my vote is based on the follow-up we have today. I think with longer follow-up, it may change both the PFS curves coming together, as was stated, as well as OS, and I would

strongly encourage industry to demonstrate a valid surrogate endpoint and pull their individual patient data together to identify this. Thank you.

DR. MADAN: Thank you, Dr. Spratt.

Dr. Lattimore?

MS. LATTIMORE: Yes. This is Susan Lattimore. I voted yes. I just want to echo the comments of Dr. Lieu and Dr. Gradishar. I struggled a little bit with some of these results, but I do think the potential for time off treatment really has to be considered. And if the overall outcomes are even similar to the standard of care treatment, this opportunity for people to have a time off treatment period in a very complicated treatment phase certainly has a higher benefit in my mind. I would say that really transparent disclosure of this risk-benefit and clarity around that disclosure with patients and families is ultimately important.

DR. MADAN: Thank you, Dr. Lattimore.

Dr. Hunsberger?

DR. HUNSBERGER: Yes. Sally Hunsberger. I

voted yes. The reason I voted yes is I think the PFS is what the study was designed to look at. It definitely met that endpoint. The study was underpowered for overall survival, so it's asking a lot to really expect to see the curves separate in a way that you will see significance, especially in the light of the crossover. I think the crossover, once you start putting a crossover in there, it leaves overall survival pretty much uninterpretable. We have statistical methods to try to look at that. There was lots of modeling done, and I think it was done well, and what I got from the modeling was that, at best, there is almost a benefit there; at worst, it's the same.

So I think the PFS drove my decision. I think there is still the bridging question and how to really implement that, but I think the study was designed for PFS, and the overall survival, it's not harmful as far as I can see. So I think you're asking too much to actually be able to expect the curves to diverge based on OS, especially at this point in the study. That's all I have. Thanks.

DR. MADAN: Thank you, Dr. Hunsberger.

Dr. Kwok?

DR. KWOK: Thank you. Mary Kwok, University of Washington, Fred Hutch Cancer Center. I also voted yes. I shared my thoughts earlier, but I think the PFS benefit is there, and the OS was greatly impacted by the pre- ide-cel period, so I think, again, it's coming to this question of bridging therapy. For me, the OS was still hard to reconcile in the light of the crossover, and I don't, again, blame the company for making it a crossover study. I echo Dr. Vasan's comments that I actually commend it. It's very patient centered, so I voted yes.

DR. MADAN: Thank you, Dr. Kwok.

I think even though we have votes for yes and no, there is some agreement on the panel here that the PFS data here is very encouraging and great for patients, and that the bridging regimen really needs to be optimized, and maybe that's across the field, but that's something I think everybody agreed on.

I think for those people who had concerns and voted no, it was more from a lack of later outcomes, whether it was survival despite the crossover or lack of plateau. But that was less of a concern for the people who voted yes, who felt that the time off of therapy was valuable, and that perhaps in the time down the road, all the bridging issues would be worked out.

So I think it was a productive discussion today. I'd like to take a moment to thank the FDA for their thoughtful presentations of the data. I would like to thank the Celgene colleagues for their openness and sharing data with us and their ideas on this trial. I'd like to thank my colleagues who helped facilitate this discussion today. And also, of course, we had some people at the open public hearing session share their very personal stories about their journeys, and I think that is always helpful for us to hear when we're trying to determine this sort of thing.

So before we adjourn, I just want to make sure there's no last comments from the FDA at all.

DR. VERDUN: Well, just to thank you again. So on behalf of the FDA, we really would like to thank all of the participants, the advisory committee, patients, caregivers, providers, and we really appreciate the very robust conversation that will really help inform our decision making. So again, thank you so much for taking the time and taking the day to really explore this with us. Thank you.

Adjournment

DR. MADAN: Alright. I think that's the end of our day, so we'll now adjourn the meeting. Thank you, everybody, for your time and participating and for those who joined us.

(Whereupon, at 5:08 p.m., the afternoon session was adjourned.)