FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Thursday, July 17, 2025

8:00 a.m. to 12:54 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

LaToya Bonner, PharmD, MBA
Division of Advisory Committee and
Consultant Management
Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

William J. Gradishar, MD
(via video conferencing platform)
Betsy Bramsen Professor of Breast Oncology &
Professor of Medicine
Deputy Director, Clinical Network
Director, Maggie Daley Center for
Women's Cancer Care
Robert H. Lurie Comprehensive Cancer Center
Northwestern University
Feinberg School of Medicine
Chicago, Illinois

Daniel Spratt, MD

(via video conferencing platform)

Associate Chief Scientific Officer, University Hospitals Cleveland Medical Center

Medical Director, Clinical Research Center

Vincent K Smith Chair of Radiation Oncology

UH Seidman Cancer Center

Chair, Department of Radiation Oncology

Professor, Departments of Radiation Oncology and Urology

Case Western Reserve University

Cleveland, Ohio

Neil Vasan, MD, PhD

(Acting Chairperson)

Director, Breast Cancer Translational Research

Assistant Professor

Department of Medicine, NYU Grossman School of Medicine

Perlmutter Cancer Center, NYU Langone Health

New York, New York

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBER

(Non-Voting)

Tara L. Frenkl, MD, MPH

(Industry Representative)

Senior Vice President, Head of Global Medical Strategy and Evidence Generation

Bayer Pharmaceuticals

Whippany, New Jersey

TEMPORARY MEMBERS (Voting)

Paul Beringer, PharmD

Professor of Clinical Pharmacy

USC Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences

University of Southern California

Los Angeles, California

Mark R. Conaway, PhD

Professor, Division of Translational Research and Applied Statistics
Department of Public Health Sciences
The University of Virginia School of Medicine
Charlottesville, Virginia

John DeFlice, MD

(Patient Representative)
Gastroenterologist, Retired
Albuquerque, New Mexico

Ravi A. Madan, MD

Senior Clinician
Head, Prostate Cancer Clinical Research Section
Genitourinary Malignancies Branch
Center for Cancer Research
National Cancer Institute
National Institutes of Health (NIH)
Bethesda, Maryland

Grzegorz (Greg) S. Nowakowski, MD, FASCO
Professor of Medicine and Oncology
Enterprise Deputy Director for Clinical Research
Mayo Clinic Comprehensive Cancer Center
Chair, Lymphoid Malignancy Group
Vice-Chair, Division of Hematology
Mayo Clinic
Rochester, Minnesota

FDA PARTICIPANTS (Non-Voting)

Richard Pazdur, MD
Director
Oncology Center of Excellence (OCE), FDA
Director (Acting)
Office of Oncologic Diseases (OOD)
Office of New Drugs (OND), CDER, FDA

Nicole Gormley, MD
Director
Division of Hematologic Malignancies II (DHM II)
OOD, OND, CDER, FDA

Nicholas Richardson, DO, MPH

Deputy Director

DHM II, OOD, OND, CDER, FDA

Bindu Kanapuru, MD

Supervisory Associate Director for Therapeutic Review

DHM II, OOD, OND, CDER, FDA

Deepti Telaraja, MD

Clinical Team Leader (Acting)

DHM II, OOD, OND, CDER, FDA

Andrea Baines, MD, PhD

Clinical Reviewer

DHM II, OOD, OND, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. VASAN: Good morning, and welcome. I would like to first remind everyone to please mute your line when you're not speaking. All members of the public are reminded to silence their phones and other devices, and to otherwise refrain from disrupting the meeting. Loud talking or applause may make it difficult for meeting participants and observers to hear the proceedings.

My name is Dr. Neil Vasan, and I will be chairing this meeting. I will now call the July 15, 2025 Oncologic Drugs Advisory Committee meeting to order. We'll start by going around the table and introduce ourselves by stating our names and affiliations. We'll start with the FDA to my left and go around the table.

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

DR. GORMLEY: Nicole Gormley, Director of

the Division of Heme Malignancies II, FDA.

DR. RICHARDSON: Good morning. Nicholas Richardson, Deputy Director, Division of Hematologic Malignancies II, FDA.

DR. KANAPURU: Good morning. Bindu Kanapuru, Associate Director, Division of Heme Malignancies II, FDA.

DR. TELARAJA: Good morning. Deepti Telaraja, Acting Clinical Team Lead, Division of Hematologic Malignancies II at the FDA.

DR. BAINES: Good morning. Andrea Baines, Clinical Reviewer, Division of Hematologic Malignancies II, FDA.

DR. SPRATT: Dan Spratt, Chair of Radiation Oncology at UH Seidman Cancer Center at Case Western Reserve University, and stuck because of a canceled flight.

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

CDR BONNER: Good morning. LaToya Bonner, DFO, CDER.

DR. VASAN: Neil Vasan. I'm a breast

oncologist at NYU Langone.

DR. NOWAKOWSKI: Greg Nowakowski. I'm a hematologist at Mayo Clinic Rochester, where I also serve as Deputy Director of the Cancer Center for Clinical Research.

DR. DeFLICE: I'm John DeFlice. I'm a patient representative, and I'd like to review why I am a patient representative from myeloma. I'm a 15-year survival of multiple myeloma. I'm involved with two support groups sponsored by the International Myeloma Foundation, one I've been involved with for 13 years. And we meet by Zoom and primarily for people in New Mexico, which is a rural state, although we have many members that join us from other states, including Canada.

I'm also involved with a Spanish support group, Las Voces de Mieloma, which meets monthly and is primarily for Spanish-speaking patients with myeloma. We have patients from South America, all the way from Argentina to Dominican Republic, and sometimes Europe. I'm also a volunteer with the LLS and the First Connection Program so that

Spanish-speaking patients are referred, and we support them through hope and understanding of their therapies.

My first seminar was one month after my diagnosis, which was 15 years ago. I've attended the American Society of Hematology for a number of years, and as a gastroenterologist, I feel like I've done a fellowship in oncology.

DR. BERINGER: Paul Beringer, School of Pharmacy, University of Southern California.

DR. CONAWAY: Mark Conaway, biostatistics, University of Virginia.

CDR BONNER: Dr. Gradishar, you're next. Can you please unmute your mic and cut on your webcam, and introduce yourself to the group?

(No response.)

CDR BONNER: Dr. Frenkl, you can go ahead and introduce yourself.

DR. FRENKL: Tara Frenkl. I am the non-voting pharmaceutical industry rep. I work for Bayer Pharmaceuticals as the head of Global Medical and Evidence.

DR. VASAN: We'll come back to Dr. Gradishar.

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

In the spirit of the Federal Advisory Committee Act and the Government in their 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 the break. Thank you.

CDR Bonner will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

CDR BONNER: Thank you.

The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the Federal Advisory Committee Act, FACA, of 1972. At today's meeting, the committee will discuss BLA 761440, belantamab mafodotin, submitted by GlaxoSmithKline, LLC, for the treatment of adults with multiple myeloma in combination with bortezomib and dexamethasone in patients who have received at least one prior line of therapy; and in combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy, including lenalidomide.

With the exception of the industry representative, the members of the committee are either special or regular government employees and

are subject to federal conflict of interest laws and regulations. Accordingly, FDA has reviewed the financial interests of the committee members for compliance with federal ethics and conflict of interest laws. We have screened the members for potential financial conflicts of interest related to today's meeting agenda, both their own interests and those that are imputed to them, including those of their spouses, minor children, and employers.

Based on the agenda for today's meeting and all financial interests reported by the committee members, no conflict of interest waivers under 18 U.S.C. 208 have been issued in connection with this meeting.

Dr. Tara Frenkl of Bayer Pharmaceuticals is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Consistent with Commissioner Makary's April 17, 2025 statement, FDA is only including industry representatives in advisory committee meetings where required by statute. FDA is required to include an industry representative

in today's meeting under 21 U.S.C. 355(n)(3)(c).

Industry representatives are not appointed as special government employees nor are they regular government employees. Industry representatives serve as non-voting members of the committee. Non-voting industry representatives represent all regulated industry and not any particular association, company, product, or ingredient, and bring general industry perspective to the committee.

Under FDA regulations, although a non-voting member serves in a representative capacity, the non-voting member shall exercise restraint in performing such functions and may not engage in unseemly advocacy or attempt to exert undue influence over the other members of the committee.

We would like to remind all members of the committee that if the discussions involve any other products or firms not already on the agenda for which you have a personal or imputed financial interest, you must recuse yourself from that discussion, and your recusal will be noted for the

record.

FDA asks that all other participants, including the industry representative and open public hearing speakers, advise the committee of any financial relationships that they have with any affected firms, its products, and if known, its direct competitors. We would like to remind the members that if the discussions involve any products or firm not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to inform the DFO and exclude themselves from the discussion, and their exclusion will be noted for the record. Thank you.

I will go back to Dr. Gradishar to see if he's available, if he can introduce himself. Please unmute your mic and cut on your webcam.

DR. GRADISHAR: Good morning. Bill Gradishar, Northwestern University, Medical Oncology.

CDR BONNER: Thank you, sir.

Now, I will turn the meeting back over to

our chair. Thank you.

DR. VASAN: We will now proceed with FDA introductory remarks from Dr. Deepti Telaraja.

FDA Introductory Remarks - Deepti Telaraja

DR. TELARAJA: Good morning. I'm Deepti Telaraja, a hematologist/oncologist in the Division of Hematologic Malignancies II at the FDA. I will provide the FDA's introductory remarks for belantamab mafodotin and the key issues for the ODAC today. I'll first provide some background about the drug's history; the proposed indications; a description of the DREAMM-7 and DREAMM-8 trials; and the current treatment landscape for patients with relapsed or refractory multiple myeloma. I'll then provide an overview of the key issues.

Today's ODAC will focus on the key safety finding with belantamab mafodotin, which is ocular toxicity, as well as the uncertainty regarding the appropriateness of the dosages that were evaluated in DREAMM-7 and DREAMM-8. And finally, I'll conclude with some dose optimization and benefit-risk considerations.

Belantamab mafodotin is a BCMA-directed antibody drug conjugate. It was previously granted accelerated approval based on a single-arm trial in August of 2020 as monotherapy for the treatment of patients with relapsed or refractory multiple myeloma after four or more therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

A postmarketing requirement was issued to conduct a randomized trial to confirm clinical benefit. Due to a failed confirmatory trial, belantamab mafodotin was voluntarily withdrawn from the U.S. market in February of 2023. Currently, it is not marketed for any indications in the U.S.

While it was ultimately approved, due to significant concerns with ocular toxicity and dosing as monotherapy at the dose of 2.5 milligrams per kilogram every 3 weeks, an ODAC was held to discuss the impact of ocular toxicity on benefit-risk. The ODAC advised that for the proposed population, which again was a late-line population of patients who had received four or

more prior therapies, the benefit-risk was favorable. Due to the concerns with ocular toxicity and dose, it was approved along with a comprehensive risk evaluation and mitigation strategy, or REMS, and a postmarketing requirement was issued to evaluate alternative dosing regimens and lower doses.

The current application is based on two randomized phase 3 trials, DREAMM-7 and DREAMM-8. DREAMM-7 evaluated belantamab mafodotin in combination with bortezomib and dexamethasone, or BVd, in patients who had received at least one prior line of therapy. The proposed dosage of belantamab mafodotin is 2.5 milligrams per kilogram every 3 weeks, which is the same dosage that was previously approved as monotherapy.

DREAMM-8 evaluated belantamab mafodotin in combination with pomalidomide and dexamethasone, or BPd, in patients who had received at least one prior line, including lenalidomide. In DREAMM-8, the starting dose of belantamab mafodotin is the same at 2.5 milligrams per kilogram, but it steps

down to 1.9 milligrams per kilogram from Cycle 2, and the dosing interval is 4 weeks. In both regimens, belantamab mafodotin is administered until progressive disease or unacceptable toxicity.

Schemas for the DREAMM-7 and DREAMM-8 trials are shown on this slide. DREAMM-7 randomized patients between BVd versus daratumumab in combination with bortezomib and dexamethasone, or DVd. DREAMM-8 randomized patients between BPd versus pomalidomide, bortezomib, and dexamethasone or PVd. In each trial, the primary endpoint was progression-free survival, or PFS, and key secondary endpoints were overall survival, or OS, duration of response, and minimal residual disease negativity.

The key results of PFS and OS from each trial are shown on this slide. Both trials met their primary PFS endpoint. In DREAMM-7, OS met statistical significance, while in DREAMM-8, OS did not reach statistical significance. DREAMM-8 is not adequately powered for OS and may not demonstrate statistical significance.

Before moving on to a discussion of the issues, I'd like to provide some context about the treatment paradigm for current patients with multiple myeloma.

In the U.S., based on recent approvals of quadruplets in the newly diagnosed setting, most patients will receive a 4-drug regimen containing an anti-CD38 monoclonal antibody, a proteasome inhibitor, an immunomodulatory agent, and dexamethasone upfront such as Dara-VRd or Isa-VRd. Patients who are transplant eligible go on to receive autologous stem cell transplant and maintenance therapy. For relapsed or refractory disease, patients may receive a subsequent 3- or 4-drug regimen with novel combination partners, CAR T-cell therapy, or bispecific antibodies.

In the current treatment landscape, there are concerns regarding the applicability of the DREAMM-7 and DREAMM-8 comparator arms, and therefore, the studies' results to current U.S. patients with relapsed or refractory multiple myeloma. I'll cover these considerations in more

detail on the next slide.

In both trials, there was very limited U.S. enrollment, less than 5 percent in each trial. The DREAMM-7 comparator arm of DVd would not typically be used in the second line or later setting, as each of the components of this regimen would have already been received, as I noted previously. And while the DREAMM-8 comparator, PVd, does include pomalidomide, which is typically not given in the upfront setting, PVd is not an approved regimen in the U.S. and has limited usage.

These factors directly impact the relevance of the trials' results to current U.S. patients, and these considerations are important in the benefit-risk assessment of belantamab mafodotin. As mentioned, the key issues include the high rates of ocular toxicity and uncertainty regarding the appropriateness of the proposed dosages.

I'd like to first provide some context regarding the ocular toxicity seen with belantamab mafodotin. The toxicity is caused by damage to the corneal epithelium, manifesting as corneal changes

and visual acuity changes. Corneal defects range in severity from mild superficial changes to severe epithelial defects and ulceration, and severe corneal defects may be vision threatening. Visual acuity changes are measured by testing of each eye on an eye chart, and are based on best corrected visual acuity. Best corrected visual acuity is the best possible visual acuity achieved with the use of corrective lenses such as glasses or contacts.

The applicant developed the Keratopathy and Visual Acuity scale, or KVA scale, with input from the FDA to grade this unique toxicity. Dose modifications were also guided by this scale, with modifications recommended for grade 2 and higher events in both trials.

The figure on this slide shows simulations of 20/50, 20/100, and 20/200 vision relative to normalized 20/20 vision. In people with best corrected visual acuity of 20/20, a change to 20/50 or worse would generally be considered clinically significant.

For additional context to these changes, in

most states, a minimum visual acuity of 20/40, which would be in between the 20/20 and 20/50 figures, is needed in at least one eye for an unrestricted driver's license. Driving restrictions are often placed for visual acuity of 20/70, which is in between the 20/50 and 20/100 figures, and at 20/200 vision, an individual would be considered legally blind.

This table provides a summary of KVA events by grade for each trial. In both trials, almost all patients experienced a KVA event, with over three-quarters experiencing a grade 3 or 4 event. There were higher rates of grade 4 events in DREAMM-7 as compared to DREAMM-8.

A substantial percentage of patients on both trials had visual acuity changes, with over 60 percent experiencing changes to 20/50 or worse. Over a quarter of patients had worsening to 20/100 or worse. As previously mentioned, this is beyond a threshold at which driving restrictions should be placed, and over 10 percent had worsening to 20/200 or worse, correlating with legal blindness.

There were high rates of recurrent events with a median of three per patient, and while many KVA events were reversible, it's unclear whether recurrent corneal epithelial damage impacts recovery. FDA's analysis focused on the last KVA event and showed that over 70 percent of patients had ongoing events at the data cutoff, including a substantial percentage who had ongoing events following treatment discontinuation.

Now I'll provide a brief overview of the dosage selection for belantamab mafodotin in the proposed combinations. In each dose-finding trial, while a range of dose levels over a range of dosing intervals were evaluated, there were limited numbers of patients enrolled at each dose level; and in general, there was a trend towards better tolerability with lower doses and longer dosing intervals. Despite this trend, the applicant selected dosages that were the same as or similar to the dosage that was previously approved as monotherapy and had known safety and tolerability concerns.

While these dosages were selected for the trials being discussed today, the ongoing and future development of belantamab mafodotin is based on lower dosages with notably longer dosing intervals.

The ongoing DREAMM-10 study of belantamab mafodotin, in combination with lenalidomide and dexamethasone versus daratumumab, lenalidomide, and dexamethasone in the newly diagnosed transplant ineligible setting, is using a dose of 1.9 milligrams per kilogram at 8-week intervals for 24 weeks followed by 12-week intervals. And as you'll hear in the FDA main presentation, available data from the dosing PMR study, DREAMM-14, which was issued at the time of initial approval, also suggest that there may be improved tolerability with lower doses and longer dosing intervals.

The lack of adequate dose optimization is also evident by the high rates of dose interruptions, reductions, and discontinuations on the belantamab mafodotin-containing arms of both trials. There were high rates of dose

modifications due to KVA events, particularly dose interruptions, which impacted approximately three-quarters of patients.

I'd now like to briefly review the FDA's evidentiary criteria for approval. Under the Federal Food, Drug, and Cosmetic Act, for a new approval in the United States, the FDA must determine that the drug is safe and effective for use under the conditions prescribed, recommended, or suggested in the product labeling. The demonstration of effectiveness requires substantial evidence that the drug will have the effect it's represented to have, and the demonstration of safety requires showing that the benefits of the drug outweigh its risks.

I'd next like to highlight some key considerations about REMS as it relates to benefit-risk. A REMS is a comprehensive drug safety program that the FDA can require for certain medications with serious but manageable safety concerns. Importantly, it is a post-approval tool that is used specifically when a drug demonstrates

a favorable benefit-risk profile but requires enhanced risk management strategies. Each REMS is strategically designed with targeted goals to mitigate this identified risk. It is important to understand what a REMS is not. It is not intended as a remedy for drugs with unfavorable benefit-risk profiles, as it cannot be used to compensate for a safety concern that is deemed unacceptable.

I'll now turn to some general dose optimization principles. It's important to note that an unnecessarily high or poorly tolerated dose may have several unwanted effects such as impacts on patient functioning, quality of life, and even their ability to remain on the intended dose and derive maximal clinical benefit.

The determination of a safe and effective dose is fundamental to the evidentiary criteria that I just reviewed. It's critically important that the dose is established prior to approval because of significant challenges with post-approval optimization. While sponsors may propose to conduct these studies as postmarketing

requirements, at the FDA, we have seen several challenges with this approach.

Marketing of a drug with an inadequately optimized dose may expose large numbers of patients to poorly tolerated dosages. While clinical trials generally involve stringent monitoring and mitigation strategies, these may be more challenging to implement in the postmarket setting. Patients, therefore, may be exposed to higher levels of risk.

There are also feasibility challenges, as there may be a lack of interest from patients and clinical trial sites, and dose optimization after a randomized trial is completed may not inform benefit-risk. Even if a lower dose is found to have a favorable safety, tolerability, and efficacy profile in a dose optimization study, it will still be unclear whether the efficacy seen in a randomized trial at the higher dose would be preserved with the lower dose. Ultimately, there is the risk that a post-approval dose optimization trial may not be complete or may not adequately

inform the benefit-risk and, therefore, may not actually provide the necessary information to establish a safe and effective dose.

I'll now turn to some key benefit-risk considerations of belantamab mafodotin for the proposed indications.

As previously described, both trials met their primary PFS endpoint, and DREAMM-7 showed a statistically significant improvement in OS. In terms of risk, there were high rates of ocular toxicity, including high rates of grade 3 or greater events, which correspond to clinically significant visual changes and/or severe corneal defects. Patients had frequent recurrences throughout treatment, and there were unresolved events at the data cutoff, including in those who had already discontinued study treatment.

There are also concerns regarding safety and tolerability at the proposed dosages. In the context of available data suggesting that lower doses at longer dosing intervals may improve tolerability and maintain efficacy, questions

remain regarding the appropriateness of the selected dosages.

As previously noted, there are concerns with the relevance of the studies' results to current U.S. patients with relapsed or refractory multiple myeloma. As patients are receiving anti-CD38, antibody-based three or four drug regimens upfront, the relevance of the control arms and the relevance of the treatment effect seen with belantamab mafodotin for current patients with relapsed or refractory multiple myeloma is questionable. There are also multiple available therapies for patients with relapsed or refractory multiple myeloma who have received one or more prior lines of therapy, many of which have more established safety profiles and demonstrated OS benefits.

It's important to consider whether the risks of this unique ocular toxicity seen with belantamab mafodotin are acceptable for this relatively early-line patient population. For the proposed population and indications, given these key considerations and the current treatment paradigm,

the benefit-risk of belantamab mafodotin remains uncertain.

We would like the committee to discuss whether appropriate dosages of belantamab mafodotin have been identified in the context of the observed ocular toxicity, tolerability of the regimens, and efficacy results from DREAMM-7 and DREAMM-8 in the proposed relapsed or refractory multiple myeloma population.

After the discussion, we will ask the committee to vote on the following questions separately for each indication.

Is the overall benefit-risk of belantamab mafodotin in combination with bortezomib and dexamethasone favorable at the proposed dosage in the proposed patient population? And is the overall benefit-risk of belantamab mafodotin in combination with pomalidomide and dexamethasone favorable at the proposed dosage in the proposed patient population?

Thank you for your attention. This concludes my presentation.

DR. VASAN: Thank you, Dr. Telaraja.

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

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

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

speaking.

We will now proceed with the presentations from GlaxoSmithKline.

Applicant Presentation - Hesham Abdullah

DR. ABDULLAH: Good morning. My name is Hesham Abdullah, Senior Vice President and Global Head of Oncology R&D at GSK. Thank you for the opportunity to present the data supporting the benefit-risk of Blenrep in patients with relapsed/refractory multiple myeloma. Blenrep offers a novel mechanism of action that targets B-cell maturation antigen or BCMA. BCMA is a cell surface receptor highly expressed on malignant plasma cells and is required for their survival.

Blenrep is an antibody drug conjugate comprised of an afucosylated humanized IgG1 BCMA-targeting antibody linked to the microtubule disrupting agent MMAF. Blenrep has a multimodal mechanism of action, including direct cytotoxic activity through the MMAF payload released into the tumor cell, as shown by the red dots; antibody-dependent cellular cytotoxicity by

NK cells; and macrophage-mediated, antibody-dependent cellular phagocytosis, as well as induction of markers consistent with immunogenic cell death, which elicit an adaptive immune response. It's this unique mechanism of action that leads to the sustained duration of response and ultimately translates to improvements in long-term outcomes.

The key data we'll share today come from two large randomized controlled studies, DREAMM-7 and DREAMM-8. These phase 3 studies assessed Blenrep-based triplet combinations versus well-known standard of care options, including a daratumumab-based triplet regimen, which is considered a gold standard in the United States. The clinical development program supports the proposed indications shown here, using the study dosing and modification guidance. Throughout the presentation, you'll hear data that supports the positive benefit-risk of Blenrep.

Despite the availability of treatment options, multiple myeloma remains an incurable

disease, and there's a need for effective therapies with novel mechanisms of action. In two randomized phase 3 studies, Blenrep consistently demonstrated meaningful benefit across all endpoints. The Blenrep combination in DREAMM-7 demonstrated a doubling of complete response and duration of response, a statistically significant two-year improvement in median PFS and a projected three-year improvement in overall survival. Additionally, DREAMM-8 demonstrated a statistically significant improvement in PFS, showing greater than a 20-month benefit in medians along with a positive trend in survival.

Importantly, the overall safety of Blenrep in DREAMM-7 and DREAMM-8 is consistent with its well-characterized safety profile. Ocular events associated with Blenrep are reversible with time and effectively managed with dose modifications, allowing patients to remain on treatment and derive benefit; and our proposed risk management strategy will enable patients to have access to treatment while further mitigating the severity of the ocular

events in clinical practice.

In today's presentation, we'll review data supporting the two key discussion topics raised by the FDA. First, it was indicated that response rates in our dose exploration studies were comparable across doses, and therefore, lower doses may improve patient tolerability. We followed the agency's recommendation at earlier stages of development to evaluate a broad range of exposure to assess if lower doses indeed improved safety while maintaining efficacy. This hypothesis was disproven by the data.

The dose and schedule of Blenrep has been extensively studied in almost 400 patients. The proposed 2.5 mg/kg starting dose and use of dose reductions and delays to manage ocular events is the most optimal approach for dosing to gain maximal benefit-risk. The higher starting dose is associated with deeper and more durable responses. It's the VGPR or better responses that translate to improve PFS and overall survival. Lowering the starting dose or using less frequent dosing

schedules may modestly improve tolerability, but at a significant loss of efficacy.

The risk of ocular events from Blenrep has been observed at all clinically active doses, and while these are unique risks from multiple myeloma treatment, ocular events are observed with other approved ADCs. When considering these events, it's important to understand the true impact they may have on the patient. They are microcyst-like deposits on the cornea most commonly found on ocular exam.

These events are transient and reversible through dose modifications, and they have not resulted in permanent bilateral vision loss with more than 7500 patients treated to date. Importantly, our proposals for labeling and risk management will further address tolerability without impact to efficacy.

With this background, here is the agenda. We also have additional responders here today to help address your questions. Thank you. Dr. Richardson will now review the unmet need.

Applicant Presentation - Paul Richardson

DR. RICHARDSON: Thank you, Dr. Abdullah.

My name is Dr. Paul Richardson, and I serve as the Clinical Program Leader and Director of Clinical Research at Dana-Farber Cancer Institute, and I'm the RJ Coleman Professor of Medicine at Harvard Medical School.

I was a co-investigator of the DREAMM-1 and DREAMM-2 studies, and I serve as principal investigator of DREAMM-5 and have been a leading enroller in the expanded access program at Dana-Farber for Blenrep. Thus, I have extensive experience with Blenrep and other targeted agents in this setting, and I greatly appreciate the opportunity to frame the unmet medical need our patients continue to face with this challenging disease.

Now, over the last 15 years, survival has improved significantly but, unfortunately, myeloma still remains clearly incurable. Before 2010, our patients typically only survived between 2 to 5 years, and at most, seven. Median overall

survival among relapsed/refractory myeloma patients initiating second-line therapy in the real world is, at best, 50 months at the moment and is significantly lower for patients with cytogenetic and functional high-risk disease.

Now, it's been my privilege to have worked to develop many of the approved drugs in the myeloma space, and I've personally witnessed this progress, and this is where, in my view, the sponsor's data really stands out. Specifically, the overall survival reported in Blenrep studies promises to be almost double what's been historically observed and I show in this slide. Critically, this data validates that we continue to need therapies with new mechanisms of action to overcome refractoriness upon relapse.

Now, as we think about our treatment options in the modern era, the key classes of approved agents used in multiple myeloma include front-line triplet, or most recently, as Dr. Telaraja pointed out, quadruplet multidrug combinations comprised of three drug classes. These are immunomodulatory

agents, proteasome inhibitors, and monoclonal antibodies targeting CD38, including daratumumab and isatuximab.

Now, because these treatments are used now in the frontline, disease is thus often refractory to combinations of these classes upon relapse. BCMA-targeted agents are becoming a key new pillar of second-line plus treatment with CAR T-cell therapies, and cilta-cel specifically, being the only currently approved option in second line. While bispecifics are up and coming, it's important to note that they are only approved in the late-line setting, four lines and beyond.

There is clearly a need for additional BCMA-targeted therapies, in my view, and to expand on this, I share a table of approved therapies in the relapsed/refractory setting adapted from the FDA's briefing document and touched on earlier by Dr. Telaraja.

While the first four rows are approved second-line options, this table does not provide the full picture of the treatment landscape. Most

of the combination options shown here contain daratumumab, which is increasingly used in front line, as we know, diminishing the effectiveness of these combinations in second line. This of course also applies to lenalidomide, which is universally used as part of induction and maintenance as a standard of care, and I have bolded these combinations in blue for emphasis. Thus, it's vital to have CD38 and lenalidomide-sparing combination approaches with different mechanisms of action to successfully salvage our patients.

This leaves us with cilta-cel as our only approved second-line treatment approach, and this does indeed show survival improvement and is where, in my view, Blenrep would clearly fit in, particularly for those patients who are not eligible for CAR T or for whom CAR T is not feasible.

Now, as we think about cilta-cel, overall survival benefit is indeed seen, and despite the benefits observed with cilta-cel, I think it's

important to note the serious limitations that CAR T treatments also have.

Cell-based therapies are not universally accessible or appropriate for all patients. Treatment is administered at specialized cancer centers with, in fact, less than 20 percent of our patients having access. Each also require individual manufacturing, which can take weeks. This leaves patients with relapsed/refractory disease at risk not only for disease progression, but actually also disease-related mortality while waiting for their cellular therapy.

Now, notably, in the pivotal phase 3 trials, approximately 15 percent of patients in the CAR T-cell arms of these studies did not receive cell infusions prior to the trial endpoints, supporting this concept. So CAR T therapy also requires patients who are fit enough to tolerate lympho-depleting chemotherapy, and this leaves our older and frailer patients in search for other viable options.

These treatments are also associated with,

unfortunately, life-threatening toxicities. This includes ICANs; CRS or cytokine release syndrome; and I think most worrisome, late-onset Parkinsonism; serious severe enterocolitis; and secondary malignancies.

Now, additionally -- and this is very important -- the most recent real-world data points to a 10 percent non-relapse mortality rate with CAR T treatment. I have experienced treating patients with Blenrep and CAR T and have seen the benefit-risk of both, and I would deeply appreciate having both options available for my patients given all of these considerations. So when we consider a new treatment for relapsed/refractory myeloma, we must consider how that therapy will actually be used and its ability to integrate into real-world practice.

I've already noted the challenges with CAR T therapy. We need a treatment that could be administered not only at academic or specialized centers but also in the community setting without the need for hospitalization, providing what I

consider a true off-the-shelf capability; and we should consider the current treatment landscape of approved agents and the ease of integration with other drugs. There's particular value for accessible options in vulnerable patient subsets, and I think this is very clear.

As we think about this going forward, this may be the type of platform that should in no way be underestimated in terms of its value. From my personal experience, Blenrep is indeed a tolerable drug with profound and undeniable efficacy, and especially when given in combination, and above all, manageable side effects.

Thank you. And I'll now turn the presentation to Dr. Mukhopadhyay.

Applicant Presentation - Pralay Mukhopadhyay

DR. MUKHOPADHYAY: Thank you, Dr. Richardson.

Good morning. I'm Pralay Mukhopadhyay, Vice President and Medicine Development Lead for Blenrep at GSK. Let me review the efficacy data beginning with the dose justification.

The dose and schedule for Blenrep has been extensively studied in nearly 400 participants. Considering prior FDA advice, we have assessed a range of doses, including from 1.9 mg/kg to 3.4 mg/kg, and a range of schedules from every 3 to 4 weeks to extended schedules of every 6, 8, or 12 weeks.

Across all studies, the starting dose of 2.5 mg/kg and a more frequent schedule of Q3 or Q4 weeks, followed by subsequent AE-guided dose modification, were associated with deeper response and clinically meaningfully longer progression-free survival. Though lower or less frequent starting doses and schedules were associated with a modest improvement in safety, ocular events were observed across all doses and schedules studied.

There was not a meaningful difference in incidence of grade 2 plus keratopathy or AEs leading to discontinuation. Ocular events were effectively managed through dose modifications, allowing participants to remain on treatment and benefit from Blenrep therapy. The extent of dose

modification was high and variable across all doses and schedules studied, resulting in a median relative dose intensity typically between 40 to 60 percent.

Here, I show the data from one of the dose-finding studies, DREAMM-6, in combination with bortezomib-dexamethasone in the second-line population that also included the dose assessed in the DREAMM-7 study. You can see, the 2.5 mg/kg starting dose at the Q3-week dosing schedule showed improved depth of response compared to the lower dose or even same dose at longer interval. FDA's briefing document states that observed trends in efficacy and safety across these studies indicate that overall response rates were comparable, but the field knows that deeper responses -- VGPR, complete response, and stringent complete response -- are critical for eliciting long-term clinical benefit with PFS and overall survival.

When considering safety, grade 3 ocular AEs and discontinuation data showed similar outcomes across doses and schedules assessed, and we saw

consistent findings from the ALGONQUIN study in combination with pom-dex, which informed the dosing used in DREAMM-8. Higher starting doses and shorter starting frequency reduced the deepest responses. Lowering the dose or frequency improves tolerability, but ocular events are observed across all dose and schedules.

The DREAMM-14 study was a randomized monotherapy dose optimization study in a fourth-line-plus population, where patients had to be refractory to all three classes of the most active myeloma agents. This study continues to show the same trends, supporting the efficacy of the 2.5 mg/kg Q3-week starting dose and schedule.

FDA mentioned in their briefing document that the ORR in DREAMM-14 was similar across arms with overlapping confidence intervals. This is true even for rates of VGPR-plus because it's difficult to see high response rates in such a heavily pretreated population; however, the randomized nature of the trial allows for a more comprehensive evaluation of PFS as well. You'll

notice that the median PFS in the 2.5 mg/kg Q3-week arm is 5.7 months, which is more than double the other doses.

We also assessed dosing through exposure-response analysis. An integrated exposure-response analysis using data from DREAMM-6, 7, and 8 confirmed the clinical findings, demonstrating that higher Cycle 1 exposure was positively associated with deeper response; and though there was a modestly increasing trend in ocular safety parameters, the slope of the exposure efficacy curve was much steeper than for the exposure safety curve. Therefore, there's a significant trade-off in efficacy while modest benefit in safety by starting at a lower dose.

Based on the totality of the clinical data and the integrated ER analysis, a starting dose of 2.5 mg/kg and a starting schedule of every 3 or 4 weeks was selected in the two phase 3 studies to elicit deeper and durable responses, followed by subsequent management of toxicities through dose holds or reductions. These dosing

recommendations led to robustly positive efficacy outcomes and a consistent and manageable tolerability profile in both studies.

FDA showed simulation results based on M protein to conclude that response rates were similar across doses and schedules. Here, we present the more clinically relevant endpoint of PFS from these simulations.

There was a meaningful loss in efficacy with lower starting doses and less frequent schedules; therefore, based on the totality of the clinical data, exposure-response analyses, and simulations, it's clear that a 2.5 mg/kg starting dose given every 3 to 4 weeks, followed by subsequent dose modifications, maximizes efficacy while having a manageable tolerability profile.

Let me now share the data from the DREAMM-7 and DREAMM-8 studies.

DREAMM-7 and DREAMM-8 shared a similar design, with both studies being global, multicentered, open-label randomized trials, evaluating Blenrep in combination with the standard

of care triplet treatment. Patients in both studies were randomized 1 to 1 to a Blenrep triplet versus a standard of care triplet.

In DREAMM-7, the starting dose was 2.5 mg/kg once every 3 weeks for the first 8 cycles, followed by monotherapy, Blenrep or daratumumab, starting in Cycle 9. In DREAMM-8, the starting dose of Blenrep was again 2.5 mg/kg for Cycle 1. We used a proactive step-down to 1.9 mg/kg once every 4 weeks starting in Cycle 2. When a grade 2 or higher ocular event occurred, dosing would switch to 1.9 mg/kg every 8 weeks.

Regardless of the different dose and schedules, both studies showed similar efficacy and safety findings. The primary endpoint in both studies was progression-free survival. Key secondary endpoints were overall survival, duration of response, and MRD, and both studies had balanced enrollments between arms.

Let's review the results.

Both the DREAMM-7 and the DREAMM-8 studies met their primary endpoint of progression-free

survival. There is clear and early separation between the treatment groups in favor of Blenrep across time points. In DREAMM-7, shown on the left, there was nearly a two-year improvement in median PFS with Blenrep at 36.6 months compared to 13.4 with DVd. In DREAMM-8, the median PFS for Blenrep had not been reached at the time of the primary analysis, but the median PFS for PVd was at 12.7 months. We also have additional follow-up data on PFS since the primary analysis, where the median PFS is now at 33 months for BPd and remains the same for PVd.

Importantly, consistent PFS benefit was observed across subgroup, favoring Blenrep combinations in both studies, including those with poor clinical outcomes such as those refractory to lenalidomide and those with high-risk cytogenetics. These results translated into overall survival improvements that favored Blenrep in both studies.

In DREAMM-7, Blenrep demonstrated a statistically significant 42 percent reduction in the risk of death, and while medians had not been

reached, the data show a projected three-year improvement in median overall survival based on the recent interim analysis. At the time of this analysis, there were 13 percent or 35 more deaths in the comparator arm. The DREAMM-8 OS showed a positive trend at the first interim analysis and follow-up for OS is currently ongoing.

In both studies, Blenrep achieved a 5 to 10 percent greater ORR than the comparator arm. More importantly, Blenrep combinations achieved much deeper responses over standard of care, with a 20 to 25 percent added improvement in VGPR or better rates in both studies. This reinforces the importance for making dosing decisions based on depth of response, further supporting the recommended starting dose and schedule.

A 2 and a half to 5-fold improvement in minimal residual disease was observed over the standard of care. This finding is consistent with the learnings from the FDA 2024 ODAC on the importance of MRD as an intermediate endpoint for

predicting PFS and OS, and in DREAMM-7, Blenrep combinations doubled the median duration of response. In DREAMM-8, median DOR was not reached for BPd while it was 17 and a half months for PVd.

To summarize, the DREAMM-7 and DREAMM-8 studies demonstrated a statistically significant and clinically meaningful improvement in Blenrep combinations when compared to standard of care. Both studies met their primary endpoint of PFS, with a PFS hazard ratio of 0.41 in DREAMM-7 and a median PFS that's 2 and a half times longer than the U.S. gold standard treatment of daratumumab. Importantly, DREAMM-7 demonstrated a 42 percent reduction in the risk of death, and while median OS had not been reached in either arm, it is projected to have a three-year improvement in median overall survival based on the current data.

DREAMM-8 demonstrated a 48 percent reduction in the risk of progression. And while the median had not been reached at the first interim analysis, with updated follow-up, the median was at 32.6 months and data were trending positively for

overall survival. These robust efficacy results were demonstrated using the recommended starting dose and dose modifications.

Thank you. I will turn the presentation to Dr. Afshari to contextualize the ocular events.

Applicant Presentation - Natalie Afshari

DR. AFSHARI: Thank you.

I'm Natalie Afshari, Chief of Cornea and Refractive Surgery at the University of California, San Diego. I am a practicing ophthalmologist subspecializing in cornea and a clinician scientist with an active laboratory, studying corneal endothelium and corneal epithelium. I've also previously sat on FDA eye-related advisory committees. I've treated many patients who have received ADCs, including Blenrep.

In order to understand the ocular events associated with Blenrep, let's start with the anatomy of a normal eye. The cornea, shown in yellow, is the clear front window of the eye. This cross-sectional area shows that cornea has several layers, each with specific functions. The clinical

events occurred in the outermost layer, the epithelium. Like skin, the epithelium regenerates naturally, so issues here are usually self-limiting.

Now, let's look at the pathophysiology behind Blenrep-related eye events. Blenrep causes microcyst-like changes in the corneal epithelium seen on slit-lamp exam on the left. These may occur without symptoms but can affect vision depending on severity and location. They begin in the peripheral epithelium, then move toward the center, where they may impact vision. As new cells grow from the periphery inward, older cells are replaced and vision recovers. It's this pathophysiology that supports the resolution of ocular events associated with Blenrep.

GSK developed the Keratopathy and Visual Acuity, KVA, grading scale to detect ocular events early, even in patients without symptoms. It assesses severity in two ways: first, visual acuity measured by the number of Snellen lines that are lost from baseline on the Snellen chart, and

second, slit-lamp exam based on the location and density of microcyst in each eye.

This scale is very both intuitive and very sensitive, helping guide Blenrep dose adjustments. In my experience with multiple drug studies, it offers a thorough way to assess eye findings in each eye. Since eyecare professionals already use Snellen and slit-lamp exams, they can readily adopt this scale to support dosing decisions.

To summarize, ocular events with Blenrep are easily identified. While these findings may be unfamiliar to some oncologists or new in myeloma, eyecare providers can easily detect them with a standard slit-lamp exam. Similar defects are seen with other ADCs and often occur without symptoms. Routine eye exams, checking each eye separately or unilateral testing, can detect these changes; however, bilateral vision, or how both eyes work together, has the greatest impact on patients, as the better eye can compensate for the other.

The KVA scale uses the worst eye to guide those adjustments while also considering changes in

both eyes to assess overall vision impact. This helps eyecare providers detect issues early and support patients in staying on treatment comfortably. Crucially, these findings are reversible. Dose holds allow the epithelium to regenerate and the cornea to heal.

Thank you, and Dr. Rasheed will now review the sponsor's safety data.

Applicant Presentation - Zeshaan Rasheed

DR. RASHEED: Thank you, and good morning. My name is Zeshaan Rasheed. I'm a medical oncologist and Senior Vice President and Head of Oncology Clinical Development at GSK. We have extensively evaluated Blenrep's safety profile, including in-depth evaluation of ocular events, throughout our clinical program. Our deep dive into the data, coupled with insights from leading ophthalmology experts and investigators, has allowed us to develop a robust and multifaceted risk mitigation strategy to effectively manage these events and ensure patient safety. I will begin by providing a brief overview of the safety

data.

Overall, more patients in the Blenrep arms of DREAMM-7 and 8 had grade 3 and 4 AEs, SAEs, and AEs leading to discontinuation. Most patients had AEs leading to dose modification across all arms, which is common in myeloma. Because patients in the Blenrep arms had a longer duration of exposure to study treatment, as would be expected based on a longer PFS, we also analyzed exposure-adjusted AEs. When adjusted for exposure, you can see that rates of AEs and SAEs between arms are relatively similar.

I will now focus on the ocular events and their management.

We collected various types of ocular data throughout our program. We collected data based on symptoms reported by patients and graded them using the standard CTCAE criteria. Also, as Dr. Afshari described, GSK developed the KVA scale in collaboration with FDA, which assesses corneal exam findings and BCVA changes. Dose modifications to Blenrep were recommended based on the most severe

grade and severe eye from either the slit-lamp exam or the visual acuity test.

The regular ocular monitoring and sensitive nature of the KVA scale enabled timely intervention and prevention of severe events. Dose modifications occurred in about 83 percent of patients. In both studies, almost all patients had a dose interruption and about half had a dose reduction. The median dose hold was 8 weeks, and it enabled about 90 percent of patients to continue treatment while maintaining efficacy.

Grade 2 or greater KVA events were common, including recurrent events, and despite multiple KVA events, there was a consistent pattern of resolution. The majority of events resolved with adequate follow-up, and the time to resolution for the first and subsequent events was consistent at a median of 3 to 4 months.

Overall, in the more than 5,300 exams performed, 899 events were identified. Eighty-seven percent of all patients' events resolved at the time of data cutoff; and of the

remaining patients whose KVA event did not resolve by the data cutoff, the majority were either still in follow-up and some had died or withdrew from the study. This prevented complete data capture of the resolution data.

We also saw similar data in DREAMM-8. In the FDA's briefing document, they focused on resolution of the last event. We know KVA events take time to resolve, and the last events are the closest to data cutoff, so it makes sense that the rate of resolution appears lower. However, when you consider all prior events, including the first five as shown on this slide, we see a high rate of resolution with adequate follow-up. We can therefore predict the pattern of resolution would be the same for the last events as well.

On the KVA scale, not all corneal findings translate into clinically meaningful reductions in visual acuity. Ninety-three to 95 percent of patients had a KVA exam finding in DREAMM-7 and 8. About one-third of patients had a bilateral BCVA reduction to 20/50 or worse, which is a clinically

meaningful change to their vision, and less than 2 percent, or 7 patients, across both studies had changes to 20/200.

Of the 35 percent of patients who had 20/50 or worse bilateral events, these events were transient. Almost all patients had documented improvement, and the vast majority of the patients achieved resolution. The median time to improvement was about 3 weeks, and the median time to resolution was about 2 to 3 months. Of the 5 patients who had 20/200 or worse, all improved, and all but one had documented resolution at the time of data cutoff.

We also collected ocular CTCAE data. You can see the most commonly reported ocular AEs here are consistent with the known profile of Blenrep. These include symptoms that can affect a patient's quality of life. Notably, the majority of ocular AEs resolved or were resolving at the time of follow-up.

To provide a direct window into how patients experience changes with treatment, we also

implemented four PRO assessments to assess the frequency, severity, and bother of these ocular events. Consistent with the known safety profile of Blenrep, there were more frequent reports of visual changes and select symptoms and impacts versus the control arm.

The overall burden of side effects peaked around month 4 across both arms, after which they trended lower, likely due to the institution of supportive care, dose modification, or dose delay and interruption. However, when it came to physical functioning or disease-specific symptoms that would impact on patients' day-to-day activities and health-related quality of life such as pain, walking, or self-care, there was a delay in time to clinically meaningful deterioration in the Blenrep-treated arms versus the comparator.

Median time to sustained meaningful deterioration in the physical functioning and disease symptoms scores were 2 and a half to 3 times longer for patients receiving Blenrep, and although patients reported more impact associated

with blurred vision, when it comes to meaningful delay in disease-specific symptoms like pain and physical functioning, the Blenrep combinations had significant advantage.

We have developed a comprehensive risk management strategy to ensure safe use of Blenrep. This is based on our vast experience in more than 7,500 patients across multiple clinical trials and the earlier postmarketing setting. All of these data have allowed us to better understand the AE profile to best inform patients and healthcare professionals on the benefits and risks of Blenrep as they navigate the treatment of relapsed/refractory multiple myeloma.

Physicians and patients are to be educated prior to Blenrep treatment such that they will be vigilant and readily recognize important ocular symptoms. Patients will receive ocular exams as part of Blenrep treatment per labeling. Clinicians will confirm that an ocular exam has been performed and then can hold or reduce therapy based on either the eye exam findings or their clinical assessment.

In addition, we will provide dose modification guidance in the Blenrep label, which is based on our experiences in the phase 3 clinical trials. Grade 2, 3, and 4 events would result in the Blenrep dose being held until resolution to grade 1 and then resumed at lower dose, and for grade 4 events, discontinuation of Blenrep can also be considered.

To conclude, Blenrep has a well-characterized and manageable safety profile. Ocular events are common and can be identified and managed with dose holds and modifications. They are reversible with appropriate follow-up and allow patients to continue treatment and receive benefit. Based on the data, permanent bilateral vision loss has not been observed. Despite transient impacts to vision, patients' quality of life was maintained overall from baseline. Based on our data and experience, we have proposed a comprehensive ocular risk management strategy to support the safe use of Blenrep in clinical practice.

Thank you. I will now turn the presentation

to Dr. Lonial to conclude with his clinical perspective.

Applicant Presentation - Sagar Lonial

DR. LONIAL: Thank you very much.

I'm Sagar Lonial, Professor and Chair in the Department of Hematology and Medical Oncology and the Chief Medical Officer for the Windship Cancer Institute of Emory University in Atlanta, Georgia. I've worked in the myeloma field for over 25 years and have been a part of the evolution of treatments improving outcomes in our field. I was principal investigator for an earlier trial with bela-maf, and I appreciate the opportunity to share my clinical perspective on the data just discussed.

As you heard, while patients with relapsed and refractory myeloma have several different treatment options upon first relapse, myeloma remains an incurable disease that will ultimately progress. Effective therapies with novel mechanisms of action that offer deep and durable responses, which can ultimately extend survival, are still needed for many of our patients. All

current second- and third-line options come with toxicities. It's important to understand the benefits and risks of each as we work with our patients to provide the best suited option for them.

As oncologists, we often ask if the efficacy observed is meaningful; can safety events be dealt with by physicians and patients; and in this case, what are the impacts of ocular events on the patient and how will dose modifications help manage and mitigate that toxicity? We also consider how the benefit-risk profile compares with other potential options. Addressing these questions allows me, the clinician, the opportunity to have an open dialogue with my patients regarding that risk-benefit profile of patients available as we move forward. So first, let's focus on the benefits.

Both phase 3 trials demonstrated impressive, more than two-year improvements in progression-free survival when using the recommended dose and schedule with modifications. The results were

consistently improved across all endpoints, including overall response rate, duration of response, MRD negativity, progression-free survival, and overall survival. These results validate the dose modification scheme outlined in DREAMM-7 and in DREAMM-8 and are among the longest progression-free survivals seen in any randomized phase 3 trial in early relapsed myeloma.

The overall survival data from DREAMM-7 is also impressive when the starting dose is 2.5 mg/kg, again, with appropriate dose modifications, and is further supported by the early data observed in DREAMM-8. This magnitude of benefit is not observed with most currently available treatment combinations.

The next question, then, is can the ocular events, which are the main safety considerations, be addressed? From the treating oncologist perspective, I agree that these events can be addressed and mitigated as described by Dr. Afshari. What we've learned over the last five years is to adjust the dose and schedule based on

ocular exams and what our patients are telling us. By doing this, we're able to provide patients a more tolerable safety profile with continued efficacy.

While ocular events were frequent with bela-maf, they did not result in significant changes in visual acuity in close to 70 percent of patients. Additionally, vision returned to baseline or near baseline with sufficient follow-up. We have clear and practical guidance on how to modify the dose, whether it be with a hold or a dose reduction. In fact, the clinical data demonstrate that patients still achieved meaningful response and duration regardless of dose holds. This would not have been the case if the ocular toxicity was such that patients could not gain benefit from treatment.

Dose modifications are a common practice in medicine, and in oncology particularly. They should be viewed as an effective means to allow patients to remain on treatment and gain benefit rather than a problem with the drug itself. If the

treatment was too toxic, no amount of efficacy could overcome the risk, and it would bear out in the efficacy endpoints, including resulting in a worse overall survival and shorter progression-free survival. That was not the case in DREAMM-7 and DREAMM-8.

While there are four trials that use CD38-based combinations in early relapse, their relative efficacy will be diminished, as previously described, because of the standard adoption of CD38 antibodies as part of front-line therapy, so the best comparable agent in early relapsed myeloma is CAR T cell. And while you see this is an indirect comparison, you can see that the bela-maf PFS, DOR, and overall survival is in line with this treatment approach, and without many of the known and more challenging side effects currently observed with CAR T-cell therapy. I just want options for my patients, and, clearly, bela-maf can be an important contribution to the treatment landscape for a large number of patients.

To conclude, the data presented today

demonstrate that there's a positive benefit-risk profile for bela-maf. Not only is it important to live longer, we want them to live better. My patients have told me that their QoL is maintained with transient impacts on visual acuity, regardless of what the ocular microcyst might look like under a slit-lamp exam.

When patients are on therapy, they will likely experience some form of an ocular event, which can be managed in partnership with our eyecare colleagues. The bela-maf safety profile is well characterized and has been extensively studied. The ocular events found on exam are observed even if the patient is without symptoms. These exam findings do not always correlate with meaningful long-term sustained loss of vision and are reversible with time.

For perspective, every treatment has some toxicity. We saw that on the FDA introductory presentation where even the control arms of DREAMM-7 and DREAMM-8 had significant dose reductions and modifications. The key question is,

can that toxicity be addressed, and does mitigation reduce efficacy? In the case of mitigation, in this case, it does not impact clinical benefit, as evidenced by the long progression-free survival in both trials.

When on therapy, patients across all subgroups are also likely to experience meaningful benefit, even those who would not have accessible options in today's treatment landscape. The improved progression-free survival supports bela-maf's unique activity and translates into substantial improvements in overall survival, demonstrating at least a 2- to 3-year benefit. Improvement in minimal residual disease also favored bela-maf, further reinforcing the ability to attain deep responses. Deep and durable responses drive the survival benefit we are seeing in DREAMM-7 and DREAMM-8.

Despite all the advances we've seen in myeloma, the disease continues to relapse in most patients, and there remains high morbidity and mortality upon relapse. Considering the robust

efficacy and well-characterized and addressable safety profile, bela-maf represents an accessible BCMA targeting treatment option for patients with second-line plus relapsed and refractory myeloma, and I look forward to again having this option to offer my patients. Thank you for your time and your attention.

DR. VASAN: We will now proceed with FDA's presentation, starting with Dr. Andrea Baines.

FDA Presentation - Andrea Baines

DR. BAINES: Good morning. My name is Dr. Andrea Baines, and I'm a hematologist and a clinical reviewer in the Division of Hematologic Malignancies II at the FDA. I'll also be joined for part of the FDA presentation by Dr. William Boyd from the Division of Ophthalmology and by Dr. Ankit Shah from the Division of Cancer Pharmacology I.

This presentation represents the collective input of members of the FDA review team. My presentation will include a brief background and key points from the regulatory history for

belantamab mafodotin, including the initial approval and withdrawal, concerns with ocular toxicity and dosing, and the proposed patient population and current treatment landscape. I'll then briefly review the results and trial designs from DREAMM-7 and DREAMM-8, and will then focus on the major issues for discussion, specifically the high rates of ocular toxicity and the uncertainty regarding the proposed dosages for belantamab mafodotin. I'll end with the discussion of the key benefit-risk considerations.

As you've heard, belantamab mafodotin is a BCMA-directed antibody and microtubule inhibitor conjugate. The two proposed indications are for the treatment of adults with multiple myeloma in combination with bortezomib and dexamethasone in patients who have received at least one prior line of therapy, and in combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy, including lenalidomide.

The proposed dosage of belantamab mafodotin

differs between the two regimens. The proposed dosage in the BVd regimen is 2.5 milligrams per kilogram IV once every 3 weeks. The proposed dosage in the BPd regimen is 2.5 milligrams per kilogram IV once, followed by a decrease to 1.9 milligrams per kilogram once every 4 weeks from Cycle 2 onward. In both regimens, the belantamab mafodotin is continued until progression or unacceptable toxicity. In the BVd regimen, bortezomib and dexamethasone are only continued for the first 8 cycles. In the BPd regimen, pomalidomide and dexamethasone are continued throughout all cycles.

Belantamab mafodotin received accelerated approval in August 2020 as monotherapy for a late-line indication in patients who had received at least four prior therapies, including an anti-CD38 monoclonal antibody, proteasome inhibitor, and immunomodulatory agent. The approved dose, 2.5 milligrams per kilogram IV once every 3 weeks, was the lower of the two doses that were evaluated in the phase 2 trial that supported

the approval.

As noted previously, due to significant concerns with ocular toxicity in dosing, the application was discussed at an ODAC. The committee advised that the benefit outweighed the risk of ocular toxicity in the proposed patient population, in the context of a proposed risk evaluation and mitigation strategy or REMS. Ultimately, belantamab mafodotin was approved for a late-line indication with a comprehensive REMS with elements to assure safe use and with a postmarketing requirement to conduct a randomized phase 2 trial to evaluate lower doses or alternative dosing regimens.

Under the accelerated approval pathway, a postmarketing requirement to conduct a randomized phase 3 trial to verify and describe clinical benefit was also issued. The applicant proposed DREAMM-3, a randomized phase 3 trial evaluating belantamab mafodotin at the same dose of 2.5 milligram per kilogram once every 3 weeks versus pomalidomide and dexamethasone, to serve as

the confirmatory trial; however, in November 2022, top-line results show that the DREAMM-3 trial failed to meet its primary endpoint of progression-free survival. The PFS hazard ratio was 1.03 and the OS hazard ratio was 1.14.

Belantamab mafodotin was subsequently, voluntarily withdrawn from the market due to failure of the confirmatory trial to verify clinical benefit. Although the reasons for failure of the DREAMM-3 trial to meet its primary endpoint are not clear, it is possible that poor tolerability of the 2.5 milligram per kilogram once every 3 weeks dosage may have negatively impacted the efficacy of belantamab mafodotin monotherapy.

To highlight an important difference for the current application, the previous application was approved for a late-line indication in patients who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, proteasome inhibitor, and immunomodulatory agent. In contrast, the currently proposed indication is for a much less refractory population of patients

who have received at least one prior line of therapy.

It is important to note that there are multiple approved therapies for patients with relapsed and refractory multiple myeloma who have received one or more prior lines of therapy and others approved for later-line settings, including multiple combination regimens and other BCMA-directed therapies. Several of these regimens have demonstrated overall survival benefits in randomized trials, and many of the more recently approved therapies, including CAR T-cell products and bispecific CD3 T-cell engagers, are currently being evaluated in randomized trials in early-line settings.

Although DVd is approved for patients who have received one prior line of therapy, the increasing usage of quadruplet regimens containing both daratumumab and bortezomib in front-line therapy in the U.S., has limited usage of DVd in the second-line and beyond setting. PVd, which is not an approved regimen in the U.S., also has

limited usage in this setting.

There have been significant advances in the treatment of multiple myeloma over the past two decades. Some of the therapies in the first half of this timeline, which were considered novel at that time, have since become standard of care; and we now have a whole new set of novel therapies, including multiple CAR T-cell products and bispecific CD3 T-cell engagers, that were approved in the last five years.

Correspondingly, there have been substantial improvements in overall survival for patients diagnosed with multiple myeloma in recent decades, as shown in this figure, based on SEER data collected between 2000 and 2019. It is now thought that patients with newly diagnosed multiple myeloma in the U.S. have a median overall survival approaching 10 years. With the approval of multiple new therapies in recent years, many of which are currently being evaluated in early-line settings, further large improvements in overall survival are anticipated.

That brings us to the designs of the pivotal trials for the current application. DREAMM-7 is a phase 3 randomized trial evaluating belantamab mafodotin, bortezomib and dexamethasone or BVd, versus daratumumab, bortezomib and dexamethasone or DVd. The primary endpoint is progression-free survival as assessed by independent review committee, and the key secondary endpoints are overall survival, duration of response, and MRD negativity rate.

DREAMM-8 is a phase 3 randomized trial evaluating belantamab mafodotin, pomalidomide and dexamethasone or BPd versus pomalidomide, bortezomib and dexamethasone or PVd; and the primary and key secondary endpoints in DREAMM-8 are the same as in DREAMM-7.

Overall, baseline demographics were balanced between arms in both trials; however, there was an underrepresentation of older adults and Black or African American patients and limited U.S. enrollment. Only 14 percent of patients in DREAMM-7 and 18 percent in DREAMM-8 were age 75 or

older. In contrast, approximately 33 percent of patients diagnosed with multiple myeloma in the U.S. are age 75 or older.

Additionally, while the prevalence of multiple myeloma in Black or African American patients in the U.S. is approximately twice that of non-Hispanic whites, only 4 percent of patients in DREAMM-7 were Black or African American, and no Black or African American patients were enrolled in DREAMM-8. Although both studies were multiregional, fewer than 5 percent of patients in each trial were enrolled in the U.S.

As previously described, given the limited usage of DVd and PVd for second-line therapy in the U.S., the selected comparator arms may have impacted the ability to enroll more patients from the U.S. The limited enrollment in the U.S. and questionable relevance of the comparator arms may further limit the applicability of the DREAMM-7 and DREAMM-8 results to the U.S. patient population.

The numbers and types of therapies were generally balanced between arms. Approximately

half of the patients on each study had received one prior line of therapy. Most patients in both trials had received a prior proteasome inhibitor and immunomodulatory agent, and approximately a quarter of patients in DREAMM-8 received a prior anti-CD38 monoclonal antibody.

To briefly summarize again the key efficacy results from DREAMM-7 and DREAMM-8, the primary endpoint of progression-free survival was met in both trials. Overall survival was also statistically significant in DREAMM-7, but OS did not reach statistical significance in DREAMM-8.

An overview of the safety in DREAMM-7 and DREAMM-8 is provided here in terms of the rates of treatment-emergent adverse events or TEAEs. In the belantamab mafodotin-containing arms in both trials, over 90 percent of patients had grade 3 or 4 TEAEs, which were higher than the rates in the comparator arms. The rates of serious TEAEs were also higher in the belantamab mafodotin-containing arms. Rates of fatal TEAS were similar between arms in both studies. As

we'll discuss further, there were high rates of dose modifications, which were considerably higher in the belantamab mafodotin-containing arms in both studies.

That brings us to the specific issues for further discussion. The ocular toxicity seen with belantamab mafodotin is a unique risk to this product that is not seen with any of the currently available therapies for multiple myeloma. There were high rates of ocular toxicity with belantamab mafodotin with a similar incidence and severity across DREAMM-7 and DREAMM-8 despite the lower dosing regimen in DREAMM-8. There were also high rates of dose modifications due to ocular toxicity in both studies.

These toxicity and tolerability concerns, coupled with limited data supporting dose selection for DREAMM-7 and DREAMM-8, raise uncertainty regarding the proposed dosages of belantamab mafodotin, and although these two key issues are interrelated, we'll first focus on the ocular toxicity.

As you've heard, to allow for a granular assessment of ocular toxicity, the applicant developed the Keratopathy and Visual Acuity, or KVA, scale with input from the FDA. The KVA scale incorporates corneal slit-lamp examination findings and best corrected visual acuity, and the worst grade by either examination method in the worst eye is used to determine the overall grade of the KVA event.

The KVA scale was also used to guide dose modifications of belantamab mafodotin. In both trials, dosage modifications were recommended for grade 2 or higher KVA events. And although there are some differences across the two trials on the criteria to resume and/or dose reduce, belantamab mafodotin was generally to be interrupted for grade 2 or higher events and held until improvement to grade 1 or better.

I'll now hand the podium over to Dr. William Boyd to provide some additional clinical context.

FDA Presentation - William Boyd

DR. BOYD: Thank you, Dr. Baines.

I am Dr. William Boyd. I'm an ophthalmologist. I'm Deputy Director of the Division of Ophthalmology here at the FDA. I'll provide an additional clinical perspective on the ocular toxicity.

As noted, the KVA scale divides keratopathy into four grades. Here, we have photographic representations of keratopathy as described in the KVA scale. These images are not for patients treated on the DREAMM-7 or DREAMM-8 clinical trials; they are representative images. The green color in these photos is from fluorescein sodium, which is used to stain devitalized epithelial cells and exposed basement membrane.

Beginning in the upper left, grade 1 superficial punctate keratopathy, or SPK, shows isolated areas throughout the cornea with devitalized epithelial cells. Below this is confluent SPK, in which the number of affected epithelial cells increases so that discrete areas begin to touch, which may be grade 2 or grade 3 depending on severity. Patients may be

asymptomatic in earlier stages, but with increasing confluence, the risk of infection and progression to epithelial defects also increases.

On the right side, epithelial defects corresponding to grade 4 are shown. In the upper right, you can see a corneal epithelial defect where the central cornea is without epithelium, and in the bottom right you can see a corneal ulcer which has an inflammatory cell infiltrate, increased hyperemia, and possible inflammatory cells in the anterior chamber.

Corneal epithelial defects are typically painful and are vision threatening because they may lead to corneal perforation, which is a rupture of the eye, endophthalmitis, an infection within the eye, or loss of the eye if not treated appropriately.

Moving on, we'll discuss the best corrected visual acuity considerations on the KVA scale. When assessing visual acuity, ophthalmologists evaluate best corrected visual acuity, or BCVA, which represents the best possible visual acuity

that each eye can achieve; and to do this, corrective lenses or contact lenses are utilized. Generally, assessments of visual acuity are performed for each eye separately, and the FDA considers unilateral changes to be clinically relevant for safety analyses.

Vision was assessed using the Snellen eye chart as depicted on the left of this slide. On the right of the slide are simulations of various levels of visual acuity. Normal vision is represented by 20/20 on the upper left, it's the clearest vision, and then down to 20/20 [sic - 20/200] in the lower right, which is considered legally blind.

For context, for an unrestricted driver's license, most states require a minimum visual acuity of 20/40 in at least one eye, and when an individual has visual acuity decreased to 20/70, this frequently results in driving restrictions. A three-line change in vision referred to in the KVA scale, which correlates to at least a grade 2 KVA event, refers to a visual acuity change, which is

considered to have clinical significance by the Division of Ophthalmology.

Thus, our clinical concerns regarding the ocular toxicity begin with potential for lower grade corneal toxicities to be asymptomatic, making close ophthalmic monitoring important. Higher KVA grade toxicities are more confluent, and are therefore more likely to have inflammatory infiltrates and three or more lines of visual acuity loss. Managing lower and intermediate grade toxicities may minimize progression to higher grade toxicities, which can result in serious outcomes such as corneal ulceration, corneal thinning, corneal perforation, and these are catastrophic outcomes. These points highlight the critical importance of early identification and appropriate management, which includes implementation of dose modifications as indicated.

I'll now turn the podium back over to Dr. Baines.

FDA Presentation - Andrea Baines

DR. BAINES: Thanks, Dr. Boyd.

With that clinical context in mind, here's an overview of the KVA events from DREAMM-7 and DREAMM-8. Almost all patients had KVA events, including grade 3 or 4 events in over three-quarters of patients, with higher rates of grade 4 events in DREAMM-7. There were also high rates of dose modifications due to KVA events, particularly dose interruptions.

Because the dose modifications were implemented for grade 2 or higher KVA events, the results in the next few slides are focused on those events. Although there was a wide range, most patients had their first event within 1 to 2 months after starting treatment, and the events lasted a medium of approximately 3 months. Additionally, most patients experienced recurrent events, with the median of 3 events per patient in both trials.

This figure summarizes a hypothetical patient experience with KVA events on DREAMM-7 based on the medians I just presented. The upward arrows at the bottom represent the planned treatment schedule based on the once every 3 weeks

administration schedule for belantamab mafodotin, with purple arrows representing administered doses and gray arrows representing missed doses due to dose interruptions.

Since the median number of grade 2 or higher KVA events per patient was 3, this time line depicts the median time to onset and median duration of each of three grade 2 or higher KVA events relative to the median overall duration of treatment. It illustrates that patients experienced recurrent and active KVA events for a substantial proportion of time on treatment, and these events occurred throughout the treatment course.

Considering the high rates of recurrence and the importance of characterizing longer term outcomes of ocular toxicity, the data presented here is based on the outcome of the last grade 2 or higher KVA event. Additionally, given the clinical relevance of assessing complete resolution, this analysis is based on resolution to normal or baseline corneal exam and visual acuity rather than

the protocol-defined criteria of resolution to grade 1 or better. As of the data cutoff, 70 and 75 percent of patients had ongoing KVA events of which approximately two-thirds had ongoing events after treatment discontinuation.

Next, I'd like to discuss the clinically meaningful changes and best corrected visual acuity that were observed, including changes to 20/50 or worse, 20/100 or worse, and 20/200 or worse. In DREAMM-7 and DREAMM-8, over 60 percent of patients experienced a change in best corrected visual acuity to 20/50 or worse. Of note, these changes were not transient. The median duration for all events was 3 to 4 weeks, and for some context, in Maryland, for example, individuals need to have better visual acuity than this to qualify for an unrestricted driver's license.

Over a quarter of patients in each trial experienced a more severe change in best corrective visual acuity to 20/100 or worse. For example, this is a level at which individuals may have difficulty with activities such as reading,

watching TV, and using a computer, and it is beyond the threshold at which driving restrictions may be required.

Lastly, more than 10 percent of patients in both trials experienced a very severe change in best corrected visual acuity to 20/200 or worse, which qualifies as legal blindness. This degree of vision loss would be expected to greatly impair a patient's independence and ability to perform everyday tasks.

In addition to KVA events, patients in both trials also experienced symptoms of ocular toxicity that were captured by investigators and graded by CTCAE; and although the patients in the control arms also experienced some of these types of toxicities, the rates of all-grade events and grade 3 or 4 events in the belantamab mafodotin-containing arms were substantially higher. Similar trends were observed in DREAMM-8.

The patient-reported outcomes data from these trials also provides important information about the patient experience and additional details

about tolerability. The FDA's review focused on results from the PRO-CTCAE, OSDI, and FACT-GP5. The applicant also used a non-validated, two-item questionnaire to assess reading and driving ability; however, there was a high degree of missing data for this questionnaire in DREAMM-7, and FDA instead focused on the data from well-established PRO measures with high completion rates. These results showed that at each assessed time point, a group of patients reported severe visual side effects related to belantamab mafodotin.

As I'll show on the following slide, there was progressive worsening in symptoms from baseline, which peaked around weeks 13 to 17, and approximately 5 to 15 percent of respondents reported severe visual symptoms at most assessed time points. Overall, the PRO results demonstrate the impact of the ocular toxicity on patients receiving belantamab mafodotin and generally support the clinician reported ocular toxicity findings.

So here are some representative results from DREAMM-7 for the PRO-CTCAE blurred vision item, which asked patients, "In the last 7 days, what was the severity of your blurry vision at its worst?" There were high rates of blurred vision reported that peaked between weeks 7 through 16, with over 50 percent of patients or respondents in the BVd arm reporting at least moderate symptoms and over 20 percent of respondents reporting severe or very severe symptoms at each of these time points.

In addition, although I'm not showing it here, for the patients who reported any severity of blurred vision other than none at that time point, a branching question was asked. "In the last 7 days, how much did blurry vision interfere with your usual or daily activities?" At the time points between weeks 7 through 16, more than 50 percent of respondents in the BVd arm reported that blurred vision interfered at least somewhat with their usual or daily activities, and over 20 percent of respondents reported that blurred vision interfered quite a bit or very much with

their usual or daily activities.

Here are some representative results from DREAMM-8 for the OSDI. The OSDI is a 12-item questionnaire that's designed to assess both frequency of dry eye symptoms and their impact on aspects of vision-related functioning such as reading, driving at night, and using a computer.

The results from driving at night are shown here, and at weeks 9 and 13, 34 percent of respondents in the BPd arm reported limitations in driving at night all of the time or most of the time, and at each assessed time point, approximately 10 to 20 percent of respondents treated with belantamab mafodotin reported severe limitations in driving at night.

Similarly, despite limitations with use of the non-validated 2-item questionnaire, the applicant noted that across both trials, 33 percent of patients treated with belantamab mafodotin had to stop driving at some point during treatment.

So that brings us to the summary of the issue of high rates of ocular toxicity. Almost all

patients had KVA events, including high-grade and recurrent events, and a substantial proportion of patients had events that had not resolved as of the data cutoff. There were high rates of dose modifications in both trials, primarily due to KVA events, and patients experienced prolonged and recurrent treatment interruptions due to ocular toxicity. There were also considerable impacts on vision with clinically significant changes in best corrected visual acuity in more than 60 percent of patients in both trials and more severe changes to 20/100 or 20/200 in a subset of patients.

Considering that multiple myeloma is primarily a disease of older adults with a median age at diagnosis of 69, this degree of vision impairment is likely to have a significant negative impact, particularly in patients who live alone or have other health conditions or functional limitations.

Lastly, the patient-reported outcomes results demonstrated a measurable impact of the ocular toxicity on patients receiving treatment

with belantamab mafodotin, with the substantial proportion of patients reporting blurred vision that interfered with their usual or daily activities and limitations in activities such as driving at night, reading, and using a computer.

So I'll now move on to the uncertainty regarding the proposed dosages, including the poor tolerability and limited data to support dose selection.

There was poor tolerability as evidenced by the high rates of dose modifications in both trials, the majority of which were due to KVA events. These graphs show the percentage of patients in each trial who received a given dose of belantamab mafodotin in each cycle of treatment. Purple represents the intended dose in each cycle, blue and light blue represent dose modifications, red represents dose interruptions, and gray represents permanent discontinuation of study treatment. By Cycle 3, more than 50 percent of patients in both studies were not receiving the intended dose, and the percentage of patients

remaining on the intended dose continued to steadily decrease over time.

As discussed, there have been significant challenges in the identification of an appropriate dosage of belantamab mafodotin throughout its development. At multiple time points, the FDA provided feedback and expressed concerns regarding the proposed dosages; however, the applicant chose to proceed with the selected doses for DREAMM-7 and DREAMM-8.

I'll now turn things over to Dr. Ankit Shah to discuss some of the issues with dose selection for DREAMM-7 and DREAMM-8 in more detail.

FDA Presentation - Ankit Shah

DR. SHAH: Thank you, Dr. Baines.

Good morning. My name is Ankit Shah, and I'm a clinical pharmacology team lead here at the FDA. As Dr. Baines just highlighted, the optimization of the belantamab mafodotin dosage has remained a key issue throughout its development program. In the next few slides, I will discuss the issues with the dose exploration study

supporting the dosage selection for the respective combination regimens in DREAMM-7 and DREAMM-8. I will also discuss the results from the dosage optimization PMR study, DREAMM-14, for the monotherapy.

The dose exploration in DREAMM-6 Arm B was used to support the dosage selection for BVd combination in the DREAMM-7 trial. This was a non-randomized, open-label study with a small number of patients in each dosage cohort that included three dose levels, 1.9, 2.5, and 3.4 mg/kg, given either once every 3 weeks or once every 6-week dosing intervals. In general, the overall response rates were comparable across dose levels that were evaluated.

With respect to the safety and tolerability, fewer grade 2 or worse corneal events were noted, and dose modifications were also fewer in the 1.9 mg/kg dose cohort, which were administered once every 3 weeks as outlined in the red box.

When looking at the effect of the dosing intervals, as shown in the blue box, the patients

treated with once every 6-week schedule experienced fewer grade 2 or worse corneal adverse events. Similarly, fewer dose modifications due to corneal adverse events were reported in the 1.9 mg/kg once every 6-week compared to the patients in the once every 3-week dosing cohort. These data suggest that a lower dose with longer dosing interval may improve the safety while maintaining the response rates; however, due to the small number of patients in each dosage cohorts, there are some uncertainties.

Given these limitations, the FDA expressed concerns with the proposed 2.5 mg/kg once every 3-week dosage and recommended that more patients should be assessed at the lower dosages and in the combination therapy before the final dose selection to support the DREAMM-7 trial. Despite these concerns, the applicant selected the 2.5 mg/kg once every 3-week dosage regimen for the DREAMM-7 trial.

The dose exploration data from the ALGONQUIN study was used to support the BPd combination regimen in the DREAMM-8 trial. This was a

non-randomized study that evaluated 1.9, 2.5, and 3.4 mg/kg dose levels in every 4, every 8, or every 12-week schedules in a small number of patients in each cohort. Of note, only 5 patients were evaluated at the proposed DREAMM-8 dosage regimen.

The data from ALGONQUIN also showed comparable overall response rates across all those levels and dosing schedules. Although there were fewer missed doses and higher relative dose intensity in the 1.9 mg/kg given with longer dosing intervals, this data is, again, difficult to interpret given the small number of patients in each cohort.

At the end of the phase 2 meeting, prior to initiation of the DREAMM-8 trial, FDA did not agree with the applicant's proposed starting dose of 2.5 mg/kg and recommended evaluating more patients at the lower dose levels. Once again, the applicant decided to move forward with the 2.5 mg/kg starting dose followed by 1.9 mg/kg once every 4-week regimen in the DREAMM-8 trial.

Turning to DREAMM-14, this study was

conducted to fulfill PMR from the original accelerated approval for belantamab mafodotin monotherapy to characterize the safety and efficacy of lower doses and/or alternative dosing regimens. DREAMM-14 was a randomized, open-label trial that evaluated 1.9 and 2.5 mg/kg dose levels in once every 3-week or once every 6-week intervals in a larger number of patients, approximately 40 per arm, compared to the previous dose exploration studies.

These dose modification plots, as you can see on the slide, show the percentage of patients at a given dose in each cycle. Data from 1.9 mg/kg dose cohorts is shown on the left and the data from 2.5 mg/kg is shown on the right. The bottom figures show the data from longer dosing intervals within same dose levels.

When you compare the different dose levels, that is from left to right, more patients on the lower 1.9 mg/kg dose were able to remain on the intended dose compared to the 2.5 mg/kg dose level. Similarly, when you compare from top to bottom,

that is from Q3 to Q6 week dosage regimen, longer dosing interval cohorts were able to remain on their intended dosage for a longer period of time compared to the patients in the once every 3-week dosage regimen.

Consistently, in the previously noted trends in DREAMM-6 and ALGONQUIN, there were fewer grade 2 or higher corneal adverse events and adverse events leading to dose modifications at the 1.9 mg/kg dose level with the longer dosing interval. The efficacy from this trial showed comparable response rates with overlapping confidence intervals across all dose levels and dosing intervals. The bottom row of the table shows exposure metrics, especially Cmax and Caverage, over 42 days associated with different dosage intervals.

Notably, no change in the efficacy was observed in the cohorts with lower belantamab mafodotin exposure. On the other hand, fewer grade 2 or higher KVA events and dose interruptions were reported with the lower belantamab mafodotin exposure arms, suggesting that the lower dosage or

longer interval may better balance the benefit-risk profile.

As highlighted by Dr. Telaraja in her presentation, identification of an optimized dosage is an important aspect of balancing the benefit-risk profile. The applicant conducted very limited dose exploration in a small number of patients to support selection of the belantamab mafodotin dosages in DREAMM-7 and DREAMM-8.

The available data also suggest that lower exposure of belantamab mafodotin may result in fewer dose modifications and corneal adverse events without necessarily affecting the efficacy. Overall, while the efficacy was observed, the safety and tolerability data suggest that the DREAMM-7 and DREAMM-8 dosages may not be adequately optimized.

Additionally, available data from multiple supporting studies suggest that the lower dose, longer dosing intervals, or a combination of these two approaches may result in fewer adverse events with similar efficacy and a more favorable benefit-

risk profile.

Now, I will turn it back to Dr. Baines.

FDA Presentation - Andrea Baines

DR. BAINES: Thanks, Dr. Shah.

I'll now summarize the key benefit-risk considerations. Although several apply to both DREAMM-7 and DREAMM-8, there are a few notable differences, so I'll go through the considerations for each study separately.

For DREAMM-7, in terms of benefit, the DREAMM-7 trial met the primary efficacy endpoint of PFS. It also showed a statistically significant improvement in OS. However, while OS is an important endpoint that serves as a metric of both safety and efficacy, the clinical relevance of the observed treatment effect in comparison to the DVd comparator arm and applicability to the current U.S. population are unclear.

In terms of risk, as we discussed, the ocular toxicity associated with belantamab mafodotin is a unique risk to this product that is not seen with other currently available therapies

for multiple myeloma. The high rates of ocular toxicity and poor tolerability, combined with the limited dose exploration and additional data suggesting improved tolerability with lower doses and longer dosing intervals, raise uncertainty regarding the appropriateness of the proposed dosage, which is the same as the prior monotherapy dosage.

As discussed by Dr. Telaraja, identification of a safe and effective dose prior to approval is critically important given the considerable challenges with conducting post-approval dose optimization studies. Furthermore, the benefit-risk must be considered in the context of the current treatment landscape for patients with relapsed or refractory multiple myeloma. There are multiple approved regimens for this population, including those with demonstrated OS benefit and established safety profiles.

While DREAMM-8 also met its primary efficacy endpoint of PFS, DREAMM-8 did not meet statistical significance for OS. Additionally, the trial is

not adequately powered for OS and may not demonstrate a statistical significance for OS. The same concerns regarding the ocular toxicity, uncertainty regarding the proposed dosage, and the challenges with post-approval dose optimization also apply to DREAMM-8. The clinical relevance of the treatment effect in comparison to the PVd comparator arm and the applicability of the results to the U.S. patient population are also a concern.

Overall, considering the totality of data, the benefit-risk of belantamab mafodotin remains uncertain in patients with relapsed or refractory multiple myeloma who have received at least one prior line of therapy.

We would like the committee to discuss whether appropriate dosages of belantamab mafodotin have been identified for the proposed patient population of patients with relapsed or refractory multiple myeloma in the context of the observed ocular toxicity, tolerability of the regimens, and the efficacy results from DREAMM-7 and DREAMM-8. And to clarify, by dosage, we mean both the dose

and the schedule of belantamab mafodotin. As a reminder, the proposed indication that is being sought is in patients with multiple myeloma who have received one prior line of therapy.

After the discussion, we'll ask the committee to vote on the following questions separately for each proposed indication. Is the overall benefit-risk of belantamab mafodotin in combination with bortezomib and dexamethasone favorable at the proposed dosage in the proposed patient population? Is the overall benefit-risk of belantamab mafodotin in combination with pomalidomide and dexamethasone favorable at the proposed dosage in the proposed patient population?

Thank you very much for your attention. This concludes my presentation.

Clarifying Questions

DR. VASAN: We will now take clarifying questions for the presenters. When acknowledged, please remember to state your name, for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a

specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Are there any clarifying questions for the presenter? I'll start out with the first question.

This is a question for GSK. Can you show us Kaplan-Meier curves for progression-free survival and overall survival for both DREAMM-7 and DREAMM-8 stratified by dose intensity?

DR. ABDULLAH: Stratified by dose --

DR. VASAN: Dose intensity.

DR. ABDULLAH: -- intensity.

DR. VASAN: You've shown overall response rates. You've shown some simulations. What I'm asking for is from the phase 3 trials, can you show us what that data are?

DR. ABDULLAH: Yes. We can certainly show you at least Kaplan-Meier curves for PFS based on Cycle 1 exposure. That is available.

DR. VASAN: This question is for overall exposure. I understand you started out 2.5; you went down to 1.9. This is the mathematical quantification of the overall dose intensity.

DR. ABDULLAH: Yes. I think we can certainly look into whether or not we can provide that after the break and get back to you, but I don't believe we have that available right now.

DR. VASAN: Okay.

Is the FDA able to comment on this?

DR. KANAPURU: Bindu Kanapuru, FDA. I don't believe we have the Kaplan-Meier curves, but we do have details on the median dose intensity for the regimens in the DREAMM-7 and DREAMM-8 trials, if you're interested in that.

DR. VASAN: Thank you.

DR. ABDULLAH: And we can certainly share that with you, the dose intensity data, the dose intensity and the relative dose intensity as well, too.

DR. VASAN: Okay. If we could show that, please.

DR. ABDULLAH: Please bring up the slide with the dose intensity and relative dose intensity for DREAMM-7 and 8, please. Slide ED-6 up, please. Thank you.

I think probably what you'll see on this slide, as represented for both DREAMM-7 and DREAMM-8, is we do see that higher exposure during the first 6 months of treatment is certainly important to help drive the disease burden down and induce what is the depth of response that we've seen across both DREAMM-7 and DREAMM-8. At least based on the exposure-response curves and exposure-response analyses we've conducted for Cycle 1 exposures, we've seen a more steep exposure-response curve relative to safety.

What you see represented on this slide, of course, at the top half is the dose intensity during the first 6 months which, again, demonstrates a higher exposure in both DREAMM-7 and DREAMM-8. And then, of course, in terms of the relative dose intensity, we see that approximately 80 percent of doses were administered at the

protocol-specified dose and schedule across both studies as well, too.

With the implementation of the dose modification guidelines, after that initial induction period, what we do see is the dose intensity comes down, and then, of course, the dose modifications are taking effect, and then the same holds true for the relative dose intensity as well.

DR. VASAN: FDA, please?

DR. KANAPURU: Yes. I would like to ask our clinical pharmacology colleague to comment on the dose intensity. Thanks.

DR. SHAH: Hi. Ankit Shah, clinical pharmacology from FDA. In order to understand the the dose intensity, we also have to look at the dose intensity plots; so can you please pull slide number 41 from the FDA presentation? Thank you.

As you can see in these plots, a majority of the patients after Cycle 2 and Cycle 3 actually did not even receive the starting dose that was intended for this patient population. And then in terms of the exposure-response analyses that is

presented by the sponsor, I would like to invite my colleague here at the FDA.

DR. LI: Hi. Yangbing Li, pharmocometrics reviewer at the U.S. FDA. Yes. In the exposure-response analysis that's for safety, we see the KVA events, especially for the grade 2 or worse KVA events, increase sharply with the exposure of the ADC at first cycle, while for the exposure-response for efficacy, the results are not very consistent with the dose response across different studies.

We also have some concerns about the current exposure-response analysis, as most of the patients received just one dose level, and also that the majority of patients have dose reductions beyond first cycle, which may not be included in the current model to be evaluated due to only the first cycle exposure was evaluated. So based on this, we may suggest that further study on the lower dose or longer dose interval will be needed in future studies.

DR. ABDULLAH: Dr. Vasan, if I may just

share some additional data that might be of relevance as well, too.

DR. VASAN: Alright.

DR. ABDULLAH: Thank you.

If I can call up slide ED-10, please. What you'll see on this slide, actually -- and this is for DREAMM-7 -- it's actually looking at the dose level and time between doses. Just as an example, for DREAMM-7, to give you some context, specifically, this is the number of doses, or percentage of doses, whether it be 2.5 or 1.9, that were administered at any time point that patients were on treatment. And as expected, we see that during that initial period of treatment, there are about maybe 41 percent of patients that received the 2.5 milligram per kilogram dose.

Subsequently, of course, as with the prespecified dose modification guidelines, patients were dose reduced, so about 59 percent of them went on to 1.9. Now again, within the context of DREAMM-7, we know that approximately 75 to 80 percent of patients ended up being dose

reduced to 1.9; however, what's probably most important to consider here is what's on the right-hand side of the slide. So about maybe 61 percent of doses were actually administered within the prespecified 3-week interval while on study, and then an additional 18 percent were administered between 3 and 9 weeks as well.

DR. VASAN: Thank you. That's all for my questions.

Dr. Nowakowski?

DR. NOWAKOWSKI: Thank you. Greg Nowakowski, and a question to the sponsor. Before we dive more into safety analysis, I would like to understand the context of efficacy to the U.S. population. For whatever reason, the study was not accruing well in the U.S. This can happen due to suboptimal control arm or inclusion criteria of the study and availability of other therapies as well.

So to better understand that, do you know what are the characteristics of the U.S. population versus the rest of the population included in this study, particularly in regards to lines of therapy?

What were the lines of therapy in patients ex-U.S. and U.S., and other characteristics?

DR. ABDULLAH: I'd like to call on Dr. Mukhopadhyay to provide some additional context around the characteristics of the U.S. population.

DR. MUKHOPADHYAY: Pralay Mukhopadhyay, GSK oncology. Within the context of the DREAMM-7 and DREAMM-8 studies, there were fewer U.S. patients enrolled, and specifically, we haven't looked into the characteristics because of the number of events that were available for the studies. But I think what's relevant is, the majority of the study, two-thirds of the patients were enrolled in Europe, 10 to 15 percent of the patients were enrolled in Australia or New Zealand.

It's important to note that the demographics, the disease characteristics, clinical outcomes, as well as available treatments in these regions, are very much also reflective of the clinical practice within the United States as well. So for both studies, the data that has been generated we believe is representative within the

U.S. Thank you.

DR. NOWAKOWSKI: Well, thank you. I understand the --

DR. VASAN: I'm sorry to interrupt.

FDA?

DR. KANAPURU: The FDA would like to comment.

DR. TELARAJA: Hi. This is Deepti Telaraja, FDA. I would just like to reiterate that this is a very important point and a significant consideration in FDA's benefit-risk considerations.

As Dr. Baines pointed out in the FDA presentation, there were several factors that contribute to potential limited applicability to current U.S. patients, one being age. There was limited enrollment of older adults, and the second being race, with limited enrollment of African American patients. As described, and as you know, there is a higher prevalence of multiple myeloma in African American patients, and these patients were underrepresented in this clinical trial.

Finally, with regard to the control arms and

their usage in the second-line and beyond setting for current U.S. patients, we feel that all of these factors may have impacted U.S. enrollment and ultimately may impact relevance to current patients. Thank you.

DR. ABDULLAH: What we would probably just also highlight as well, too, is we've treated approximately 300 U.S. patients across our broader development program and exposed approximately 4,000 U.S. patients, whether it be across the development program, investigator-sponsored studies, expanded access, or the prior approval as well, too, so just to provide some context.

In terms of the representation of the elderly population in the study as well, I'd like to call up CO-27, please. And again, just based on the data that we've observed across a number of different prespecified subgroups, we see a consistent treatment effect across both DREAMM-7 and 8 for progression-free survival, even in the elderly population as well.

In addition, what we've also looked at is

African American representation across our development program, and while we acknowledge that we didn't necessarily or were not able to recruit African American patients in the U.S., in DREAMM-7 and 8, we actually did treat a number of different African American patients across our broader development program. We conducted population PK analyses to look at whether or not race or ethnicity was a key covariate, and then subsequently, exposure-response analyses as well, too, and they did not show that race or ethnicity was a key covariate-predicting response to belantamab therapy.

We did treat about 70 African American patients across our broader development program, and we do have data, if I can bring up, please, slide DM-8. We actually do have data from a late-line study. It was a single-arm study that supported the initial approval in the U.S., which was the DREAMM-2 study, and it was in a triple-class refractory multiple myeloma patient population. And again, what we see here is the

response rate across both African American patients or Caucasian patients is very consistent.

I'd actually like to call on Dr. Craig Cole to provide his perspective as well, too, in terms of how he's seen the treatment effect for Blenrep across patients of different ethnicities.

DR. COLE: Craig Cole from Karmanos Cancer Institute, Michigan State University. One point is that when you look across BCMA-related therapies, in general, regarding race, looking at bispecific CAR T, there's been no difference in efficacy and not much difference in the way of toxicity.

The other thing is, I really want to make clear that my love, my passion, is health equity in myeloma. We know that black patients have been underrepresented in myeloma trials for years. Black patients and brown patients have not had access to transplant for 20 years, have very poor access to CAR T therapies, and have very poor access to other BCMA therapies. This is the opportunity to level the playing field for multiple myeloma regarding those therapies because my little

black lady in Detroit is not going to get CAR T because she's too scared of it. My patients in Lansing that are farmers are not going to get CAR T and second line because they don't have access to it.

This BCMA therapy has the opportunity to treat those patients with equal efficacy and the ability to see their own eye doctors in order to mitigate the toxicity. Thank you.

DR. ABDULLAH: Thank you.

DR. NOWAKOWSKI: Well, thank you. I understand those responses, but I'm less concerned about biological differences. I'm more concerned about the difference, the geographical differences, based on the ability of therapies across geographical regions at the time that the study was conducted. So I know the population is small, but you surely must have some analyses comparing the U.S. population characteristics with the rest of the population of the study and some efficacy endpoints.

DR. ABDULLAH: Yes. We've actually looked

at this in DREAMM-7, as an example, as well, too, and specifically to your point, to look at treatment effect and whether or not there are any differences. And I'd like to actually bring up slide SP-28, please.

Again, as you probably see, of course, the limited number of patients recruited in North America doesn't necessarily certainly enable us to conduct a meaningful analysis. But again, as we've looked at the study recruiting two-thirds of patients in Europe -- and another 10 to 15 percent in Australia and New Zealand, where we know the medical practice but also the disease demographics are very consistent with what the U.S. population would look like -- we see, certainly, the treatment effect that's been observed.

I'd actually like to call on Dr. Sagar Lonial to provide his clinical perspective on the relevance of the data, especially recruited in these regions, to a U.S. population.

DR. VASAN: I'm sorry. We're bringing up multiple points here.

Would the FDA like to comment on the previous comment?

DR. KANAPURU: Yes. This is Bindu Kanapuru from the FDA. We appreciate what the applicant is saying, but we are here today to discuss the benefit-risk of these two proposed combinations in first-line relapsed/refractory multiple myeloma, and what we are seeing here is that we don't have data, adequate data, in the U.S. patient population, including those who are older than 75 years, and I think that's a significant limitation.

DR. PAZDUR: This is for GSK. Over the past five years, we've been on record at the FDA really emphasizing enrollment of a U.S. population for generalizability to the U.S. population, and U.S. practice. That's a different issue than just the U.S. population.

You obviously, during the course of a study, are looking at where the enrollment is coming from. What did you do during the conduct of this study to increase U.S. enrollment here? Because this is

somewhat disappointing that after all of the conversations that we've had over the past five years with the community, that we're seeing less than 5 percent enrollment here. So what did GSK do during the enrollment of this study to increase U.S. participation in the trial?

DR. ABDULLAH: We actually did a number of different things.

DR. PAZDUR: Were you soliciting?

DR. ABDULLAH: Yes, please.

First of all, we actually initiated the study at 14 sites, DREAMM-7 but also DREAMM-8, across the U.S. Second, we engaged with patient advocacy groups to make sure that we raise awareness around these clinical trials being ongoing as well, too. And then third, we actually did feasibility across more than 200 sites in the U.S., across each respective study, to try to help encourage recruitment.

Now, what's probably important to highlight here is that as we look at published literature on recruitment of multiple myeloma studies in the U.S.

as well, too, we've seen typically that they've ranged anywhere between 8 to 12 percent in terms of U.S. patients being recruited and about maybe 4 percent of African American patients being recruited in the U.S. as well, too. So this is something that I think the entire field is continuing to try to improve on but, yet, at the same time --

DR. PAZDUR: Let me just interrupt you. You went through all of these efforts. Why didn't you get more enrollment, then?

DR. ABDULLAH: I think, certainly, there are a number of ongoing --

DR. PAZDUR: Was it the control arm, was inadequate?

DR. ABDULLAH: There are certainly a number of key, probably, elements that relate to competitive clinical trials that are ongoing across the U.S. as well, too. I think if we look at also some of the precedence around some of the recent studies that have supported approval in multiple myeloma, including in newly diagnosed patients, we

see less than 5 percent of patients who are actually recruited in the U.S. as well, too.

So it's not necessarily any different than what we've recently seen in multiple myeloma studies that have recently supported regulatory approval by the FDA.

DR. PAZDUR: And let's go to this issue of generalizability to the U.S. practice, which is different than what goes on in Western Europe and Australia, because we have a unique U.S. practice here.

Since you only have 5 percent of the patients in a large randomized trial -- and a large randomized trial is supposed to represent what kind of goes on in the real world as best as we could do in the context of a trial; it's not the phase 1 study, so to speak. So we're dealing with a unique toxicity here.

How is that toxicity really going to be managed? And do we have confidence with this ophthalmological toxicity that this is going to be manageable in the U.S. population here, given only

5 percent of the population in this trial, with this individual population? How do we get that confidence with so low numbers being enrolled in this trial?

DR. ABDULLAH: I think that's certainly an important topic, and it's one of the reasons why we've tried to really characterize what this ocular toxicity is.

First, we develop this KVA scale in collaboration with the FDA to make sure --

DR. PAZDUR: Yes, but let's take a look at the practicality. You guys are practicing doctors. How easy is it to get an ophthalmological consult like that? It's going to be very hard to do. So how are you going to really manage this?

DR. ABDULLAH: As I've mentioned and alluded to previously, we've actually had 4,000 patients exposed in the U.S. to Blenrep previously --

DR. PAZDUR: Yes, but many of those were at tertiary medical centers, right?

DR. ABDULLAH: We actually have a number of different, I would say, elements that we're

actually incorporating into our risk mitigation strategy. Those include education of eyecare professionals, treating hematologists/oncologists, the patients as well, too, but also establishing across different parts of the U.S. infrastructure for eyecare professionals to be connected to hematologists/oncologists as well, too.

I'd certainly like to call on Dr. Cole to share his experience, as a practicing community physician, of how that has worked currently or in the past as well, too.

DR. PAZDUR: I think our time is limited, so we could forego that.

DR. VASAN: We have several questions.

Next, I'll call Dr. Gradishar.

DR. GRADISHAR: Thank you. Bill Gradishar, Northwestern, and a follow-up on two issues related to toxicity, and Dr. Pazdur just touched on one of them, and one question to Dr. Afshari and the other to Dr. Rasheed. Dr. Pazdur was touching on the availability of ophthalmologic assessment, and since this, if approved, would be in the community,

how equipped do you think the average ophthalmologist is to deal with this as opposed to a corneal specialist?

The second question is to Dr. Rasheed to try and get some more granular understanding of reading ability and driving, two very commonly done things by people. How much of a dissatisfier was this in your quality-of-life instruments, if you were able to glean that? Because it seemed to have happened, perhaps repetitively, with subsequent cycles of therapy, and I'm just wondering how much of a dissatisfier this was to patients. It's clearly a quality-of-life consideration.

Thank you. Those are my questions.

DR. AFSHARI: Thank you. Natalie Afshari from the University of California, San Diego. I practice at a university setting, so we have a cancer institute, and I do see patients from a cancer institute. But I also see many patients from outside that are referred in.

You know, everybody wants to help cancer patients, and in the eye world, we don't see cancer

patients every day. So when there is a cancer patient, we fit them right away, and we make sure we communicate with the oncologist, whether that is through the electronic health record, or a phone call or phone call messages, any which way. There is also precedence with this. There are other medications, whether that's rheumatology or anything that has eye side effects, and we do communicate with the physicians.

Also, we deal with other ADCs that are in the market; not in multiple myeloma but in ophthalmology, we are seeing them, and we are communicating with the physicians. So basically, these patients get in as they need, and we do follow them. Thank you.

DR. VASAN: Thank you.

Dr. Spratt?

DR. GRADISHAR: But are you speaking for the community as a whole, the ophthalmology community, or your own personal practice as an academic subspecialist?

DR. AFSHARI: Thank you, Dr. Gradishar.

Both. At every major eye meeting, there is a talk about these new ADCs, what we find, the little microcysts in the cornea, because this is the way of the future, and we all, as ophthalmologists and optometrists, are seeing these patients. So I'm speaking for both; that we are aware of it, and we see these patients as they need to.

And to be honest, as ophthalmologists, we are a little less worried about the microcysts of the cornea as our oncology colleagues are because corneal epithelium just comes from periphery, and within a few days fills in the center. And once the drug is held, or before the next dose of drugs, the patient has much better vision. Both the patient and us, we know that their vision dips down and then comes back up, so we are much less worried. And the patients, once they've gone through some cycles, are less worried about their vision, in general. Thank you.

DR. VASAN: Could the FDA please comment?

DR. GORMLEY: Yes. This is Nicole Gormley, FDA. Thank you for the question, Dr. Gradishar. I

think it's really important, particularly the second portion of your question where you asked the question how this relates specifically to the patient-reported outcomes.

While it's important to understand how this will be implemented in the clinical practice and in the community more broadly, I just want to wholeheartedly acknowledge that this will be a challenge, for prescribers, and oncologists, and ophthalmologists, and patients. It requires very close collaborations, and there is a REMS, but this is a challenge with this product.

I'd like to specifically ask Dr. Bhatnagar to come up and share a little bit more information regarding the patient-reported outcomes because while it is important to understand what the clinicians reported and what the clinician findings were, it is really important to understand from the data the patient-reported outcomes, how this impacted their functioning and the impact.

DR. BHATNAGAR: Sure. I'm happy to do so. My name is Vishal Bhatnagar. I'm Associate

Director for Patient Outcomes in the Oncology Center. I'm also an oncologist and hematologist with a specific focus in multiple myeloma.

So, we reviewed the patient-reported outcomes data, and I won't rehash what Dr. Baines presented in her presentation, but what we saw was a sustained and a clear signal of serious limitation and ability to perform vision-related functioning, so driving and reading. And although I can recognize what was just said about what the interplay is between practicing ophthalmologists and hematologists, it's patients who are the ones that are dealing with these significant side effects, and limitations, and ability to conduct their ADLs.

So I just wanted to bring that out, and it was a very clear signal that was presented by Dr. Baines, but not so much in the applicant's presentation.

DR. ABDULLAH: Dr. Vasan, if I may just --

DR. VASAN: Sorry. In the interest of time, I think we need to move on.

Dr. Spratt?

DR. SPRATT: This is Dan Spratt, UH Seidman. I had put my hand down. It was related to just why there's so few U.S. patients enrolled, and that was, I think, thoroughly addressed. Thank you.

DR. VASAN: Thank you.

Dr. Madan?

DR. MADAN: Yes. Ravi Madan, National Cancer Institute. Sorry if you showed this. From the DREAMM-7 trial, do you have the data on, basically, the subsequent therapies for the patients that were treated? And if somebody could comment maybe from both sides in terms of how applicable that is to the U.S. practice.

DR. ABDULLAH: Thank you very much, Dr. Madan. We do actually have the data from the DREAMM-7 study, if I may bring up slide EF-12. I think just some context to provide here, first, of course, these studies actually started in 2021. The trial started in 2021, and then, of course, subsequently read out at the end of 2023, DREAMM-7 specifically as well, too.

What we saw in terms of subsequent therapies that patients may have received, they may have received either a proteasome inhibitor, other immunomodulatory agents, and then, of course to a lesser extent, certainly BCMA-directed therapies that may have included T-cell engagers as well, too.

DR. GORMLEY: The FDA, our comments, we did not perform analyses based on U.S. patients versus others because there were just too few U.S. patients to really have a meaningful interpretation.

DR. MADAN: Just to follow up, though, can anyone inform how representative these subsequent therapies are to the current U.S. standards, or at least the standards contemporary with this trial?

DR. KANAPURU: This is Bindu Kanapuru, FDA. Can we have this slide up please, again?

I just wanted to highlight, as was pointed out both in the FDA introductory presentation and the main presentation, current standard of care for newly diagnosed patients is quadruplet or triplet

regimens that include an anti-CD38. And if you had seen the slide in the BVd regimen, the subsequent therapy, the most common was a CD38, anti-CD38, which patients would have already received in the current treatment landscape. So, certainly, they're not reflective of what would happen currently in the U.S.

DR. VASAN: Is that all, Dr. Madan?

DR. MADAN: Yes. Thank you.

DR. VASAN: Thank you.

Dr. Beringer?

DR. BERINGER: Paul Beringer, USC. I had a couple of questions about the the dose-response relationships, and in particular, slide 22, which was used as an argument for going with a higher dose initially, and then dose adjustment down later on. These exposure-response curves are based on DREAMM-6 through 8, which was a relatively narrow range of dosing. DREAMM-14 had more dosing regimens that were included, and there's only a separate exposure-response curve for that one.

Do you have data that incorporates all four

trials, and the curves, are they the same?

DR. ABDULLAH: Yes. We've actually looked at this across what is extensive PK modeling that we've conducted, and I'd like to call on Dr. Melhem to provide some additional context around this.

DR. MELHEM: Murad Melhem, GSK, clinical pharmacology modeling simulation. To answer directly the question, we did pull the data from DREAMM-6, 7, and 8 for the analysis that you've seen. DREAMM-14, just because it happened in different types and stage of patients, it was done actually separately.

The trend actually that you saw in the separation and the safety and efficacy was conserved across all. So when we did DREAMM-6 alone, DREAMM-14 alone, this was the same conclusion as that pooled analysis, but we didn't pool DREAMM-14 with the rest of them.

DR. BERINGER: Okay. Because looking at the DREAMM-14 exposure-response curves, the curves are both shifted to the right, and there's overlap between the efficacy and safety curves at the

concentrations that are expected with the recommended dosing.

DR. MELHEM: And that was actually a different line of therapy, like I said. And what you see and the differences, exposure-response actually conveys the same conclusion, but the relationship, a grade 3 and 4, is a little different. However, the bilateral BCVA worsening, which we think also is clinically relevant, is conserved.

DR. ABDULLAH: I think what's probably important to highlight as well, too, is when we've looked at the efficacy data more specifically from DREAMM-14, we do see that, again, the higher starting dose, the more frequent dosing intervals, are associated with a greater depth of response but also improved PFS, as outlined on CO-20. So we do see that the data in terms of the exposure-response relationships actually do hold out, whether it be across DREAMM-14, the ALGONQUIN study, or the DREAMM-6 trial.

DR. BERINGER: Okay. And on slide 23, you

did these dose simulations looking at progression-free survival with these doses, which include ones with longer intervals. This does not include dose reductions due to adverse effects; correct?

DR. ABDULLAH: It actually incorporates the dose modifications as well, too.

DR. BERINGER: Okay. So this would represent data as if they had ocular events and had dose reductions.

DR. ABDULLAH: That is correct. What you do see is there is a meaningful loss in efficacy, again, if you lower the starting dose or prolong the dosing intervals.

DR. VASAN: Would FDA like to comment?

DR. LI: Thank you. Hi. This is Yangbing Li, the primary pharmacometrics reviewer at the U.S. FDA. Yes. For the first question, for the exposure-response analysis in DREAMM-14, as I mentioned before, we have several concerns about the exposure-response analysis due to the drug modification beyond Cycle 1, which was not included

in the modeling. Also, we also see that there are some possible trends for both efficacy and safety in this analysis.

For the second question, for the M protein modeling with the dose modification, for this model that has not been fully reviewed by the agency, well, we do have some concerns about these results due to we can see from the simulation result, the 2.5 mg every 3-week dose shows a higher PFS compared to the observed data in DREAMM-7.

We also have some concerns about the extrapolation for PFS and dose modification information in these models and simulation. This is mainly driven by the lack of data in the lower dose with longer dosing intervals due to the limited number of patients in the study who received combination treatment.

DR. VASAN: Does that conclude your question, Dr. Beringer?

DR. BERINGER: Yes. Thank you.

DR. VASAN: Okay.

Dr. Frenkl?

DR. FRENKL: Thank you. Tara Frenkl, industry rep. I had a question for one of the scientific experts, please. I see from the data, what's presented in both of the briefing books and also today, that FDA makes their conclusion that a lower dose may not have affected efficacy based on, really, ORR, that was achieved, while the applicant uses VGPR or better.

So I'm just interested in really understanding both, clinically, which target is the physician really shooting for with the patient and also what is the data in the literature about the correlation with PFS and OS.

DR. ABDULLAH: I'd like to call on Dr. Lonial to address that question but also provide some context on the current relapsed/refractory multiple myeloma disease setting.

DR. LONIAL: Thank you very much. Sagar Lonial from Emory. What we know is that the deeper response is associated with longer progression-free survival and better clinical outcomes. So VGPR is

clearly a deeper response. It's a 90 percent reduction in the protein as opposed to PR or better, which is a 50 percent reduction in the protein. We've had workshops with the FDA identifying MRD as an important endpoint, and the MRD, as you saw, was clearly higher in the groups of patients that received bela compared to the control arms.

So I think it is a really reasonable approach. In the modern era of myeloma therapy, overall response rate is nice, but it's always 80-90 percent, and you need something to discriminate efficacy and VGPR or MRD as a way to help us do that, and it clearly identified a benefit from the patients receiving bela.

If I may respond to a previous question about population relevance?

DR. VASAN: Yes, please.

DR. LONIAL: Thank you.

I think if you look at the subsequent therapies, as Dr. Madan was asking, it would look similar to what we would give in the U.S. I think

the question about the use of anti-CD38 antibodies as part of an upfront treatment, limiting the applicability of this treatment, it will only magnify the difference because we agree, people are getting anti-CD38s.

And it doesn't matter which control arm, quite honestly, you chose; nothing is going to give you a PFS comparable to 33 months, with the exception of a CAR. And we showed you the efficacy in terms of all the endpoints in my talk were similar compared to a CAR. Whether you combine pomalidomide, whether you combine carfilzomib, any of these with anti-CD38s, it's going to be less than 33 months.

So while I recognize the concern of the applicability of the control arm, first of all, I think it is an applicable control arm, but more importantly, we're losing sight of the absolute clinical benefit that's seen with that very long progression-free survival.

DR. VASAN: Thank you, Dr. Lonial.

Dr. Frenkl, was that all your questions?

DR. KANAPURU: I think she wanted the FDA to respond as well.

DR. VASAN: Okay. FDA, please.

DR. KANAPURU: And just to note, I just wanted to follow up on what was recently said. I think we still don't have the data. I appreciate that there could be a theoretical improvement and relevance, but on top of that, just to point out, the overall data for dose exploration is very, very limited, and I think the DREAMM-14 data also highlights some of the issues with the post-approval dose optimization.

There are a lot of reasons why the dose modifications may be preferentially made in the lower doses when people know that there's an approved 2.5-milligram dose. I think there are a lot of challenges in interpreting the data from a post-approval study, in addition to the limited number of patients overall at the proposed dosages for the DREAMM-7 and DREAMM-8. Thank you.

DR. VASAN: Thank you.

Dr. Frenkl, is that all your questions?

DR. FRENKL: I had one more. Actually, just with regard to the dose selection that then was made for DREAMM-10, what were the reasons that led you to a different conclusion for that population?

DR. ABDULLAH: Yes. We've actually taken a very data-driven approach, whether it be across the relapsed/refractory multiple myeloma setting, where we've actually explored a number of different doses and schedules, ranging between 1.9, all the way to 3.4, and then Q3, 4, 6, 8, and 12W across three different studies and close to 400 patients.

We've done the same in newly diagnosed multiple myeloma patients. We actually have data from a number of different doses and schedules in the front-line setting, and what we do observe, based on the exposure-response analysis that we've conducted, is newly diagnosed patients are actually more sensitive to Blenrep therapy, so therefore, you don't necessarily see the same steep exposure-response curve. It's actually shifted more towards the left. So therefore, we're able to go to a lower dose of 1.9, and then stretch out the

schedule to every 8 weeks without necessarily any loss in efficacy, while also trying to improve the tolerability as well, too.

DR. VASAN: Does that answer your question, Dr. Frenkl?

(Dr. Frenkl gestures yes.)

DR. VASAN: Okay. Thank you.

Dr. Spratt?

DR. SPRATT: No, my hand's down.

DR. VASAN: I apologize. Sorry. It's the snafus of virtual.

Dr. Nowakowski?

DR. NOWAKOWSKI: To follow up on some of the dose-finding studies, the number of patients in dose-finding studies are relatively limited, and here, early on, you had significant dose interruptions and significant toxicity in this study, with relatively wide confidence intervals in terms of efficacy because of small cohorts.

I'm just curious from the sponsor perspective why you didn't decide to expand those cohorts to a better handle on the dosing early on

in the study development? I know time is critical for the study development as well, but it looks to me like a missed opportunity for better dose optimization upfront.

DR. ABDULLAH: Well, as I've alluded to, we've actually looked at close to 400 patients worth of dose exploration data. You kindly refer to the limited number of patients that were explored across each dose court or dose schedule cohort. It was about maybe 12 to 18 patients, which is very typical of what is early-phase dose exploration, and again, we looked at a number of different doses and a number of different dosing intervals.

What's probably important to highlight is the relative dose intensity across all clinically active doses remain between 40 to 60 percent, but what we do see is, there is a trade-off on efficacy that actually happens if you lower the starting dose or extend the dosing schedule. And what we saw, probably -- and I think this is the most important part -- is with the starting dose of

2.5 mg/kg, a higher exposure during the first 6 months of treatment, and appropriate implementation of the dose modification guidelines, we saw the clinically meaningful effects in progression-free survival, overall survival in DREAMM-7, and a positive trend in DREAMM-8 and the the depth of response.

This committee met last year to discuss the relevance of depth of response and its correlation to longer term endpoints such as progression-free survival and overall survival. We see 2 and a half to 5 times improvements in MRD negativity rates, and I think that's all with the current dose and schedule that have been implemented.

If it's possible, I'd like to actually call on Dr. Paul Richardson to provide his perspective on that, too.

DR. RICHARDSON: Thank you very much. Dr. Paul Richardson, Dana-Farber, and a number of points to share. I think most importantly, this construct of increased dose, then dropping as you move to a continuous therapy phase, is so well

established in myeloma. If you actually think about it, every single drug we use in myeloma, we actually employ a dose escalation/de-escalation strategy, and I think that's incredibly important to understand.

I think the other point is that in our own experience, both as part of clinical trials and our real-world experience in EAP, at Dana-Farber, we've treated over 166 patients. It's incredibly important to understand this construct of severity of toxicity. Our hospitalization rate, over 166 patients to attributable bela toxicity, is 5 out of 166. In contrast, our CAR T patients have 100 percent hospitalization rate. Our bispecific rates are 100 percent. Our toxicity profiles are radically different.

So I would argue that in the setting of belantamab mafodotin use, dose adjustment is utterly appropriate to achieve these kinds of outcomes with benefits seen. And most importantly, in the management of toxicity, I fully understand Dr. Pazdur's point, but we've actually had a very

good working relationship with ophthalmologic consultants to manage eye toxicity in a very manageable way, and you'll hear from our patients in a moment about this. But I think this dose escalation and de-escalation strategy is something we're very comfortable with.

So I hope that's helpful, Dr. Nowakowski, in understanding it.

DR. NOWAKOWSKI: Well, thank you. That's helpful, but I'd like to circle back maybe to my original question about the size of those cohorts, exploratory cohorts, the dose optimization part. I agree with you that this would be an average size of the cohort typically seen in this study, provided there are no unexpected problems, but you did see them early on. You did see this unexpected toxicity, and yet those cohorts were not expanded. I'm just trying to to understand better the rationales.

DR. ABDULLAH: Yes. I'd like to call on Dr. Mukhopadhyay to provide some additional context around that as well, too.

DR. MUKHOPADHYAY: Thank you, and thank you for pointing out the dose modifications as well. As Dr. Abdullah pointed out, the dose modifications were also happening even in the lower doses, extended schedules. That's because the ocular events happened, and there was a variability in the resolution that happens across the board.

What's important with the dose modifications -- if I can have CO-18, please -- it's not just the size of the cohorts, but it's the consistency of the findings from three different studies. So when you look at the combination with bortezomib-dex, we had the higher starting dose, more frequent schedule, followed by subsequent modifications, and had the one that has the greatest depth of response.

We had the same finding when we look at -- if I can have CO-25 -- the ALGONQUIN study, please. Thank you. You see, again, the consistency from a separate independent study. And as pointed out, the DREAMM-14 trial, which was a randomized trial with four different dose cohorts

with 40 patients each, again, the same finding with monotherapy where, granted, the response rates in this heavily pretreated population was similar, but when we look at DREAMM-14, slide CO-20, what's important is, in this randomized trial, we saw 6 months of median PFS in a fourth-line plus treated population compared to the other ones that were ranging from 2.1 to 2.8 months.

If I may clarify, if I can also have that simulation slide from the core deck up, please? Thank you. CO-23.

It's important to note that these were simulations that were performed, assuming dose modifications in the same context as has been happening with 7 and 8. What you see clearly with that is that a lower starting dose, a less frequent starting schedule, has sub-efficacious benefit when it comes to PFS. It's important to note that we performed also the same simulations without modifications as well, and we see the exact same results.

So what's important to note is not just the

size of the cohort, but the consistency of the results from three separate studies, the exposure-response analyses, as well as the simulations, they all come to the same conclusion. Thank you.

DR. NOWAKOWSKI: Thank you.

DR. VASAN: Can the FDA please respond to this?

DR. TELARAJA: Hi. This is Deepti Telaraja, FDA. I just wanted to comment that the applicant has focused a lot on the efficacy and the depth of response in the dose-finding studies; however, it is also important to take into account the safety and tolerability. And as presented in our main presentation, there were very limited numbers of patients in some of these cohorts, which limit the conclusions that can be made; but there were certain trends seen with lower doses and longer dosing intervals having improved safety and tolerability. So this really brings the question of, if these cohorts had been larger, whether more clear trends would have been seen. Thank you.

DR. PAZDUR: I would just also like to comment, these were non-randomized studies that you're looking and comparing PFS, which is quite dangerous to do here.

DR. VASAN: Thank you.

DR. ABDULLAH: Just to clarify, just one comment. Actually, DREAMM-14 is a randomized study.

DR. VASAN: Okay. Thank you.

DR. ABDULLAH: Thank you.

DR. VASAN: So now, we will take a quick 15-minute break. We're a little over on time, so we'll start the OPH session at 10:55. Panel members, please remember there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience.

DR. ABDULLAH: Dr. Vasan, if it's possible, can I respond to --

DR. VASAN: I'm sorry. We'll need to continue. Thank you.

(Whereupon, at 10:42 a.m., a recess was

taken, and meeting resumed at 10:55 a.m.)

Open Public Hearing

DR. VASAN: 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 statement to advise the committee of any financial relationship that you may have with the applicant. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your participation in the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect, therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

We do have 14 speakers, and we would like to hear from everyone. So in the interest of respect and time, at the 4-minute point, I will acknowledge that, and please know that we want to hear from all

of you. Thank you.

For speaker number 1, please unmute and turn on your webcam. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you're representing, for the record. You have four minutes.

MS. YOUNG: Good morning. My name is Ann Quinn Young, and I am Chief --

DR. VASAN: I'm sorry. We can't hear you.

(Pause.)

DR. VASAN: If it's alright, Ms. Young, we'll skip, and then we'll come back to you.

Speaker number 2, please unmute and turn on your webcam. Will you please begin and introduce yourself? Please state your name and any organization you are representing, for the record. You have four minutes.

DR. USMANI: Thank you. Can you all hear me?

DR. VASAN: Yes.

DR. USMANI: Good morning, everyone. My name is Saad Usmani. I'm a practicing hematologist

and medical oncologist. I serve as the Chief of the Myeloma Service at Memorial Sloan Kettering Cancer Center in New York. I also serve as the Chair of the NCTN Alliance Myeloma Committee, one of the three U.S. cooperative groups that conducts clinical trials focused on multiple myeloma and associate disorders. I would like to thank all of you to allow me to speak in today's session. To declare CoI, I have previously served on the IDMC and as a PI on previous GSK studies. I'm not being compensated by GSK for this testimony.

I have had the privilege of treating multiple myeloma patients over the past 18 years in the states of Arkansas, in North Carolina, and more recently in the tri-state area in the northeast. I've had direct and indirect interactions with patients, caregivers, and oncologists in urban, suburban, and rural settings.

Access to myeloma drugs in rural and suburban communities remains a significant challenge. It contributes to disparities in treatment outcomes. Patients in these areas often

face limited availability of specialized care, few clinical trial options, and delays in diagnosis. In specific, access to novel immune and cellular therapies is almost non-existent for many of these myeloma patients due to travel distances to tertiary care centers and the challenges in logistics. This is especially true for elderly or socio-economically disadvantaged patients, as you heard from several of the colleagues early in the morning as well.

Additionally, I hear from our suburban and rural providers about the challenges of timely referrals, especially for commercial cellular therapy options. So having an effective off-the-shelf option like belantamab mafodotin triplets will be very important to improve the multiple myeloma care access across the United States.

As a practicing clinician, I have no doubt, hearing the testimony and talks from both sides, about the positive primary endpoint results of the DREAMM-7 and 8 trials and the dosing and schedules

examined to mitigate ocular side effects and their management. I do feel as a clinician, for my patients, this tips the benefit-risk scale in favor of bela-maf triplets for my patients.

I have to note that both these trials provide one of the highest PFS rates among the contemporary phase 3 studies. DREAMM-7 shows OS benefit as well, and that's reassuring to see. Even for DREAMM-8, there is no detriment in OS; in fact, there's a trend favoring the bela triplet there as well. Importantly, while corneal side effects do remain an issue, they are fewer severe ocular side effects compared to some of the earlier experienced.

At our center, we have advanced relapsed/refractive myeloma patients who responded to bela-maf as monotherapy back in the year 2020 and 2021, who remain on treatment with sustained responses, with minimal ocular side effects to this day. That's a testament that mitigation strategies can be effective and help our patients. Within the Alliance Myeloma Committee, we actually have a

novel bela-maf triplet with every 8-week dosing, which is actually enrolling across the United States in various communities, urban, suburban, and rural communities. That would not be possible if logistics were a real issue.

Every patient facing cancer deserves hope. That includes access to new innovative treatments. Oncologists and patients must be empowered to explore all available options together, weighing the potential benefits and risks as a team. These conversations are vital. They ensure care is not only evidence based, but it's also deeply personal. New therapies may offer improved outcomes, even when side effects are possible. We observe this in our clinics every day, and we try to do our best to create that balance for our patients.

By fostering open, informed dialogue, we give our patients the urgency --

DR. VASAN: I'm sorry. We're at four minutes now.

DR. USMANI: -- to their journey. And as oncologists, I would really appreciate if we get

the opportunity to provide the best individualized care, grounded in both science and compassion. Thank you.

DR. VASAN: Thank you.

Speaker number 1, please unmute yourself and turn on your webcam. Could you please begin and introduce yourself? Please state your name and any organization you're representing, for the record. You have four minutes.

MS. YOUNG: Good morning. My name is Anne Quinn Young, and I am Chief Mission Officer at the Multiple Myeloma Research Foundation where I've worked for almost 23 years. I'm speaking today on behalf of the organization and the hundreds of thousands of patients, caregivers, and families we serve. The MMRF is a national 501(c)(3) and is the largest private funder of myeloma research. While we receive support for research initiatives and educational programming from nearly every company with a myeloma program, often in the form of cost sharing and/or grants, we are not being compensated for this testimony.

The mission of the MMRF is, and always has been, to accelerate a cure for each and every patient. As a patient-founded and focused organization, everything that we do as an organization prioritizes patients over anyone else. The MMRF supports the development of safe and effective treatments for patients at every stage of their disease on the path to a cure. Patients with relapsed/refractory disease has always been a focus of ours given the significant and enduring unmet need in this population.

Multiple myeloma remains an incurable disease where patients nearly uniformly relapse, and typically with each line of therapy, the likelihood of response and the duration of response meaningfully declines. The MMRF supports belantamab mafodotin, or bela-maf, as a safe and efficacious therapeutic option for relapsed and refractory multiple myeloma. This is because until we have curative therapy, having options like bela-maf available, particularly earlier in the disease course, will help to extend

progression-free survival and time to next therapy, allowing patients greater opportunities to reach and celebrate special milestones.

Furthermore, as an off-the-shelf option, bela-maf can be administered in community oncology settings. This has the potential to reduce access disparities for patients who are unable to travel to major academic centers, furthering our commitment to promote health equity and ensure all patients benefit from advancements in care.

When considering bela-maf, with its unique mechanism as well as safety and efficacy profile, the MMRF emphasizes the importance of shared decision making between patients and providers. As part of our focus on empowering patients in the myeloma community, in pursuit of more equitable access to quality care and outcomes, the MMRF believes in providing patients with the resources and tools to critically evaluate treatment options and make the most informed decision for their individual situation. The MMRF is strongly committed to educating both patients and

caregivers, as well as healthcare providers, about treatment options such as bela-maf and clinical strategies in all settings.

Finally, successful use of bela-maf requires a team-wide approach to toxicity management, including dose modifications, monitoring, and supportive care. We advocate for strategies that engage the full care team to help patients remain on effective therapies while maintaining their quality of life.

Thank you so much to the committee for providing me with the time to present today and to the FDA for its long-standing commitment to making effective and safe treatments available to myeloma patients at every disease stage over the last 20-plus years. Many of these treatments have been transformative, and most patients are enjoying a longer survival and better quality of life after their diagnosis than ever before.

DR. VASAN: Thank you for your comments.

Speaker number 3, please step up to the podium and introduce yourself. Please state your

name and any organization you are representing, for the record. You have four minutes.

MS. CARTWRIGHT: My name is Kathy Cartwright, and thank you for letting me come and share my experience with Blenrep. GSK is reimbursing me for my travel. I cut our family vacation in half to be here today with all of you because it's that important to us and to my family.

I'm here because I started Blenrep four years ago. It saved my life. It's one of the easiest drug treatments I've had. It's only a 30-minute infusion, no pre-meds, no GI issues, no headaches, no steroids. A few days before infusion, I see my eye doctor. He gives me a thorough eye exam. I get to see the chart, eye pressures checked, and he examines my cornea.

My side effects from Blenrep are very minor and they're very manageable. I get blurry vision, dry eyes, sometimes sensitive to bright glares and lights, but I use non-preservative eye drops that you can get at any drug store, sunglasses, and readers, but only use them when I need them. I

also have had multiple myeloma for 24 years. I've taken many, many treatments, and I've had many, many side effects, and some of them are permanent side effects.

In 2020, when my myeloma turned into high-risk, extramedullary myeloma, I had 12 tumors that I could see and feel. I also had tons of tumors inside of me that I couldn't see or feel. With just two treatments of Blenrep, I could no longer feel or touch the 12 tumors. I couldn't see them. I couldn't feel them. So my doctor had a PET scan and MRI done, and my tumors internally were shrinking from 8 centimeters down. They shrunk, they disappeared, and no new ones grew.

That was four years ago. Today, my myeloma test that I just recently had and a bone marrow biopsy, not one myeloma cell was found in millions of cells. I had my PET scan and my MRI done. No more tumors. I don't have any of them. This is a miracle for me. This drug pulled me literally off my deathbed. I was this close to calling hospice. I was up against a wall. I didn't have any more

treatment options.

For me, these side effects of dry eye, blurry vision, and sensitivity are definitely worth it. If Blenrep can help me, it can help a lot of patients. Please, whatever you do, please get it out there. Thank you.

DR. VASAN: Thank you for that testimony.

Speaker number 4, please step up to the podium and introduce yourself. Please state your name and any organization you're representing, for the record. You have four minutes.

MR. TEITELMAN: Good morning. My name is David Teitelman, and I was diagnosed with multiple myeloma in December of 2018. I am not receiving a fee or compensation for my time today, but I will have my travel expenses reimbursed by GlaxoSmithKline. I am also a volunteer on the GlaxoSmithKline Multiple Myeloma Patient Expert Council.

I wish to convey my experience as a patient regarding the treatment's effectiveness, side effects, and impact on my quality of life. My

treatment with a triplet of belantamab mafodotin, pomalidomide and dexamethasone began in March of 2022, and I have been in remission since that time. This followed six prior failed lines of treatment, with each ranging from 2 to 11 months. The effectiveness of the belantamab mafodotin began almost immediately. Approximately one month following beginning of treatment, my light chain numbers and free kappa-lambda ratio were all normal, and I've remained so for approximately 3 years and 4 months. In my case, the effectiveness of the treatment has been miraculous. I would not be alive today without this treatment.

Regarding side effects, I have only one, and this involves my vision. At approximately 2 weeks following infusion, my vision is impacted. I am normally nearsighted and only wear glasses for assistance with distance such as improving roadside recognition while driving or going to a movie. My vision usually remains impacted for approximately 3 weeks, and during this time, my vision actually flips where my distance vision greatly improves and

my near vision becomes blurry with some difficulty focusing when reading.

I read a lot, and to overcome the impact on my near vision, I change to a dark background on my phone or tablet, which allows me to continue reading without any difficulty. For example, my most recent infusion was approximately four weeks ago, and this is a font in a format which I could read while my eyes are still impacted from the last infusion.

When driving during the time frame when my eyes are impacted, I can read traffic signs in the distance, read license plates of cars passing me or even several car lanes ahead of me. At the conclusion of the approximate 3 weeks of vision impact, my eyes return to an acceptable grade to allow my next scheduled infusion to take place.

From a quality-of-life standpoint, I could not be happier. When I first began this treatment regimen over three years ago, I was scheduled to receive infusions every 4 weeks, but this was not enough time for my eyes to return to an acceptable

grade to be cleared for my next scheduled infusion. Within the first year of treatment, infusion schedule was extended to 6 weeks, which provided enough time for my eyes to recover, then 8 weeks during the early portion of year 2. This was followed by extending the infusion schedule to 10 weeks and possibly every 12 weeks in the future.

A few days prior to each scheduled infusion, I have a brief appointment, which is usually 15 to 20 minutes with an ophthalmologist to ensure my eyes have returned to an acceptable grade to allow the scheduled infusion to take place. The treatment schedule has had minimal impact on my life and my family's involvement with my care. The infusion schedule is far from a hardship and is low impact and very easy to manage. As a comparison, I have dental checkups scheduled every three months, so I think everyone can understand why my wife and I are so happy with the freedom the treatment schedule affords us.

The treatment schedule has allowed me to plan, schedule, and attend events with my family

and friends with minimal thought or effort regarding potential conflicts. I can also reflect on and compare this to prior treatment lines that in some cases required weekly visits. The difference is certainly dramatic. I want to thank everyone for their time and allowing me to present my story and perspective.

DR. VASAN: Thank you.

Speaker number 5, please step up to the podium and introduce yourself. Please state your name and any organization you're representing, for the record. You have four minutes.

MS. OLSON: Thank you. I'm Deialia Olson from North Carolina. Thanks so much for having me here to talk with you today about Blenrep. I have no relationship with GSK other than using the drug; however, they are reimbursing me for my travel experience expenses for attending this conference.

I'm a long-term myeloma survivor having been diagnosed 20 years ago. And back then, the prognosis and possibilities seemed pretty scary, but I've been one of the really fortunate ones.

I've managed so far to avoid many of the more devastating possible effects of the disease, such as bone pain and fractures, numbness and tingling, worst-case scenario, and early death. Mostly, I've had to deal with fatigue and other side effects from the many drug trials I've been involved in, along with a stem cell transplant in 2008.

As my oncology team has worked to keep my myeloma under control, some of the side effects that I've had from the chemotherapy drugs I've taken over the year are neuropathy, which caused pain in my lower legs that lasted about a year, and that was awful. I've also been on drug combos that left me nauseated 24 hours a day, and of course, I've been on chemotherapy drugs that just didn't work for me or that eventually stopped controlling my myeloma.

Then in May 2022, I was fortunate to be included in a Blenrep trial, and it immediately brought down my M spike and has kept it down consistently for the past three years. I was, of course, briefed about the side effects that I might

experience with Blenrep with my eyes and my vision, and that's gone very much as expected. After my infusion, I'll experience dry, itchy eyes and the gradual blurry of my vision. It's like a roller coaster. As you've heard from others, my eyesight worsens for a few weeks following my infusion, and then gradually improves afterwards.

But it can be challenging. I'm a proud American so, of course, I have my big 70-inch TV in the living room and a chair about 10 feet away. My husband, when I first started the treatment, I would ask him to read everything on the TV, on that 70-inch TV, and finally he bought me a little pair of binoculars so I could actually see that.

My optometrist determines, of course, whether I'm ready for my Blenrep infusion each time, depending on my corneal condition, and he always asks if I'm remembering to use my eye drops. I tell him I definitely remember to take my eye drops because my eyes will remind me, drops during the day, an ointment at night, and occasionally a session with my heated eye mask. That's my

routine.

Other things I do routinely are walking daily for exercise, gardening, cooking, and traveling to see friends and family. And I'm so thankful to feel well enough to enjoy these activities because, bottom line, dealing with my eye issues seems a small price to pay to keep my myeloma at bay and leave me feeling well enough to enjoy my life.

I'm very excited that you're on the verge of making Blenrep available to other myeloma patients. I hope very much so. It has been a godsend for me, and I hope that I and many others will be able to continue benefiting from this drug for many years to come. Thank you so much.

DR. VASAN: Thank you very much.

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

MS. MORAN: Good morning. I'm Diane Moran,

the interim CEO of the International Myeloma Foundation. I have no conflicts to report as it relates to our testimony. We are speaking today to strongly support BLA 761440, use of Blenrep, belantamab mafodotin.

The International Myeloma Foundation brings both the patient voice and the science to this conversation. As the convener of the International Myeloma Working Group, a global network of 350 myeloma experts in partnership with more than 150 myeloma support groups across the U.S., IMF serves as the bridge between evidence and lived experience. These are our superpowers, convening world class research while standing shoulder to shoulder with patients navigating an incurable and unforgiving disease.

There's a saying, "Man plans and God laughs," but for myeloma patients, it often feels like the disease laughs last. This is a cancer that doesn't just threaten life, it changes it instantaneously and irreversibly, robbing patients of control and choice, shrinking their dreams,

stretching their fears.

Now imagine, not as a scientist, not as a regulator, but as a human being, what it feels like to be told you have myeloma. Imagine the stillness in the room, the air leaving your lungs, the plans you made, retirements, weddings, graduations, replaced by doctor visits, infusions, scans, statistics. Now imagine learning there are treatments that work, that offer real hope, but they may not be available to you. Maybe you're too sick. Maybe you're on the wrong insurance plan. Maybe the treatment was once available and then is taken away. This is the lived reality of too many patients we serve.

Myeloma remains incurable. We're making powerful progress, deeper remissions, longer survival, a pipeline full of innovation, but progress must be matched by access. A therapy that exists but is out of reach is not hope; it is heartbreak. Belantamab mafodotin offers an evidence-based path forward for patients who need options. When it was first introduced, it brought

promise and, for many, meaningful benefit. We have seen patients even treated as a single agent experience deep and durable responses. Some have successfully stayed on treatment for years.

Today, we have stronger data to support belantamab's value through the DREAMM-7 and DREAMM-8 trials. We now understand how to better manage the ocular side effect. The real-world clinically experienced physicians are mitigating these risks effectively through proactive monitoring and dose adjustments.

Now, these are real adverse effects but, importantly, they are reversible. And for many patients, the benefit and progression-free survival outweighs the potential risks. This is a chance to expand the toolbox for patients who need time they do not currently have. What patients want is not unreasonable. They want time to see one more graduation, walk a daughter down the aisle, watch a grandchild take their first steps. They want the dignity of options. They want the power to hope.

These patients did not choose myeloma;

myeloma chose them. Now, we must choose them. We must give them choices because without options, there is no control. Without access, there is no hope. Belantamab mafodotin gives patients a chance, not a guarantee, but a chance to reclaim moments that matter, to rewrite the timelines this disease tries to erase.

There's no such thing as acceptable loss when it's your life or your loved one's. If we can offer a therapy that helps, we must offer it. If we can relieve suffering, we must not delay. If we can deliver hope, real hope, we must make it real. And with the right options, it is patients who may laugh again, not because the disease is gone, but because possibility has returned, because they have been seen, heard, and given a chance. Let's give them the power to plan again, to dream again, to live again. I thank you for listening and keeping both the science and the patient voice at the center of this critical decision.

DR. VASAN: Thank you.

Speaker number 7, please step up to the

podium and introduce yourself. Please state your name and any organization you are representing, for the record. You have four minutes.

MS. AHLSTROM: Good morning. My name is Jenny Ahlstrom. I'm a multiple myeloma patient diagnosed in 2010 and the CEO of HealthTree Foundation, the leader in digital health advocacy in the multiple myeloma and hematology space. GSK supports various HealthTree educational programs but is not paying for my travel or compensating me for my time to be here.

Thank you for the opportunity to speak to you today as a patient and someone who represents hundreds of thousands of myeloma patients. Through our programming, we serve over 1.5 million patients, caregivers, family members, and others interested in myeloma annually. I'd like to deeply thank each member of the FDA. Myeloma patients' lives are being lengthened thanks to innovative work from companies like GSK and others you are approving. Your approvals are giving patients choices and longer life.

Myeloma care has radically changed the length of life in the last 20 years, yet we still do not have a known cure. According to current SEER data, 38 percent of patients are still dying in under five years, and even with CAR T and bispecific antibodies, why we all hope to be curative saviors, patients are still relapsing and dying of multiple myeloma.

Blenrep represents another needed choice, one more tool in the toolbox that can help patients live longer and better with myeloma for several reasons. First, this is a treatment that can be easily given in the community setting. Access remains a big issue for CAR T, and today only 18 percent of patients who are eligible for CAR T are receiving CAR T. Bispecifics face a similar issue. Any therapy that has planned hospitalization is going to have this challenge.

These exciting options are just harder to access, and the reality is that over 80 percent of patients are seeing local community providers for their care. Blenrep is a convenient treatment

option in frequency and location, and the low rate of hospitalization and easy administration makes it an attractive option for both the patient and clinical team for close-to-home access.

Second is treatment does not depend on a fully functional immune system to be effective. Given the older patient population and immune system damage caused by myeloma itself, many immunocompromised patients may not respond to immunotherapies regardless of their potency because their immune systems are simply too impaired.

Third, the side effects are known, manageable, and reversible. Dr. Robert Kyle of Mayo Clinic says there is no drug on the market today that doesn't have a side effect. We as patients have gotten quite used to dealing with side effects in myeloma like neuropathy on Velcade, feeling OCD and angry on dex, or having daily diarrhea or rash on Revlimid, all side effects that affect daily living. CAR T and bispecifics bring new and serious side effects: cytokine release syndrome, neurotoxicity, ICANs, Parkinsonianism,

and increased rates of infection, particularly upper respiratory.

The eye-related side effects are clearly documented with Blenrep. Patients know that they need to be monitored by an optometrist or ophthalmologist. And as an advocacy leader who is in constant communication with patients and providers, I've not heard any instance of permanent visual damage, and I know some Blenrep patients who report no blurry vision at all. One patient, a HealthTree coach who has been on over 10 lines of therapy, comments to me all the time that Blenrep was the easiest tolerated therapy she's ever been on. And it's very normal to work with your doctor to make dose and treatment adjustments in myeloma therapy. Patients do that all the time. Side effects are part of this package that we get with having myeloma. We wish we could avoid them, but they are better than death by myeloma, so we make decisions and move forward.

As a patient and advocate, I support the approval of Blenrep based on the DREAMM-7 and 8

studies. The progression-free survival benefit clearly shows that this drug is very effective and works extremely well. It can be given locally. It can be flexibly used in common myeloma combinations. Approving Blenrep gives me the choice and freedom to decide with my doctor what is best for my unique and individual situation for my disease burden, for my travel requirements, and for my side effects. Thank you.

DR. VASAN: Thank you.

Speaker number 8, please step up to the podium and introduce yourself. Please state your name and any organization you are representing, for the record. You have four minutes.

DR. SUNSHINE: Thank you. My name is Dr. Sarah Sunshine. I'm a cornea specialist and ophthalmologist at the University of Maryland School of Medicine. I study and treat patients with ocular complications from cancer therapies. I'm in a unique position there to have a dedicated eye clinic within our cancer center, which has allowed me to care for many of these patients.

I've also spoken with colleagues across the country about their experiences treating ocular side effects from antibody drug conjugates, which are becoming increasingly common.

It is important for me to note that I've consulted for GSK specifically on their Eye Care Provider Advisory Council, as well as other pharmaceutical companies, but I'm here on my own behalf today. I'm uncompensated for this because I really think it's important to preserve access for our patients and the patients that I've had the opportunity to treat.

Belantamab is a second-line treatment for relapsed or refractory multiple myeloma. Like many effective cancer therapies, it carries risks, including ocular toxicity. These events are predictable, manageable, and reversible, especially when patients are monitored appropriately. Many of our patients experience some form of ocular events, but it varies widely. It can be subtle, like corneal surface changes like you saw today, or more noticeable like the blurry vision or discomfort

that you've heard about. But the most important point that I hear, and that I feel repeatedly taking care of these patients, is that most patients can continue treatment with dose modifications, and these events resolve.

In my practice, I've seen patients with moderate or even significant changes regain functional vision after dose modification. The corneal epithelium recovers. These are not intraocular complications. Unlike some other ADCs, these do not cause uveitis or inflammation inside the eye, and it doesn't cause retinal swelling or inflammation. While those intraocular events may be less common, they're still more severe, and the toxicity with belantamab is limited to the corneal surface, and we can manage that.

How does this work in real life? In my experience, and talking to other eyecare providers, I think it's threefold. First, these patients are highly motivated. You've heard from many of them today. This is a second-line therapy. Even those with visual symptoms that I've had the ability to

treat repeatedly tell me how they would do whatever it takes to stay on this drug. They understand the risks and overwhelmingly view the temporary vision changes as worth it.

Second, the corneal side effects, though common, are manageable. With artificial tears and close monitoring, and the reassurance that dose holds don't reduce efficacy, patients can maintain both vision and access to this life-extending therapy. And third, this model of care, in my opinion, is scalable. Ocular monitoring is done with standard tools. A slit-lamp exam and fluorescein staining and visual acuity are standard of care for every eyecare provider. We all have those tools and are comfortable using them.

In addition to the educational programming that's been implemented, both ophthalmologists and optometrists in the community and academic settings can safely manage these patients. Belantamab requires a baseline eye exam and close monitoring, but I've seen firsthand how this system works in practice with both my own clinic and in

coordination with community physicians.

In summary, I just want to clarify, ocular events occur in many of these patients, but they're predictable, reversible, and manageable. Every eyecare provider is equipped to monitor and support these patients, and with dose holds and modifications, patients can maintain their vision and stay on therapy; and critically, patients overwhelmingly want to continue this treatment. I want to thank you for the opportunity to share my experience. Thanks.

DR. VASAN: Thank you.

Speaker number 9, please unmute yourself and turn on your webcam. Please begin and introduce yourself. Please state your name and any organization you're representing, for the record. You have four minutes.

DR. LEE: Good morning. My name is Dr. Hans Lee, and I'm a medical oncologist and the Director of Myeloma Research at the Sarah Cannon Research Institute. I have received consulting fees from the applicant GSK in the past, although I'm not

being compensated for this testimony.

I have dedicated my career to advancing the treatment for patients with multiple myeloma and have significant personal experience in administering belantamab mafodotin in both the research and standard of care context. I want to share three points today -- number one, efficacy; number two, safety; and number three, access -- to convey my strong support for the regulatory approval of bela-maf in combination with bortezomib and dexamethasone and pomalidomide and dexamethasone.

First, efficacy. The efficacy of bela-maf has been demonstrated in the DREAMM-7 and DREAMM-8 clinical trials in relation to depth of response, progression-free survival, and in the case of DREAMM-7 overall survival. How it really stands out is the magnitude of benefit, with a nearly tripling of the numeric progression-free survival in the bela-maf-based triplets versus standard of care triplets. The study design in itself is also noteworthy since these were head-to-head 3 drugs

versus 3 drug comparisons with daratumumab and bortezomib-based triplets.

I think this also speaks to the biological significance of BCMA as a targeted myeloma consistent with the strong efficacy we have seen with BCMA targeting CAR T and bispecific antibodies, and having brought access to BCMA-targeted therapies is critical for myeloma patients in the United States, which I'll touch on more later.

Now, to point number two regarding safety, the safety profile of bela-maf has been well characterized. It is well established that the drug can lead to ocular adverse events, primary keratopathy, and it is important that prescribers are aware of this and work together with their local eyecare specialists to manage these adverse events. However, in my own personal experience, the ocular adverse events are effectively managed with dose delays and dose reductions and is reversible when employing such strategies.

Importantly, the majority of patients had

deepening or stabilization of responses despite dose delays and dose reductions of bela-maf in DREAMM-7 and DREAMM-8. This is also very consistent with my own personal experience with bela-maf. When decreasing dosing frequency to every 8 or even every 12 weeks as done in DREAMM-8, the rates of ocular toxicity are much lower at such infrequent dosing intervals.

Finally, I want to discuss my third and final point regarding access, which is so critical. I have already mentioned the importance of BCMA as a target, and while we do have CAR T and bispecific therapies at target BCMA, which are highly efficacious, the reality is that the majority of myeloma patients in 2025 who are eligible to receive these therapies do not have access to CAR T or bispecifics in their local treatment setting.

The administration of CAR T and bispecific antibodies require additional clinical infrastructure to monitor for potential toxicities, including cytokine release syndrome, ICANs, and infection monitoring. Consequently, the

administration of these agents still remains mostly limited outside of academic and large community based practices. On the other hand, bela-maf provides a highly effective, off-the-shelf option with no risk of CRS and ICANs that will allow patients access to a highly effective BCMA-targeted therapy who otherwise may not be candidates for CART T or bispecifics due to geography, frailty, patient preference, or other reasons.

In summary, I want to reiterate the three points I discussed: efficacy, safety, and access. While it may sound cliche, the reality is that one size doesn't fit all for myeloma patients when it comes to treatment. The addition of belantamab mafodotin, which has shown overall survival benefit, to the myeloma therapeutic armamentarium will provide broad and critical access to an off-the-shelf, BCMA-targeted option for patients with multiple myeloma. Thank you.

DR. VASAN: Thank you. That was perfectly four minutes.

Speaker number 10, please unmute yourself

and turn on your webcam. Please introduce yourself. Please state your name and any organization you are representing, for the record. You have four minutes.

DR. BERDEJA: Good morning, and thank you for allowing me to address the committee. My name is Dr. Jesus Berdeja. I'm here representing myself and not being compensated for my testimony. I am a clinical researcher, and I work with most pharmaceutical companies working in myeloma, including the sponsor. I'm the Director of Multiple Myeloma Research at the Greco-Hainsworth Tennessee Oncology.

Tennessee Oncology is a large, greater than 100 physician practice that cares for over half of cancer patients in Middle and East Tennessee. We are a sophisticated practice that can provide state-of-the-art research and standard of care treatment such as CAR T therapy. Unfortunately, not all therapies are readily available in all of our clinics, and as a result, many of our patients may need to travel long distances, often

4 to 5 hours to reach us.

My personal practice solely focuses on seeing patients with multiple myeloma. In my opinion, in a patient who has been exposed to a proteasome inhibitor, an IMiD, and an anti-CD38 antibody, the optimal next line of treatment should be a BCMA-directed therapy. Most patients will be triple-class exposed, possibly refractory as early as in their second line of treatment, and currently the only BCMA-directed therapy approved in this setting is CAR T.

Unfortunately, as you know and have heard, CAR T is a treatment that for many reasons is currently only available to a small minority of the patients that could benefit. Many patients live too far from specialty centers, they lack sufficient caregiver support, and they're unable to drive or just too frail. And this is just to name a few roadblocks to logistically complicated therapies such as CAR T. Thus, introducing another effective and accessible BCMA-directed therapy into this space would be of significant benefit to a

population in great need.

The DREAMM-7 and DREAMM-8 studies were head-to-head triplet versus triplet comparisons that showed impressive progression-free survival and overall survival benefit favoring the belantamab combinations, even against an anti-CD38-containing triple regimen. I truly believe these data show that belantamab mafodotin combinations can help fill an unmet need.

I am equally impressed by the relatively good tolerance of belantamab mafodotin. Except for the potential ocular toxicity, there's very little other toxicity, and patients often tell me they feel like they are not on any treatment. And patients who do develop ocular toxicity, most do very well, often are asymptomatic, and the symptoms they do develop are invariably reversible with dose adjustments or holds, with the assistance of readily available optometrists and ophthalmologists. And when I say readily available, unlike in academic centers in the community, they are very readily available, and I

have many patients that have come back with business cards from their eyecare providers to consider sending other patients to them.

In summary, belantamab mafodotin is an effective, manageable, patient-centered therapy that can be easily given in the community in both rural and urban settings. That means we could be able to bring an effective therapy to patients where they live rather than ask patients and their caregivers to travel as required for other BCMA-directed standard therapies.

I urge you to vote in favor of the benefit-risk profile of the belantamab mafodotin combinations. It's an effective drug with manageable and a reversible side effect profile that would allow therapy to come to the patient and not vice versa. And with that, I'd like to thank you for your attention and for listening.

DR. VASAN: Thank you.

Speaker number 11, please unmute and turn on your webcam. Please begin and introduce yourself, and state your name and any organization you're

representing, for the record. You have four minutes.

(No response.)

DR. VASAN: Speaker number 11?

MS. KEOGHAN: I apologize.

Good morning. My name is Kathleen Keoghan. I'm from Alger Island. I'm age 69 and a multiple myeloma patient. I have no relationship with any hospital, medical facility, biomedical research place, or facility of any kind or anyone who's employed there, and I'm not being compensated for this testimony.

I was diagnosed 16 years ago with kappa light chain myeloma. Prior to my retirement, I raised four children with my husband and worked with special needs students. Upon my initial diagnosis, I received radiation and my first regimen of Thalomid, bortezomib, and dexamethasone. Following a stem cell transplant in February of 2010, I went on a maintenance therapy of a daily dose of Revlimid, and it was successful at keeping the myeloma at bay for 12 years.

When I relapsed several years ago, my team and I decided on a trial with a medication related to Revlimid, but that trial and a subsequent one in a similar vein were unsuccessful. My team then suggested either CAR T-cell therapy or the trial with belantamab mafodotin, bortezomib, dexamethasone, and Pomalyst. The initial difficulties associated with CAR T-cell therapy -- the hospitalizations, et cetera -- were very daunting for me, as I was caring for my elderly mother.

The belantamab trial seemed a better fit for me at the time, considering all the possible side effects and the potential issues with each course of treatment; and the restriction of being within shouting distance of the hospital, less than 30 minutes away after a discharge with CAR T-cell therapy, was not an option for me. The belantamab trial began in August 2023, and my kappa light chain numbers dropped significantly, and by late September and October, my numbers had settled in to 3 to 4 milligrams per liter and have remained there

ever since.

The treatment never comes without a cost, and with this combination of drugs -- the belantamab, the bortezomib, and the dex and Pomalyst -- I've experienced some slight anemia, some minor fatigue, and the occasional diarrhea for which I watch my diet and take Imodium as needed. Also, I am impacted by the dryness, especially to my cornea, which do impact my vision to a degree, as they cause fuzziness depending on where the patches occur. It becomes most noticeable, at least to me, by the end of the first week after treatment, slowly clearing over time. The dry patches can be mitigated using lubricating eye drops. It has not prevented me from reading, from watching TV, or any of my other daily activities.

My ophthalmologist has found that delaying treatment for one or two cycles improves the situation. Foregoing belantamab for this amount of time has not impacted how well this medication works on my myeloma numbers, and that is very impressive. I have not experienced any other side

effects from receiving belantamab. Infusions have gone smoothly and without incident right from the start.

It's not an easy thing to navigate treatment options, but having a medical team that fully includes you in all aspects of your treatment program, giving you complete information in layman's terms so that as a patient you can make the choices that suit you best and to be supportive in those choices, is priceless. I'm very thankful to have such a team and to have this treatment of belantamab available that is so successful for me, easy to tolerate, and it allows me to live my life on my terms. I'm very grateful that the FDA is considering this, and I do hope they allow it to go forward. Thank you so much for the opportunity to share my story.

DR. VASAN: Thank you for your testimony.

Speaker number 12, please unmute yourself and turn on your webcam. Will speaker number 12 begin and introduce yourself? Please state your name and any organization you are representing, for

the record. You have four minutes.

MS. GALLEGOS: Good morning. My name is Jane Gallegos. Before I tell you about my journey, it's important that you know that I do not have a relationship to the sponsor or competitors, and I'm not being compensated in any way. The reason I volunteered to speak will be made clear.

The year was 2019, excruciating back pain, compression fractures, and a bone marrow biopsy confirmed what I dreaded, multiple myeloma. Seven years earlier, a blood test showing an elevated M spike led me to a local oncologist; diagnosis, MGUS. I followed up with the oncologist regularly through those seven years. Once the myeloma diagnosis was confirmed, I was given six different chemo cocktails over a three-year period, along with radiation treatments and a failed stem cell transplant in between.

After the sixth chemo failed, the oncologist took my hand and said, "I'm sorry, but there's nothing more that I can do for you." He suggested that I see a myeloma specialist, Joseph Mikhael, at

the Research Institute in Scottsdale. We met, and I was enrolled in a trial; however, the kappa light chain rose even higher. I believe it was nearing 15,000. I was receiving weekly blood transfusions and became exceedingly weak. Dr. Mikhael and his team met with me, along with my husband, and said that he had one more drug to try. He explained the possible side effects, including cysts on the corneas. This drug was called Blenrep. He said if this didn't work, I could be gone in a matter of weeks.

I will never forget the genuine care and kindness that he showed to us that day. My husband began making arrangements, and I started giving personal items away. We were preparing for my death. The results were nothing short of miraculous. The myeloma did not like this drug. That was three years ago. I do get infusions of Blenrep and gamma globulin from time to time as a preventative measure, although there is no sign of cancer in the blood work or the PET scans.

The cysts do cause blurred vision, but there

is no pain, and Christmas lighting is magnificent. I do use preservative-free eye drops several times a day, which helps tremendously. I can still read on my iPad because I can enlarge the font. I still drive. When it's difficult to see street signs from a distance, I use the GPS for direction. The cornea specialist I see regularly said there is no permanent damage to my eyes from this drug. Are the cysts annoying? Yes, but the trade-off is worth it. I am still here enjoying the second chance of life that I have been given. Thank you.

DR. VASAN: Thank you.

Speaker number 13, please step up to the podium and introduce yourself. Please state your name and any organization you are representing, for the record. You have four minutes.

DR. ZUCKERMAN: Thank you, and can you put my slides up, please?

Hi. I'm Dr. Diana Zuckerman. I'm president of the National Center for Health Research, and thanks for the opportunity to speak today. Our center is a non-profit think-tank that focuses on

safety and effectiveness of medical products, and we do not accept funding from companies that make those products or have a financial interest in them. My perspective is as a cancer survivor who's trained in epidemiology and public health and who held research positions at Yale and Harvard before coming to DC to work in the U.S. Congress, HHS, the White House, and as president of this research center. On a personal and professional level, I understand the importance of today's meeting, and I thank you for your service.

To consider whether the benefits outweigh the risks, it's important to think about who was studied in the research. Fewer than 5 percent were U.S. patients. Why is that? And I especially want to thank Dr. Pazdur for his comments on that. Five percent and 0 percent were black, and that's only 12 people. That's more important than the percentage. The fact that there were so few, you cannot generalize from those data. Patients over 75 were also very underrepresented, much fewer than half of the percentage that's typical and, again,

too few to really generalize.

Under these circumstances, would the treatment not be approved for black people or would it be approved only for white people under 75? Of course not. Nobody would want that.

There are other flaws in the study. The comparator arm in DREAMM-8 is not an approved regimen in the United States. There are other treatments. And I want to just say I agree with the FDA statement that it's a problem that half the patients had only one previous treatment, so other and better options might have been available to them; and also just to say that the lower dosage, due to poor tolerability, is also a major problem. So how can FDA approve it for the dosages in the indication when those weren't followed?

I just want to say I've attended hundreds of FDA advisory committee meetings, sadly, but I've never seen such a serious side effect as ocular toxicity that actually affects most of the patients. And blurred vision can certainly be very debilitating and very risky for the people who have

it, and I wonder why it is that we didn't hear from those patients who've been harmed today.

As you've heard, ocular toxicity may be asymptomatic at first, and that is especially dangerous because then it continues, it won't be diagnosed early enough, and it may not be reversible. And in the real world, of course, toxicity monitoring will not be as careful as in a clinical trial, and for those same patients that may not have access to CAR T, they may not have access to the kind of monitoring that they would need for that.

In conclusion, although this drug has benefits, are they enough to outweigh the risks? The primary endpoint has been met, but it's compared to an unapproved treatment in DREAMM-8 and not to optimal treatments in DREAMM-7. Overall survival is an unknown, really. We only have one study, and given all these risks; and the small number of U.S. patients; and the underrepresentation of Blacks and older patients; and the fact that other effective treatment options

are available, can patients be adequately informed of benefits and risks if this treatment is approved, especially given that the data are primarily based on one study? Thank you very much.

DR. VASAN: Thank you.

Speaker number 14, please unmute yourself and turn on your webcam. Please introduce yourself and state your name and any organization you are representing, for the record. You have four minutes.

(No response.)

DR. VASAN: Speaker number 14?

(No response.)

DR. VASAN: Speaker number 14, are you there?

(No response.)

DR. VASAN: Can you unmute yourself, please?

MR. CACCIOPPOLI: Yes. Can you hear me?

DR. VASAN: Yes.

MR. CACCIOPPOLI: I am a patient. I have no conflict of interest. My name is Frank --

DR. VASAN: Sorry. Can you please state

your name, for the record?

MR. CACCIOPPOLI: My name is Frank Caccioppoli. Good morning. I am here today not just as a patient, but as someone whose life was saved by Blenrep. I'm speaking to you as a living example of how crucial this treatment is, not just for me, but for many others like me fighting multiple myeloma.

I've been battling this cancer for over five years when Blenrep was introduced to me. I had already been through chemotherapy and two stem cell transplants. I was running out of options. My doctors asked me if I wanted to try this new treatment that had been just approved by the FDA. I said yes. I didn't have many choices left. At the time, I was told it might work or might not, but I was willing to take the risk, even knowing it could affect my eyes, which is dryness and blurred vision, which I can handle. I was one of the first patients to receive Blenrep. I felt like a guinea pig, so to speak, back in 2020, and here I am today speaking with the panel. Let me explain just the

difference this treatment made in my life.

Before Blenrep, I was barely able to function, couldn't walk, couldn't drive. I relied on others for rides. I had gone through radiation; I was told that it didn't respond. I might not make it much longer, I was told. I was suffering deeply, physically and emotionally. I had tried so many treatments and nothing held my cancer down. Multiple myeloma kept coming back, attacking a different part of my body each time, but then came Blenrep. With the grace of God and the power of the treatment, something finally clicked.

Today, my cancer is stable. I go for PET scans every 4 to 5 months, and every time they show no major progression. It's under control. I have an MRI every 6 months for lesions; now, it's once a year. That's a drastic improvement. Yes, the treatment has side effects, which I mentioned, the eyes. I take steroids like dexamethasone. Yes, there were tough days, but Blenrep worked, and not just in numbers. It gave me my quality of life back.

This treatment allowed me to look back and see how far I've come from barely able to stand, to walking again; from mentally and emotionally drained, to hopeful and engaged with my life. When the treatment was suspended temporarily, it was terrifying, not just for me, but for many others relying on it.

Please understand, this isn't a clinical statistical report. This is my life, and others. This is the life of someone who had no other options and is still here today because of this treatment. The science behind Blenrep matters, but so does the story of those it saves. Mine is just one. I ask you today, please keep this treatment available for me and for others. I'm praying, and I hope you will stand with patients like me and others. Thank you.

Questions to the Committee and Discussion

DR. VASAN: Thank you.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. I think in the

interest of time, and no other clarifying questions that have been made to attention for me, we will move on.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments. We will turn to the FDA for further instructions.

DR. GORMLEY: We wanted the committee to have a discussion of the discussion question regarding the dose and whether or not that's been appropriately characterized for this product. So we wanted you to have the discussion, and then we thought it was wise to have both of the votes. And then after you've voted, though there are two voting questions, have the discussion together for both products.

DR. VASAN: Thank you.

We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees

may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording.

We will proceed with our first question, which is a discussion question. Discuss whether appropriate dosages of belantamab mafodotin have been identified for the proposed relapsed/refractory population.

Are there any questions or comments about the wording of the question?

(No response.)

DR. VASAN: Alright. We will now open the question to discussion.

Dr. Madan?

DR. MADAN: Ravi Madan, National Cancer Institute. I think the question of dosing is difficult across any therapeutic development. I'm not a multiple myeloma doctor, but I would argue that probably across oncology, we have suboptimal dosing, understanding, and strategies for a lot of our treatments. So I think it's really the unique

toxicity here that adds some gravity to this question.

I think it's easy to criticize the dosing strategy, but I actually think it's not that different than a lot of other dosing we have across other therapeutic developments. I think it's important to at least contextualize that for this conversation. That's all, the end of my statement.

DR. VASAN: Any other comments?

Dr. Spratt?

DR. SPRATT: Thank you. Dan Spratt, UH Seidman Cancer Center, Case Western Reserve University. I saved these comments for here because they're not really questions. If you could pull up slide CO-26, and then I'll be showing slide 23.

Effectively, they showed in two trials, you pick the median PFS somewhere around 33 to 36 months. That's what's in slide 26, as you guys can see here with the experimental arms. Then if you just go back to CO-23, just back a few slides, this is from the applicant, so I'll say this is

favorable. I'm not pulling up the FDA's analysis, but if you look here, obviously, we're not seeing anywhere near 48 months. We're not seeing, really, even 38 months. You're seeing somewhere between what would be the Q8 dosing and Q6 dosing, what was observed. So this is really what patients were able to even tolerate.

I don't know if you're able to pull up from the briefing document table 29 from the FDA. It's a big table. But when I look at this, again, knowing there were not enough patients in these dosing studies, it seems to me, again knowing these are variable endpoints and limited sample size, that you get about 90 percent of the benefit if you go to a dose of 1.9 Q6 to Q8 weeks, or maybe the 2.5 at a longer interval, while halving, cutting in half, the grade 3-4 ocular events.

So it is troubling because there's no question, hearing from the patients, seeing the data, that there is clear benefit or efficacy of this therapy. But at the same token, if you could cut that toxicity by a meaningful amount, the

patients that just spoke, maybe they wouldn't have to do all the things they're doing and not being able to see street signs.

This is the table here. It is a little troubling. Again, the enrollment is the enrollment, but it is really disappointing. And I think the fact we're still allowing drugs to gain approval with less than 5 percent U.S. enrollment just because that's what it is, I think if it was mandated, I think you'd find that enrollment to be different.

I just don't know. I tried finding anywhere in these documents black patients. There is a higher incidence of diabetes. Patients with diabetes were allowed on this trial. Is there any crosstalk in complications? Again, there just won't be enough patients to analyze any of these things, so there are just major limitations. But I believe the drug is efficacious. I don't believe the dose they chose is the optimal dose based on the data we have. Thank you.

DR. VASAN: Thank you.

I'll make a comment piggybacking on Dr. Spratt. The word of this discussion question is discuss whether appropriate dosages have been identified, and I think that they have been. It's just that it was in these earlier phase trials. It was in ALGONQUIN. It was testing these fewer frequencies. And I think that in some ways it's borne out in the trial design even because DREAMM-8 allowed for this 2.5 starting dose, then going down to 1.9 . It's almost baked into these clinical decisions and the strategies that GSK would have decided when conceptualizing these trials.

So I just think this was a real missed opportunity because there could have been more dose exploration in those early phase trials, or there could have even been a third arm added to one of these trials looking at lower dosages; and, certainly, that approach we have seen in many clinical trials across all cancer types, where AEs are an issue.

I agree that I don't know what to make of the fact that we have this very, very low

population of American patients. As one of the audience members pointed out, that could trickle down into the fact that maybe this patient population, if there were more American patients, there would have been more older patients, there would have been more black patients, there would have been more patients who perhaps would have answered those PRO questions differently about driving. America's a big country. People drive. So it would have skewed the patient population, I think, so it makes it just very hard to interpret.

But I just want to reiterate, I feel this was a really missed opportunity for a drug that we also knew had a lot of toxicity from the earlier experiences with belantamab and accelerated approval. Thank you.

Next, Dr. Conaway?

DR. CONAWAY: Mark Conaway, University of Virginia. In answer to the question, have appropriate dosages been identified, I think yes. The problem is we don't know which one. I think too many doses have been perhaps identified; and I

think, yes, there is some missed opportunity here for having explored doses that may have given very similar efficacy at a lower adverse event rate.

I think it's really difficult to evaluate the dosages given that it's such a moving target. And I appreciate that that's done often in the clinical setting, that doses are adjusted, but from a policy, or for evaluating a drug, it's very difficult to know what the appropriate dose is when it seems like every patient gets a different regimen of doses.

DR. VASAN: Thank you.

Dr. Frenkl?

DR. FRENKL: I guess my comment is that I agree with Dr. Madan that I think that this program is kind of very typical, if not even a little bit more expansive in that there are -- I think they mentioned -- 400 patients that were included in this. For me, it also depends on whether you're looking at the very good PR and above, which the meta-analyses, and we heard from our expert, have shown is actually more predictive of PFS and OS

than ORR. So if we believe that, I think that the data that was presented actually clearly shows that the higher dosing is needed to achieve those rates.

So, for me, there's less of a question with that. And I think most of the patients in the study did get the higher dose in that first cycle, so even the simulations can't really predict what would happen without that. So what was that impact of that higher dose, which, again, to me, in these dose-ranging studies, is pretty clear.

DR. VASAN: Thank you.

Dr. Nowakowski?

DR. NOWAKOWSKI: Thank you. I think putting this question in a context of efficacy and applicability to the U.S. population is also very important, which was already brought here several times. I understand there was no biological, maybe, differences between ethnic origins, but nevertheless, there are differences in geographical access to different therapies where the study was conducted and, unfortunately, DREAMM-7 and 8 do not have significant enough U.S. representation to

conclude in this regard.

Now, the second issue is obviously toxicity, and if you have toxicity like this, you really have two ways to mitigate this. One is to better optimize upfront, and this looks to me like a missed opportunity here, or mitigate with subsequent dose interruptions and dose reductions with careful ophthalmological follow-up, which was applied here in a drug development program. The problem with the second approach, it does require significant monitoring, and it does result in potentially higher toxicity than normally would be expected if a better optimization was done upfront.

I think the theme, which we've heard here from several speakers, including key opinion leaders, was that this is the therapy which potentially would be able to cross the boundaries to more a community rather than being reserved to their tertiary centers, but those are exactly the same patients in the rural areas and the community which actually do struggle with access to careful ophthalmological examination. In fact, one of our

problems in my current role as deputy for clinical research is to provide patients on clinical trials access to those timely ophthalmological examinations, and in the community, we're trying to decentralize some of those trials. That basically provides an additional level of complexity for monitoring those patients in real time and try to mitigate with the dose reductions and interruptions.

I guess my underlying question here, and maybe Dr. Boyd could comment on that, is I'm trying to think about the worst-case scenario, and if somebody doesn't have access to opthalmological care on a routine basis, or some of those appointments aren't kept for different reasons, what would happen with the natural history of those? If this was not caught early on by opthalmological examination and the vision had worsened, how reversible would it be in the long term? And I know we may not be in a position to answer it because there's no significant data, but I'm curious about natural history without

interruption.

DR. BOYD: This is Bill Boyd from the FDA. Speaking in a really general sense, you're looking at this progression of the corneal cysts and their confluence, et cetera. If you had a patient who was not evaluated by an eyecare professional but somehow they continued to get medication, presumably that could worsen to the point that they could develop a denuding of the epithelium and possibly a corneal ulcer and perforation.

The situation that's been set up where the dosing should be managed by the ophthalmic evaluation should prevent that, but I know in the real world that's difficult. You're looking at a situation like that, that, also, by the time you reach that point, I presume that patient would be symptomatic, and they are more likely to seek care. But that's the type of situation you're looking at. And I know that's not common and was not seen in the trial, but that's the best-case scenario.

DR. ABDULLAH: If I could just highlight, first, across both DREAMM-7 and DREAMM-8, we had

actually conducted more than 7500 ocular exams. We also have a risk mitigation strategy in place as well, too, that per the label, of course, we'll have prespecified ocular exams taking place before each dose is administered; so again, and as clinically indicated, of course, as well, too.

I'd actually like to call on Dr. Afshari to provide some additional context to address your question specifically.

DR. VASAN: The question is about these repeated events, not about the safety that's in place to monitor these events, but the natural history of the repeated events themselves.

DR. AFSHARI: Thank you.

Because corneal epithelium regenerates, even when we don't see these patients, they actually get better on their own because often when we see them, we actually don't do much. We just are grading, and they are taking their artificial tears. Also, just to point out, seeing these patients is actually pretty simple because all we need is just the very front of the eye exam. We don't need the

dilated exam that you and I go for on our annual eye exam. It's just the quick minute of the slit-lamp examination of the very front of the eye.

Also, your question, would repeated offense to the corneal epithelium in these patients cause a problem, we have not seen that repeated microcysts cause a problem in these patients. As you know, the data of GSK showed there was just one patient that had a corneal infection. Thank you.

DR. VASAN: Alright.

Are there any other questions from the advisory committee?

Dr. Boyd?

DR. BOYD: Just quickly. This is Bill Boyd. I think you were asking the question of whether these repeated insults build. I think the answer to that, it's not clear. They're supposed to be evaluated in a real-world scenario where the drug is not held or stopped. I could perceive that as building. The cornea does regenerate, but if you have continued damage without the opportunity to resolve, I can see that leading to problems.

DR. NOWAKOWSKI: That's exactly the scenario. So without examination and early stopping, what would happen with repeated exposure? Thank you.

DR. AFSHARI: May I make a --

DR. VASAN: I think we've answered the question.

Dr. Spratt?

DR. SPRATT: Thank you. Dan Spratt. UH Seidman, Case Western. I don't know if it's so much as a disagreement with what Dr. Frenkl said, but I guess the question is, is this really normal, what she and Dr. Madan said? Again, I'm not a myeloma expert, but looking across different drug approvals in this space, from the monoclonal antibodies to proteasome inhibitors, et cetera, what I'm seeing here is 13, 25, 30 percent dose interruptions or dose skipping. We're talking 70-80 percent, and this drug regimen that we're discussing today, we're talking double, triple, quadruple, and it's very early on.

So I guess from people on the panel -- and I

apologize that I don't have your name right in front of me, the invited experts, Dr. Nowakowski -- how common is this that you guys are seeing with these drugs and classes in general so early on? This seems like an outlier to me, or is this not?

DR. NOWAKOWSKI: Yes. I think from my own experience with hematological malignancies, we frequently see some of those interruptions with regimens, probably not to the degree which we had seen in this study. And I think the key difference is the severity and potential for toxicity, typically interruptions which we see are due to reversible hematological toxicities or some other toxicities, not necessarily the ocular toxicity which we had seen here. So this is a new element which we see with antibody drug conjugates in general, but particularly in this situation, myeloma, in a very high frequency.

I don't know if the FDA -- again, looking at the other FDA-approved regimens in this space -- if you guys can put this in context for us; and it

goes to the question we have here.

DR. KANAPURU: Yes. Bindu Kanapuru from the FDA. This is a very high rate of dose modifications that we are seeing with this particular application. So yes, this is definitely higher than what we have generally seen.

But I also just wanted to point out that we are not always beholden to what we did in the past, and I think, really, here, there's been a lot more interest in having adequate dose optimization. Again, this development has been ongoing for a long time. They've been informed repeatedly that dose optimization and having an adequate dose, and risk of ocular toxicity. I do agree with most of what the panel members say, that this is truly a missed opportunity. We don't have adequate information to say that a lower dose would not be equally efficacious and that there would be a better safety profile. So I think this is really setting us back by multiple years, and we should try to move forward. Thanks.

DR. VASAN: Dr. Madan?

DR. SPRATT: Real quick.

DR. VASAN: I'm sorry, Dr. Spratt. I cut you off.

DR. SPRATT: Yes. So what is the reason that was given? I guess, really, we're focused to the FDA. To the FDA, what is the reason that was given when you recommended further dose finding and they chose to just proceed with the dose? What was the reason they gave you?

DR. GORMLEY: This is Nicole Gormley. I think it was clearly highlighted in Dr. Baines' presentation that multiple times the dosing was brought up. And oftentimes, there was discussion regarding many of the principles outlined by the sponsor here today, that there's greater efficacy when you initially dose, and we don't want to lose that efficacy. And we wholeheartedly understand and appreciate that there is a balance of maintaining efficacy, but trying to improve tolerability.

I think the issue was just that there was not exploration done at lower doses. Even before,

and going back many years, like to 2019, when for these studies it was recommended explicitly that you should evaluate more patients at the lower cohorts because there's not confidence in the dose, and it just wasn't done.

DR. VASAN: Yes. Could GSK please respond?

DR. SPRATT: Thank you.

DR. ABDULLAH: Dr. Spratt, I would say that we explored all of these different doses and schedules, for a reason, across 400 patients. We've done a randomized study, the DREAMM-14 study, which was a postmarketing commitment, with 40 patients per arm exploring different doses and different schedules. So I think we've actually, certainly, continued to listen to the FDA feedback and input, taking them on board, and conducted the appropriate, at least, dose exploration work.

As you probably saw from our analyses, certainly, like I said, exposure-response, we see a steeper curve with the exposure-response analyses relative to key ocular parameters and exposure safety. And you need that depth of response to

decrease the disease burden initially, and then the dose modifications begin, and then you're able to stretch out the schedule and decrease the dose as well.

I'd actually like to just call on Dr. Paul Richardson to also contextualize the rate of these dose modifications relative to other agents in the multiple myeloma space, given his expertise in this area.

DR. VASAN: I'm sorry. The question was about -- was your question answered already, Dr. Spratt?

DR. SPRATT: Yes. I didn't actually ask the applicant a question. Thank you so much. I really appreciate it. That's helpful.

DR. VASAN: Thank you.

Dr. Madan?

DR. MADAN: Just for discussion purposes, I would say that it's probably hard to compare this toxicity profile to other drugs, even in the myeloma space, but even in the oncology clinic. I know ADCs are coming on board and we're seeing this

more, but certainly it sounds like in the myeloma space, this is pretty unique toxicity, the ocular findings. People coming with vision changes, you're probably more apt to react than if they have nausea, which every patient probably, unfortunately, has to some degree.

So the thresholds for discontinuation and dose modification might be a little different. Again, it's not a perfect understanding of all this stuff, but I do think that we're kind of in a new frontier with this toxicity, and it's probably impacted some of the data we're viewing today.

DR. VASAN: Neil Vasan. One thing to add is that I think both the FDA and the applicant, rightly acknowledging this is a new toxicity, at a previous ODAC, Dr. Gormley used the phrase "new territory." The fact that this new grading scale was developed in the first place, I think this is very helpful for us today. It's going to be very helpful for the future for other studies with belantamab. It will also be helpful for other ADCs as well.

So I do applaud, from a very broad macroscopic view, this approach where when a new toxicity at this degree is identified, that everyone is seeking to characterize it in the most rigorous way possible.

Mr. DeFlice?

DR. DeFLICE: Yes. I think this is a new class of drug with a unique toxicity. In patients with very serious disease that's been through many therapies, with the attention given to this toxicity by the ophthalmologists, I think even now on social media, ophthalmologists are commenting on this drug and this therapy.

So I think that providing this drug for this unique group of myeloma patients, like I say, it's totally a new class of drug. There are side effects with CAR T that have been developed and are addressed, and with bispecifics, now they give immunoglobulin now to people getting bispecifics. So I think, likewise, with this therapy, the attention to eye disease, I think that's something that should just be accepted with this therapy.

I mean, we all know on television about eye diseases. Macular degeneration, the commercials are just amazing right now. There are three different drugs that are advertised on TV for macular degeneration, so there's a sensitivity for eye disease, and there's no difficulty for getting patients in if they have macular degeneration, which is not a reversible disease. So I think looking at this very minor detail of eye effect that is reversible should not limit the use of this drug that has a great potential to help so many patients, as we've heard today.

DR. VASAN: Dr. Beringer?

DR. BERINGER: Yes. I just want to comment that I think the risk mitigation strategy is a good approach to manage adverse effects, but when it's happening that almost all the patients have to go through a risk mitigation strategy, it's more common than what should be for a drug, where you should have a clear dose-response relationship.

So I think it would have been beneficial to have more information on the lower dosing and, in

particular, have some information about what the concentrations are that are effective and reduce risk for toxicity. It seems to be a narrow therapeutic index drug.

DR. VASAN: Mr. DeFlice?

DR. DeFLICE: Yes. I was on Revlimid, and we went through REMS. Every time I got my prescription, I went through REMS, and I could not get my prescription without going through REMS. So it would be the same thing with this drug, is that you'd go through REMS and qualify for your next dose. So I don't think that was an issue. For 15 years, I had to go through and answer specific questions on the computer regarding my therapy with lenalidomide, so I don't see this as a hindrance for the use of this drug that may be so effective.

DR. VASAN: Alright. Are there any other comments?

Dr. Frenkl?

DR. FRENKL: I think it was, essentially, just made, but it was just that we're really focusing on the eye toxicity, but to take a step

back and put it in the context of the resolution of the disease symptoms that patients had, it will be really important.

DR. VASAN: So I will sum up this discussion. I think there are a lot of points of view that have been brought up in this discussion. I think, clearly, this is a very active compound and, clearly, it is an an effective compound from the clinical trial data. But balanced with that is this extremely high toxicity signal, a unique toxicity that we're still grappling with how to view it. Do we view it in the same way as other toxicities? There's a new grading system that was developed. As Dr. Frenkl and Dr. Madan pointed out, is this sort of par for the course for what we see with other drugs or other ADCs?

There was acknowledgement that this really was a missed opportunity -- I think at multiple levels -- from conversations years back when this drug was first developed; a missed opportunity from the initial phase 1 data to explore all dosages; a missed opportunity at the phase 3 level to perhaps

explore more dosages at the RCT level.

There was some discussion about real-world tolerability and how this would deploy in the real world. On one hand, we have some acknowledgement that there are different toxicities with CAR T cells and with other products in the space, but those risks really face rural patients in similar ways perhaps with this drug, where you would need a much more regimented ophthalmologic follow-up, which may or may not be accessible by everyone in this country. That was also balanced by the fact that there were a very, very small number of North American patients enrolled in this trial. So I think we've heard a lot of differing interpretations as well of this data, but then also some shared interpretations.

Alright. If there are no further questions, we will now move to our next question, question 2, which is a voting question. The voting question, is the overall benefit-risk of belantamab mafodotin in combination with bortezomib and dexamethasone favorable at the proposed dosage in the proposed

patient population?

Is there any question about the wording of the vote?

(No response.)

DR. VASAN: Alright.

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

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Then we'll have the second voting question, and then everyone will state their name and vote into the record.

I'm sorry. Dr. Nowakowski, do you have a question?

DR. NOWAKOWSKI: Yes. I'm sorry. Just a

quick clarifying question to FDA in the context of this question.

Let's say in the postmarketing environment, what is your ability to require additional dose optimizations or conduct of the studies with adequate U.S. presentation?

DR. GORMLEY: So that was an issue that Dr. Baines tried to address in her presentation, and I believe perhaps also Dr. Telaraja. Really, we found that there are a lot of challenges with conducting further dose optimization after approval. We've even had a lot of postmarketing commitments that are done for dosing, and we've had a lot of postmarketing commitments that have been done to improve the U.S. representation, and oftentimes, there are a lot of challenges that are associated with those trials in that, oftentimes, there may not be the interest from centers in the U.S. in participating and competition for other trials that may be ongoing with other therapeutics.

Oftentimes, the data that we acquire in those populations, it's single-arm data, so it's

not randomized. And it's hard to extrapolate what was found with the registrational pivotal trial and if that's really able to be extrapolated to the single-arm data with either a U.S. population or a different dose.

So it's really challenging to get additional information on either of those issues in the post-approval setting. So it's one of the main reasons why we emphasize trying to get that information prior to approval; not to mention, additionally, if you don't have the right dose upfront, you're exposing a lot of patients to an incorrect dose before you would even get that information, which is then hard to interpret and often challenging to conduct.

DR. NOWAKOWSKI: And if those commitments are not fulfilled for different reasons with difficulties you describe, do you currently have a mechanism to actually withdraw their license?

DR. GORMLEY: No. Those are postmarketing commitments; they aren't postmarketing requirements. Postmarketing requirements can be

issued for a product, for example, that has accelerated approval and there's a postmarketing requirement for a confirmatory trial to verify the benefit. Those are required, and there are mechanisms to ensure that those are done. Those can also be done for safety findings. You can have a postmarketing requirement where there's a requirement to conduct the study.

Oftentimes, these are postmarketing commitments for representation of the U.S. patient population or for dosing, and those often are very challenging to do, and there's no regulatory authority to subsequently require them or have consequences if they aren't completed.

DR. NOWAKOWSKI: Thank you.

DR. VASAN: If there are no further questions or comments concerning the wording of the question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection,

the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

CDR BONNER: We'll have a five-minute break. This is LaToya, and we'll be right back. Thank you. We may be having some technical difficulties, so just five minutes. The time now is 12:31. We will start again at 12:36. Thank you.

(Whereupon, at 12:31 p.m., a recess was taken, and meeting resumed at 12:36 p.m.)

CDR BONNER: The time is 12:36. We're going to go ahead and proceed with the voting questions. We're going to re-vote again for question 2. The the voting box is blinking, and we can go ahead and place your vote. Thank you.

DR. SPRATT: Can you confirm you have my vote -- this is Dr. Spratt -- or do I need to email you?

CDR BONNER: Yes, Dr. Spratt. I have your vote, and I sent you a quick e-mail, too.

DR. SPRATT: Thank you.

CDR BONNER: Alright. Thank you.

(Voting.)

CDR BONNER: LaToya Bonner. For the record, for vote question number 2, we have 3 yeses, 5 noes, 0 abstain.

We'll go to the next voting question.

DR. VASAN: Question 3, is the overall benefit-risk of belantamab mafodotin in combination with pomalidomide and dexamethasone favorable at the proposed dosage in the proposed patient population?

Are there any issues with the wording of the voting question?

(No response.)

DR. VASAN: Alright. Please press the button on your microphone.

(Voting.)

CDR BONNER: LaToya Bonner. I'm still waiting for a vote from Dr. Spratt and Gradishar, if you can email me your votes, please.

DR. SPRATT: I have already emailed you.

CDR BONNER: Okay. Thank you.

DR. GRADISHAR: So did I.

CDR BONNER: LaToya Bonner again. For those in the room voting, can you please vote again and press a little harder? Thank you.

(Voting.)

CDR BONNER: LaToya Bonner. The voting results for vote question number 3: 1 yes, 7 noes, 0 abstain, for the record. Thank you. I will turn the floor over to the chair.

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

Dr. Madan?

DR. MADAN: Sure. Ravi Madan, National Cancer Institute. For question 1, with the combination with bortezomib, for a terminal disease, you have a PFS benefit and an overall survival advantage. The regulatory question of approval was not part of the scope of the question.

I'll leave that hard stuff to the FDA to figure out. It is concerning that there are so few U.S. accruals, but nonetheless, I did think that in the context of the disease state, an overall survival and a progression-free survival advantage, with a toxicity that's noteworthy but manageable to some degree, was worth, I think, the risk-benefit ratio so to speak.

Then, simply for the pomalidomide combination, it's PFS now. It's trending to OS, but it's a different dosing and a different combination, and it could have a different result, and I think more time will tell on that from my perspective. So to confirm, I voted yes on question 1 but no on question 2. Thank you.

DR. VASAN: Thank you.

Neil Vasan, NYU Langone. I voted no for question 2 and 3. This was a challenging decision because the efficacy data were strong, but the toxicity data were also very strong, and I took a textualist interpretation to this question. And I'd like to emphasize the words "at the proposed

dosage." This was, for me, what swayed the decision.

I said this before. I really think this was just a missed opportunity over the course of many years of development of this drug to explore these different dosages. We've heard impassioned testimonials from key opinion leaders, from many in the myeloma community, and many researchers as well. I think all of the building blocks are here to explore this question in the future from patients, to researchers, to physicians. But that was the rationale for why I voted no. Thank you.

DR. NOWAKOWSKI: Greg Nowakowski. I voted yes to the first question and no to the second one. This is probably one of the most difficult votes I've done as a member of this committee. I think on one hand, from a regulatory perspective, the whole drug development program probably made all the possible mistakes which could have happened, including the lack of U.S. representation in the pivotal studies and also the lack of the early dose optimization, which could avoid a lot of the

toxicity discussion which you had here.

On the other hand, I'm also a practicing hematologist, and the drug is clearly active. I think in the DREAMM-7 study, in addition to PFS benefit, there was some evidence of overall survival benefit and clearly some activity of this combination, which could be mitigated to some degree, although without reservations and worries, in a setting of careful ophthalmological follow-up and dose reductions or interruptions.

I voted no to the second question because in contrast to the first study, this did not necessarily translate to overall survival benefit as well. Also, the comparison arm would be less prone now or less pertinent in a changing landscape of treatment of multiple myeloma. So hence, I vote no for the second question.

DR. DeFLICE: I actually voted yes on the questions. I think they are the the wrong issues to be evaluated. Based on the clinical experience of the researchers and the testimonies that we've heard, this is an amazing drug, for an incurable

disease.

DR. BERINGER: Paul Beringer, USC, and I voted no for both questions. I think, for me, the relationship between what's the optimal dose for safety and efficacy still is not fully answered. I acknowledge the drug has significant effects on progression-free survival, and that weighs heavily. But the question is asked, do we have a safe and effective dose, and I think there needs to be more work done to do that.

DR. GRADISHAR: Bill Gradishar, Northwestern. I voted no times two. The rationale has already been stated by other folks. I don't think anybody's disputing the activity of the drug, but I think, as others have said numerous times, there was a missed opportunity to optimize dose schedule. And I think we're subjecting patients to a lot of side effects that perhaps could be mitigated with a more optimal dosing. So according to the letter of the question, the answer for me is no times two.

DR. CONAWAY: Mark Conaway, University of

Virginia. Just echoing what other panelists have said, how difficult this decision was based on the apparent efficacy and compelling testimony. But in the end, I voted no on both questions because of my concern about the percentage enrollment in the U.S., the relevance of the control groups and, of course, we've all talked about the safety of this drug at the proposed dose.

DR. VASAN: Dr. Spratt?

DR. SPRATT: Yes. This is Dan Spratt, UH Seidman, Case Western Reserve University. I voted no for both. Also, it is not my position to say whether this will be approved by the FDA, so I'm just voting based upon the verbiage in the question. It specifically states "in the proposed patient population."

As I've said before at this meeting, this is the United States FDA, so the proposed patient population is the United States patients. The clinical development program enrolled almost no patients in the United States, so it precludes any assessment of the benefit-risk profile in the U.S.

There are concerns that have already been raised that due to demographic representation, or treatment patterns, or other demographic information that are crucial to evaluate the safety and efficacy, it is disappointing that we have numerous internationally renowned experts that spoke on behalf of GSK, from Dana-Farber, from Emory, and there were people that spoke from Memorial Sloan Kettering.

So the fact that across these institutions alone, they can't enroll a few dozen patients is really disappointing to be able to, hopefully, get this drug optimized and available to patients in the U.S.

DR. VASAN: Before we adjourn, are there any last comments from the FDA?

DR. PAZDUR: Yes. I just want to echo our concerns in the agency about adequate U.S. enrollment in trials here; again, because if a drug is so good, patients should be enrolled in the United States on this. I think it's a question that has haunted us in the past. We see, across

the board over the years, about 20 percent in all international trials coming from the United States, and that's not increasing. If anything, it's decreasing.

So it's something that we're going to be paying more attention to in the United States. We'll have discussions with sponsors, and they will be continuing on two fronts: number one, what sites are being enrolled, and we want to have discussions with proposed enrollments at sites; and, in addition, another project that we're looking at is control arms. What are the control arms being used in studies to make sure that they are applicable to the U.S. population?

Remember, pharmaceutical companies are developing a drug worldwide, but also, they're coming to us for consideration. And many times, studies are not using adequate control arms -- and I'm not referencing this study, just in general -- and it really poses many problems about applicability to the United States.

It's not just about ethnic representation;

it's also about the applicability to the U.S. healthcare delivery system that I think is important for people to understand, especially when one has unique toxicities and something that hasn't been worked out before, how this really applies and how it would be conducted, not in major cancer centers, but in rural America, in underserved populations, et cetera.

So these are considerations that we have. We really want to use this forum, really, to highlight this.

Also, we want sponsors to really meet with us to discuss their sites that they're enrolling on, not only in the United States but worldwide, and also the control arms that are being done because we do have grave reservations about the applicability of studies when you have very, very small numbers of patients, almost a minuscule number of patients, being enrolled in the United States.

Adjournment

DR. VASAN: We will now adjourn the meeting.

Thank you all.

(Whereupon, at 12:54 p.m., the meeting was adjourned.)