FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)

Tuesday, July 14, 2020

9:02 a.m. to 4:12 p.m.

Virtual Meeting

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Yvette Waples, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Massimo Cristofanilli, MD, FACP

Associate Director of Translational Research and

Precision Medicine

Robert H. Lurie Comprehensive Cancer Center

Chicago, Illinois

Jorge A. Garcia, MD, FACP

Chair, Division of Solid Tumor Oncology

George and Edith Richman Distinguished Scientist Chair

Director, GU Oncology Program

University Hospitals Seidman Cancer Center

Case Comprehensive Cancer Center

Case Western Reserve University

Cleveland, Ohio

Susan Halabi, PhD

Professor of Biostatistics and Bioinformatics

Duke University Medical Center

Durham, North Carolina

Christian S. Hinrichs, MD

Investigator & Lasker Clinical Research Scholar

Experimental Transplantation and Immunology Branch

National Cancer Institute (NCI)

National Institutes of Health (NIH)

Bethesda, Maryland

Philip Hoffman, MD

(Chairperson)

Professor of Medicine

The University of Chicago

Section of Hematology/Oncology

Department of Medicine

Chicago, Illinois

David Mitchell

(Consumer Representative)

Founder, Patients for Affordable Drugs

Bethesda, Maryland

Anthony D. Sung, MD

Assistant Professor of Medicine

Duke University School of Medicine

Duke Adult Blood and Marrow Transplant Clinic

Durham, North Carolina

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBER

(Non-Voting)

Jonathan D. Cheng, MD

(Industry Representative)

Vice President and Oncology Therapeutic Area Head, Merck Research Laboratories, Oncology Clinical Research

North Wales, Pennsylvania

TEMPORARY MEMBERS (Voting)

James Chodosh, MD, MPH

Edith Ives Cogan Professor of Ophthalmology

Massachusetts Eye and Ear

Harvard Medical School

Boston, Massachusetts

John DeFlice, MD

(Patient Representative)

Albuquerque, New Mexico

Brad H. Feldman, MD

Assistant Professor of Ophthalmology

Wills Eye Hospital and Thomas Jefferson University

Philadelphia, Pennsylvania

Heidi D. Klepin, MD, MS

Professor of Internal Medicine

Section of Hematology and Oncology

Wake Forest University Health Sciences

Winston Salem, North Carolina

Grzegorz S. Nowakowski, MD

Assistant Professor of Medicine

Mayo Clinic Rochester

Rochester, Minnesota

Gita Thanarajasingam, MD

Consultant, Division of Hematology

Assistant Professor of Medicine

Mayo Clinic

Rochester, Minnesota

Thomas S. Uldrick, MD, MS

Deputy Head, Global Oncology

Associate Member, Vaccine and Infectious

Disease and Clinical Research Divisions

Fred Hutchinson Cancer Research Center

Associate Professor of Medicine

University of Washington

Seattle, Washington

FDA PARTICIPANTS (Non-Voting)

Richard Pazdur, MD

Director, Oncology Center of Excellence (OCE)

Acting Director, Office of Oncologic Disease (OOD)

Office of New Drugs (OND), CDER, FDA

Nicole Gormley, MD

Director (Acting)

Division of Hematologic Malignancies 2 (DHM2)

OOD, OND, CDER, FDA

Bindu Kanapuru, MD

Multiple Myeloma Team Lead (Acting)

DHM2, OOD, OND, CDER, FDA

Andrea Baines, MD, PhD

Clinical Reviewer

DHM2, OOD, OND, CDER, FDA

Wiley Chambers, MD

Director (Acting)

Division of Ophthalmology

Office of Specialty Medicine

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

(9:02 a.m.)

Call to Order

Introduction of Committee

DR. HOFFMAN: Good morning, and welcome. Thank you for taking some time from your best field day activities. I would first like to remind everyone to please mute your line when you are not speaking. For media and press, the FDA press contact is Nathan Arnold. His email address is nathan.arnold@fda.hhs.gov, and his phone number is 301-796-6248. My name is Philip Hoffman, and I will be chairing today's meeting.

I will now call today's meeting of the Oncologic Drugs Advisory Committee to order. We'll start by going down the meeting roster. When I call your name, please introduce yourself.

Dr. Cristofanilli?

DR. CRISTOFANILLI: Good morning. This is Dr. Massimo Cristofanilli from Northwestern University Medical Oncology in Chicago.

DR. HOFFMAN: Dr. Garcia?

(No response.)

DR. HOFFMAN: Dr. Garcia, can you unmute?

DR. GARCIA: Good morning. Jorge Garcia, chief, medical oncology, University Hospitals, Seidman Cancer Center, Case Western Reserve University, Cleveland, Ohio.

DR. HOFFMAN: Dr. Halabi?

(No response.)

DR. HOFFMAN: Dr. Halabi, can you unmute?

(No response.)

DR. HOFFMAN: Let's go to Dr. Hinrichs.

DR. HALABI: Good morning. This is Dr. Susan Halabi, Duke University.

DR. HOFFMAN: Dr. Hinrichs?

DR. HINRICHS: Christian Hinrichs, senior investigator, NCI, Bethesda, Maryland.

DR. HOFFMAN: Mr. Mitchell?

MR. MITCHELL: Yes. I'm David Mitchell. I'm the consumer representative. I am more importantly for this meeting a multiple myeloma patient.

DR. HOFFMAN: Dr. Sung?

DR. SUNG: Anthony Sung, Division of Hematologic Malignancies and Cellular Therapy, Duke University.

DR. HOFFMAN: Dr. Cheng?

DR. CHENG: Good morning. Jonathan Cheng. I'm the industry rep, and I work for Merck Pharmaceuticals.

DR. HOFFMAN: Dr. Chodosh?

DR. CHODOSH: Morning. Jim Chodosh, Mass Eye and Ear in Boston. I'm a corneal specialist.

DR. HOFFMAN: Dr. DeFlice?

(No response.)

DR. HOFFMAN: I don't see him on the line.

Dr. Feldman?

DR. FELDMAN: Good morning. I'm Brad Feldman. I'm an ophthalmologist and corneal specialist in Philadelphia at Wills Eye Hospital.

DR. HOFFMAN: Dr. Klepin?

(No response.)

DR. HOFFMAN: I will come back.

Dr. Nowakowski?

DR. KLEPIN: Sorry. I was muted. Good

morning. This is Heidi Klepin. I'm a geriatric oncologist at Wake Forest School of Medicine.

DR. HOFFMAN: Dr. Nowakowski?

DR. NOWAKOWSKI: Good morning. Greg Nowakowski. I'm a hematologist at Mayo Clinic, Rochester.

DR. HOFFMAN: Dr. Thanarajasingam?

DR. THANARAJASINGAM: Good morning. This is Gita Thanarajasingam, also a hematologist at Mayo Clinic, Rochester.

DR. HOFFMAN: Dr. Uldrick?

(No response.)

DR. HOFFMAN: Dr. Waples?

DR. WAPLES: Hi. Good morning. This is Yvette Waples as the DFO for the ODAC.

DR. HOFFMAN: Dr. Pazdur?

DR. PAZDUR: Hi. Rick Pazdur, director, Oncology Center of Excellence at the FDA.

DR. HOFFMAN: Dr. Gormley?

DR. GORMLEY: [Inaudible] -- division director for the Division of Hematologic Malignancies 2.

DR. HOFFMAN: Dr. Kanapuru?

DR. KANAPURU: Good morning. Bindu Kanapuru. I'm the multiple myeloma team lead, acting.

DR. HOFFMAN: Dr. Baines?

DR. BAINES: Good morning. This is Andrea Baines. I'm a hematologist with the Division of Hematologic Malignancies 2 at FDA.

DR. HOFFMAN: And Dr. Chambers?

DR. CHAMBERS: Good morning. This is Wiley Chambers. I'm an ophthalmologist. I'm the acting director of the Division of Ophthalmology in the Office of New Drugs, FDA.

DR. HOFFMAN: For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if

recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Dr. Yvette Waples will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. WAPLES: Good morning again.

The Food and Drug Administration, FDA, is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the

Federal Advisory Committee Act, FACA, of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs

his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

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

Today's agenda involves the discussion of biologic license application, BLA, 761158 for belantamab mafodotin, submitted by GlaxoSmithKline Intellectual Property Development Limited, England. The proposed indication, use, for this product is for the treatment of adults with relapsed or

refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

This is a particular matters meeting during which specific matters related to BLA 761158 will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

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

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

employed by Merck & Company.

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

DR. HOFFMAN: Thank you.

We will now proceed with FDA's opening remarks from Dr. Bindu Kanapuru.

FDA Opening Remarks - Bindu Kanapuru

DR. KANAPURU: Good morning. I am Bindu Kanapuru, a hematologist/oncologist with the FDA's Division of Hematologic Malignancies 2. I'm the cross-discipline team leader for the belantamab mafodotin application. I will present a brief introduction to this application and the key issues

this application presents.

Significant advances have been made in the treatment of multiple myeloma in recent decades. There are 12 drugs currently approved for the treatment of relapsed or refractory multiple myeloma and 7 new drugs or biologics have been approved since 2015, including a histone deacetylase inhibitor, an oral proteasome inhibitor, monoclonal antibodies, and a nuclear export inhibitor.

Despite the availability of multiple therapies, treatment of relapsed or refractory multiple myeloma remains challenging and the disease remains incurable. In general, the duration of remission shortens with each subsequent line of therapy, and patients who have received multiple lines of therapy and who become refractory to the major classes of available anti-myeloma therapies have poor outcomes.

Belantamab mafodotin is a first-in-class B-cell maturation antigen directed antibody conjugated to a microtubule disrupting agent

monomethyl auristatin or MMAF. The proposed indication for belantamab mafodotin is for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

Our review and presentation is primarily focused on the pivotal phase 2 study 205678, which I will subsequently refer to as the DREAMM-2 study. DREAMM-2 is an open-label, multicenter study evaluating belantamab mafodotin in patients with relapsed or refractory multiple myeloma. The trial did not include a comparator arm but evaluated two dose levels of belantamab mafodotin with overall response rate as a primary endpoint.

Eligible patients were those with multiple myeloma who had received at least 3 prior lines of therapies that included a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. The study also included a cohort to evaluate a lyophilized formulation at 3.4 milligram

per kg dose.

Based on an identified risk for ocular toxicity with belantamab mafodotin, from preclinical data and safety experience from the phase 1 dose escalation and expansion trial, DREAMM-1, patients on DREAMM-2 were monitored with ophthalmic exams at baseline and before each dose of belantamab mafodotin. The DREAMM-2 study also included a small ocular substance to assess whether topical corticosteroids may mitigate some of the observed ocular toxicity. Treatment with belantamab mafodotin continued until disease progression or unacceptable toxicity.

I will now discuss the top-level efficacy and safety results observed in the DREAMM-2 trial. 2.5 milligram per kg is the proposed dose for the marketing application. Efficacy data for the 3.4 milligram per kg dose will be presented later on in the presentation. The patient population with multiple myeloma, enrolled at the 2.5 milligram per kg dose, received a median of 7 lines of prior therapy.

The overall response rate in this heavily pretreated population was 31 percent at the 2.5 milligram per kg dose with a median duration of response that was not reached with 6.3 months of follow-up. This efficacy represents a treatment benefit in this heavily pretreated patient population.

With regards to safety, the most common treatment-emergent adverse reactions are listed here. Keratopathy or damage to corneal epithelium was the most frequent adverse event in the pivotal DREAMM-2 trial and was noted in greater than 70 patients on the trial in both dose cohorts. Other common ocular toxicities included symptoms of blurred vision and dry eyes.

Although the rates of cytopenias and other toxicities shown above were less frequent with a lower dose of 2.5 milligram per kg as compared to the 3.4 milligram per kg dose, there was not a substantial difference in the rates of keratopathy between the two dose levels.

This slide highlights the issue for

discussion today, which is ocular toxicity, a major safety concern with belantamab mafodotin. The incidence and severity of keratopathy observed in the DREAMM-2 trial was high. Only a quarter of the patients treated did not have a keratopathy event, and more than 40 percent of the patients had severe keratopathy based on ocular exam findings.

Keratopathy was associated with a decrease in visual acuity, including severe vision loss in some patients with an impact on patients' activities of daily living and on the ability to drive and read. Only 43 percent of patients had keratopathy findings by exam-reported ocular symptoms.

Because many patients had significant keratopathy on ophthalmic exam, in the absence of other ocular symptoms, there is also a concern that keratopathy could go undetected in the absence of close monitoring, potentially leading to serious sequelae, including development of corneal ulcers.

It is also important to note that this is a novel toxicity that is not typically seen with

other kinds [inaudible – unmuted voice]. An adequate characterization of ocular toxicity and appropriate mitigation strategies are important to ensure safe and effective use of belantamab mafodotin.

There remains several uncertainties regarding the ocular toxicity with belantamab mafodotin. While ocular toxicities, including keratopathy, have been reported with other antibody drug conjugates, especially MMAF-containing antibody drug conjugates, they were noted in the preclinical and phase 1 studies with belantamab mafodotin.

The mechanism of ocular toxicity with belantamab mafodotin is not completely understood. As such, to date no therapeutic strategies have been identified to mitigate ocular toxicity with belantamab mafodotin.

The limited ocular substudy evaluating the use of prophylactic steroid eye drops failed to show any mitigating effects on the incidence of severity of keratopathy. Dose modifications,

including dose interruptions, reductions, and discontinuation are the primary mitigation strategies for ocular toxicity at this point.

Despite close monitoring and implementation of dose modifications, many patients on the DREAMM-2 trial had severe and recurrent events of keratopathy. Recurrent events of keratopathy were reported in nearly 40 percent of the patients on the DREAMM-2 trial --

DR. PAZDUR: Hi. This is Dr. Pazdur. I am stuck on slide 2 and haven't heard anything.

DR. KANAPURU: A high proportion of patients with keratopathy did not have resolution as of the last follow-up, and in some patients, complete information on severity or reversibility may never be available, resulting in an incomplete characterization of reversibility and severity. Thus, there is an uncertainty if the dose modification strategy is sufficient to mitigate the toxicity.

Other strategies, including evaluation of alternate dosing regimens, or a lower dose at

2.5 milligram per kg, have not been adequately explored. The concerns and uncertainties regarding the characterization of ocular toxicities and mitigation strategies raises questions about the overall benefit-risk profile of belantamab mafodotin with the proposed patient population. The characterization of the ocular toxicity and appropriation mitigation strategies are important to allow for an assessment of the impact of ocular toxicity on the benefit-risk profile of belantamab mafodotin.

Today, we would like for the committee to discuss whether the risk of ocular toxicity has been adequately characterized in study 205678, DREAMM-2, to allow for an assessment of the benefit-risk profile, and --

(Crosstalk.)

DR. HOFFMAN: I think we need to take a brief break.

DR. KANAPURU: -- of ocular toxicity on the benefit-risk profile for belantamab mafodotin.

DR. HOFFMAN: I'm sorry to interrupt.

DR. KANAPURU: We know that belantamab mafodotin has a treatment [inaudible - distortion.]

DR. PAZDUR: I agree. This is Rick Pazdur. I haven't heard a thing of this presentation. I got stuck on slide 2.

Can you hear me?

DR. KANAPURU: However --

DR. HOFFMAN: I can hear you. I've been hearing the full presentation, but the speaking is not fluent, along with it's very choppy. And I'm also hearing a lot of noise on the phone separate from what's in the recorded presentation.

This is Philip Hoffman.

DR. GARCIA: Dr. Hoffman, this is Jorge. I can see the presentation and I can hear the presentation. I did have issues before, but I think I corrected the audio in the computer, so that was probably the key.

DR. HOFFMAN: Okay.

DR. PAZDUR: This is Dr. Pazdur. My computer's stuck on slide 2. It hasn't moved.

DR. HOFFMAN: I can't seem to stop the

presentation from moving to let us fix this.

This is Philip Hoffman. We're trying --

DR. KANAPURU: An adequate characterization --

DR. HOFFMAN: -- to resolve some technical issues here. I'm the chair of the meeting.

DR. WAPLES: Good morning. This is the acting DFO of the ODAC. We will take a 10-minute break. Thank you for your patience.

MALE VOICE: Guys, I can hear the presentation. I wonder if maybe, Dr. Hoffman, you could become the presenter of the presentation forward.

FEMALE VOICE: But I'm unable to enter the meeting.

DR. HOFFMAN: You're giving me credit for technical savvy that I don't have.

(Laughter.)

MALE VOICE: Fair enough. That's how highly I think of you. How about that?

DR. HOFFMAN: I'm up to slide 8 on the presentation, but the voice is not fluid --

DR. KANAPURU: -- belantamab mafodotin in the proposed patient population.

DR. HOFFMAN: -- with the slide presentation, so it's not easy to pay attention.

DR. KANAPURU: Characterization of the ocular toxicity and appropriate mitigation strategies are important to allow for an assessment of the impact of ocular toxicity on the benefit-risk profile of belantamab mafodotin.

CAPT VO: Hello? This is Thiep. Can we have a 5-minute break?

DR. HOFFMAN: Yes. We've already announced a 10-minute break. We've announced a 10-minute break.

CAPT VO: Okay.

DR. KANAPURU: -- study 205678, DREAMM-2, to allow for an assessment of the benefit-risk profile, and to discuss the impact of ocular toxicity on the benefit-risk profile for belantamab mafodotin.

We note that belantamab mafodotin has a treatment benefit in the proposed patient

population [inaudible – unmuted voice], however given the available data, regarding the risk of ocular toxicities and the incomplete characterization of this toxicity, with several residual uncertainties at this time, our question to the committee is, does the demonstrated benefit of belantamab mafodotin outweigh the risk in the proposed patient population with multiple myeloma? Thank you.

MALE VOICE: Could it be possible that some of us are having difficulties because we are not using Chrome as a browser? I don't know if that's the case.

DR. HOFFMAN: Got me. I'm using --

MALE VOICE: The application is Adobe Connect, so we have downloaded Adobe Connect.

(Whereupon, at 9:44 a.m., a recess was taken.)

DR. HOFFMAN: My name is Philip Hoffman, and I will be chairing today's meeting. Thank you for your patience with our delay. We're going to introduce ourselves once again. The members of the

committee who are present, please unmute yourself as you introduce yourself.

Dr. Cristofanilli?

DR. CRISTOFANILLI: Massimo Cristofanilli from Northwestern University in Chicago, medical oncologist.

DR. HOFFMAN: Dr. Garcia?

DR. GARCIA: I'm here, Dr. Hoffman. This is Jorge Garcia, chief medical oncology, University Hospitals, Seidman Cancer Center, Case Western Reserve University in Cleveland, Ohio.

DR. HOFFMAN: Dr. Halabi?

DR. HALABI: Hi. Good morning, everyone. This is Susan Halabi, Duke University.

DR. HOFFMAN: Dr. Hinrichs?

DR. HINRICHS: Christian Hinrichs, senior investigator, NCI, Bethesda, Maryland.

DR. HOFFMAN: Mr. Mitchell?

MR. MITCHELL: Yes. I am David Mitchell. I am a consumer representative, and I am also a multiple myeloma patient.

DR. HOFFMAN: Dr. Sung?

DR. SUNG: Anthony Sung, Hematologic Malignancies and Cellular Therapy, Duke University. I will be leaving at 1:30 p.m. [inaudible – distortion].

DR. HOFFMAN: Dr. Cheng?

DR. CHENG: Jonathan Cheng, oncologist, industry rep and with Merck Pharmaceuticals.

DR. HOFFMAN: Dr. Chodosh?

DR. CHODOSH: Jim Chodosh. I'm in Boston, Massachusetts. I'm a corneal specialist.

DR. HOFFMAN: Dr. DeFlice?

DR. DeFLICE: I'm John DeFlice. Thank you, Dr. Hoffman. I'm a gastroenterologist, and I'm a 10-year multiple myeloma survivor, and I'm a patient advisor.

DR. FELDMAN: Thank you, Dr. Hoffman. This is Brad Feldman. I'm a corneal specialist in Philadelphia at the Wills Eye Hospital.

DR. HOFFMAN: Dr. Klepin?

DR. KLEPIN: Hi. This is Heidi Klepin. I'm a geriatric oncologist at Wake Forest School of Medicine.

DR. HOFFMAN: Dr. Nowakowski?

DR. NOWAKOWSKI? Hi. Greg Nowakowski. I'm a hematologist at Mayo Clinic. Rochester.

DR. HOFFMAN: Dr. Thanarajasingam?

DR. THANARAJASINGAM: Hi. This is Dr. Thanarajasingam. I'm also a hematologist at Mayo Clinic in Rochester, Minnesota.

DR. HOFFMAN: Dr. Uldrick?

DR. ULDRICK: Hi. Thomas Uldrick, medical oncologist, Fred Hutchinson Cancer Research Center.

DR. HOFFMAN: Dr. Waples?

DR. WAPLES: Good morning. This is Dr. Waples. I'm the acting DFO for the ODAC.

DR. HOFFMAN: Dr. Pazdur?

DR. PAZDUR: Hi. Richard Pazdur, FDA, director of the Oncology Center of Excellence.

DR. HOFFMAN: Dr. Gormley?

DR. GORMLEY: Hi. I'm Dr. Nicole Gormley. I'm the acting division director in the Division of Hematologic Malignancies 2 at the FDA.

DR. HOFFMAN: Dr. Kanapuru?

DR. KANAPURU: Hi. Good morning. I'm Bindu

Kanapuru. I'm the acting team lead of multiple myeloma in the Division of Hema Malignancies 2.

DR. HOFFMAN: Dr. Baines?

DR. BAINES: Hi. This is Dr. Andrea Baines. I'm a hematologist at FDA with the Division of Hematologic Malignancies 2.

DR. HOFFMAN: Dr. Chambers?

DR. CHAMBERS: Hi. This is Wiley Chambers. I'm an ophthalmologist. I'm the acting director for the Division of Ophthalmology at FDA.

DR. HOFFMAN: Okay. Thank you.

Let's now move to the FDA's opening remarks by Dr. Kanapuru.

FDA Opening Remarks - Bindu Kanapuru

DR. KANAPURU: Good morning. I'm Bindu Kanapuru, a hematologist/oncologist with the FDA's Division of Hematologic Malignancies 2. I'm the cross-discipline team leader for the belantamab mafodotin application and will present a brief introduction to this application and the key issues this application presents.

Significant advances have been made in the

treatment of multiple myeloma in the recent decades. There are 12 drugs currently approved for the treatment of relapsed or refractory multiple myeloma, and 7 new drugs or biologics have been approved since 2015, including a histone deacetylase inhibitor, an oral proteasome inhibitor, monoclonal antibodies, and a nuclear export inhibitor.

Despite the availability of multiple therapies, treatment of relapsed or refractory multiple myeloma remains challenging and the disease remains incurable. In general, the duration of the remission shortens with each subsequent line of therapy, and patients who have received multiple lines of therapy and become refractory to the major classes of available anti-myeloma therapy have poor outcomes.

Belantamab mafodotin is a first-in-class B-cell maturation antigen directed antibody conjugated to a microtubule disrupting agent, monomethyl auristatin F or MMAF. The proposed indication for belantamab mafodotin is for the

treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

Our review and presentation is primarily focused on the pivotal phase 2 study 205678, which I will subsequently refer to as the DREAMM-2 study. DREAMM-2 is an open-label, multicenter study evaluating belantamab mafodotin in patients with relapsed or refractory multiple myeloma. The trial did not include a comparator arm but evaluated two dose levels of belantamab mafodotin with overall response rate as a primary endpoint.

Eligible patients were those with multiple myeloma who had received at least 3 prior lines of therapies that included a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody. The study also included a cohort to evaluate a lyophilized formulation at 3.4 milligram per kg dose.

Based on an identified risk for ocular

toxicity with belantamab mafodotin, from preclinical data and safety experience from the phase 1 dose escalation and expansion trial, DREAMM-1, patients on DREAMM-2 were monitored with ophthalmic exams at baseline and before each dose of belantamab mafodotin.

The DREAMM-2 study also included a small ocular substudy to assess whether topical corticosteroids may mitigate some of the observed ocular toxicity. Treatment with belantamab mafodotin continued until disease progression or unacceptable toxicity.

I will now discuss the top-level efficacy and safety results observed in the DREAMM-2 trial. 2.5 milligram per kg is the proposed dose for the marketing application. Efficacy data for the 3.4 milligram per kg dose will be presented later on in the presentation. The patient population with multiple myeloma, enrolled at the 2.5 milligram per kg dose, received a median of 7 lines of prior therapy.

The overall response rate in this heavily

pretreated population was 31 percent at the 2.5 milligram per kg dose with a median duration of response that was not reached with 6.3 months of follow-up. This efficacy represents a treatment benefit in this heavily pretreated patient population.

With regards to safety, the most common treatment-emergent adverse reactions are listed here. Keratopathy or damage to corneal epithelium was the most frequent adverse event in the pivotal DREAMM-2 trial and was noted in greater than 70 patients on the trial in both dose cohorts. [Inaudible – distortion].

Although the rates of cytopenias and other toxicities shown above were less frequent with a lower dose of 2.5 milligram per kg as compared to the 3.4 milligram per kg dose, there was not a substantial difference in the rates of keratopathy between the two dose levels.

This slide highlights the issue for discussion today, which is ocular toxicity, a major safety concern with belantamab mafodotin. The

incidence and severity of keratopathy observed in the DREAMM-2 trial was high. Only a quarter of the patients treated did not have a keratopathy event, and more than 40 percent of the patients had severe keratopathy based on ocular exam findings.

Keratopathy was associated with a decrease in visual acuity, including severe vision loss in some patients with an -- [inaudible – distortion] -- raised questions about the overall benefit-risk profile of belantamab mafodotin in the proposed patient population – regarding the characterization of ocular toxicity and mitigation strategy raises questions about the overall benefit-risk profile of belantamab mafodotin in the proposed patient population.

[Inaudible.]

Today, we would like for the committee to discuss whether the risk of ocular toxicity has been adequately characterized in study 205678, or DREAMM-2, to allow for an assessment of the benefit-risk profile and to discuss the impact of ocular toxicity on the benefit-risk profile for

belantamab mafodotin.

We note that belantamab mafodotin has a treatment benefit in the proposed patient population with multiple myeloma. However, given the available data regarding the risk of ocular toxicity and the incomplete characterization of this toxicity, and the several residual uncertainties at this time, our question to the committee is, does the demonstrated benefit of belantamab mafodotin outweigh the risks in the proposed patient population with multiple myeloma? Thank you.

DR. HOFFMAN: Thank you very much.

Before we move to the sponsor's presentation, I just want to remind everyone please to have your phones on mute if you're not actually speaking to avoid any extraneous noises.

Thank you, Dr. Kanapuru.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee

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

For this reason, FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the applicant such as consulting fees, travel expenses, honoraria, and interests 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 this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with presentations from GlaxoSmithKline immediately followed by the FDA presentation.

DR. HOOS: GSK presenters are on the call.

We're waiting for the slides to come up.

Applicant Presentation - Axel Hoos

DR. HOOS: Good morning, Mr. Chair, members of ODAC, and members of the FDA. I'm Axel Hoos, senior vice president of oncology at GlaxoSmithKline. Thank you for the opportunity today to present the data underlying our application for accelerated approval of belantamab mafodotin, referred to hereinafter as Belamaf, for the treatment of patients with relapsed/refractory multiple myeloma.

Belamaf offers a novel and specific mechanism of action that targets B-cell maturation antigen, or BCMA, a cell surface receptor required for cell survival. This receptor is widely expressed in multiple myeloma cells. Belamaf is an antibody drug conjugate comprised of an afucosylated humanized IgG1 BCMA-targeting antibody linked to the microtubule and disrupting agent MMAF. Belamaf has a multimodal mechanism of action that contributes to the clinically meaningful activity we have observed. Our presentation will

demonstrate that Belamaf provides a positive benefit to risk profile.

There's a clear unmet medical need in advanced myeloma. Patients with myeloma who have become refractory to the most effective therapies have poor outcomes. If patients have only one remaining approved treatment option, namely selinexor plus dexamethasone, at this stage, response duration with selinexor and dexamethasone is 4.4 months, and patients have a short median survival of 6 to 9 months and need effective therapies with novel mechanisms of action.

We agree with the FDA that the Belamaf results may be beneficial in this heavily pretreated population. The responses were deep and durable with medium duration of response of at least 9 months and estimated overall survival of 11.9 months. This would improve response and survival expectation by twofold.

The overall safety profile of Belamaf is manageable and predominantly characterized by ocular events. This represents a novel adverse

event for myeloma physicians and requires training. We understand this risk, and our label will include a box warning to communicate the risk to physicians and patients. We also are proposing a risk evaluation and mitigation strategy, or REMS, including elements to assure safe use or ETASU. Despite corneal events, patients' disease-related symptoms were controlled and quality of life was stable without accelerated decline for myeloma progression.

Throughout our clinical program, we collected various types of data that provide a comprehensive assessment and characterization of corneal adverse events, which is a known class effect associated with MMAF antibody drug conjugates. These include patients' symptoms, adverse events based on objective eye examination, and quality-of-life measures to assess the function and impact of the event on patients.

Furthermore, we continue to follow patients to evaluate resolution of events once off treatment. To fully characterize actual events,

GSK used the protocol specified, Keratopathy and Visual Acuity, or KVA, scale, which focuses on corneal exam findings. This scale accompanied the use of standard CTCIA [ph] criteria.

While ocular events are unique in multiple myeloma, they're well understood by ophthalmologists. Should they appear, interventions can be considered. Such interventions include dose modifications and eye drops. Ocular events are often asymptomatic without meaningful change in visual acuity. No patient experienced complete vision loss and only 3 patients discontinued Belamaf due to an ocular adverse event.

We have designed a REMS with ETASU to ensure education, ocular monitoring, and timely management of events. In this context, Belamaf will only be administered in a certified healthcare setting after confirmation of an eye exam.

We're here today seeking accelerated approval for the treatment of adults with relapsed or refractory multiple myeloma who have received at

least 4 prior therapies, which include an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. The recommended dose of Belamaf is 2.5 milligrams per kilogram administered once every 3 weeks.

Belamaf received breakthrough therapy designation for patients with multiple myeloma who failed at least 3 prior lines of therapy. The designation was granted based on the promising clinical results observed in our phase 1 study, DREAMM-1. The pivotal study, DREAMM-2, enrolled patients consistent with this designation, and comparable results were observed. As part of our accelerated approval commitment, we have initiated DREAMM-3, a randomized phase 3 study which has begun and is ongoing.

Here's the agenda for the remainder of our presentation. We have also invited additional experts with us today as shown here. Thank you. I'll now turn the presentation to Dr. Anderson.

Applicant Presentation - Kenneth Anderson

DR. ANDERSON: Thank you. I'm Ken Anderson,

professor of medicine at Harvard Medical School and director of the Myeloma Center at Dana-Farber Cancer Institute, and I've been treating my patients with multiple myeloma for more than 40 years.

While we've seen great progress in multiple myeloma, relapse of disease will occur in most patients. Those patients whose myeloma has progressed on current therapies or is refractory urgently need novel effective options that will decrease disease burden and improve longer term outcomes while affording them an acceptable quality of life.

Multiple myeloma is the second most common hematologic malignancy. In 2020, an estimated 32,000 patients will be newly diagnosed with myeloma and more than 12,800 myeloma-related deaths will occur in the United States. The median overall survival for newly diagnosed patients with myeloma is approximately 5 to 10 years.

Nearly a dozen agents have been translated from the bench to the bedside resulting in FDA

approval of the agents shown here. Once patients' myeloma relapses from initial therapy, we commonly treat them with a combination of regimens that contain either a proteasome inhibitor, immunomodulatory agent, or an anti-CD38 antibody as the backbone. Unfortunately, their disease will relapse or become refractory to the three most effective classes, and we are essentially left with one option, the recently approved nuclear transport inhibitor, selinexor.

Once myeloma becomes triple-class refractory, patient outcomes are poor, as shown in the MAMMOTH study. Here, Gandhi and colleagues investigated patient outcomes in advanced myeloma. This paper divided patients by refractoriness of their myeloma and found that survival diminishes as myeloma becomes more refractory, with median survivals between 5.6 and 9.2 months. The triple and quad refractory red line is most comparable to the population in today's discussion.

As noted, the only currently approved option for these patients is the selinexor combination.

These results further reinforced how difficult treatment can be at this late stage with an overall response rate of 26.2 percent, a relatively short duration of response of 4.4 months, and median survival of 8.6 months.

There are also tolerability issues observed with selinexor. Sixty percent of patients experienced a serious adverse event and high rates of dose modifications and discontinuations were observed. As the only remaining option for patients we are discussing today, this highlights the urgent unmet medical need.

In addition to the poor outcomes in relapsed/refractory myeloma, the quality of life for our patients also decreases with each relapse and each subsequent line of therapy. Physical functioning even in patients with stable relapsed/refractory multiple myeloma may be significantly compromised, and it can be associated with reduced ability to work, carry out domestic chores, and leisure activities.

The quality of life is impacted by the

disease burden such as fatigue and pain, as well as by the treatment-related adverse events. Discontinuation from treatment is a measure of tolerability. Some current treatments have significant side effects and high discontinuation rates. Thus, stability of the quality of life is an important consideration when we discuss therapeutic options with our patients.

In summary, patients with triple-class refractory myeloma have one available option once their disease becomes refractory to effective treatments, and this option has its own safety limitations. Patients with relapsed/refractory multiple myeloma have short survival and their disease greatly impacts their overall quality of life.

These patients are therefore in urgent need of new therapies with alternative mechanisms of action to overcome drug resistance that inevitably develops. Most importantly, patients need effective and tolerable therapies that achieve clinical responses, which are both durable and

associated with clinical benefit.

Thank you. Dr. Gupta will now discuss the efficacy data.

Applicant Presentation - Ira Gupta

DR. GUPTA: Thank you, Dr. Anderson.

Good morning. I'm Ira Gupta, vice president and the development lead for belantamab mafodotin at GlaxoSmithKline. I'm pleased to be here today to present the results from our clinical development program demonstrating that Belamaf provides clinically meaningful overall response rate with a durable duration of response in patients otherwise expected to relapse quickly from their disease.

The data supporting our accelerated approval application comes from our dose-finding study, DREAMM-1, which explored doses from 0.03 to 4.6 milligrams per kilogram and our pivotal DREAMM-2 study. These studies provide consistent evidence of clinically meaningful efficacy in heavily pretreated patients with multiple myeloma who have failed at least 4 prior lines of therapy, which is

our indicated population.

DREAMM-2 is an ongoing phase 2, open-label, randomized, multicenter trial. Enrolled patients had a confirmed diagnosis of relapsed or refractory multiple myeloma with disease progression after 3 or more prior lines of therapy. All patients had an ECOG performance status of 0 to 2. The patients were stratified by previous line of therapy and cytogenetic features to receive 2.5 or 3.4 milligrams per kilogram Belamaf via intravenous infusion every 3 weeks until disease progression or unacceptable toxicity.

As corneal events were an expected adverse event, an ocular substudy was included to evaluate the effect of corticosteroids on corneal findings. Both doses demonstrated comparable efficacy, however, the 2.5 milligrams per kilogram dose had a more favorable safety profile, therefore we will focus our presentation on 2.5 milligrams dose.

The primary endpoint was overall response rate as assessed by an independent review committee. Secondary endpoints as shown on the

slide were also assessed. 196 patients were enrolled. The majority of patients remained in the study with 23 percent on treatment and 39 percent of the patients in follow-up. The primary reason for discontinuation was disease progression. Based on demographics, they are reflective of patients with relapsed/refractory multiple myeloma.

DREAMM-2 enrolled heavily pretreated patients with a median of 7 prior lines of therapy. 84 percent of the patients had received more than 4 prior lines. All were refractory to an anti-CD38 antibody or proteasome inhibitor and immunomodulator.

Moving to the primary endpoint results, 31 percent of the patients achieved a partial response or better, demonstrating a clinically meaningful overall response rate in this refractory patient population. The achieved responses were deep with more than half of the responders achieving a VGPR or better.

At the time of the primary data cutoff, the median duration of response was not reached.

Furthermore, overall survival data was not mature at the time of the primary analysis. The estimated median overall survival was 9.9 months with a 6-month survival rate of 72 percent.

Additional follow-up data continues to show the benefit of Belamaf. As of the 9-month data cut, median duration of response was still not reached, however, based on a worst-case sensitivity analysis, it is estimated to be at least 9 months. In addition, overall survival is estimated to be at least 11.9 months.

In conclusion, the results from our clinical development program demonstrated clinically meaningful treatment responses in patients with heavily pretreated relapsed/refractory multiple myeloma. The responses were deep and durable. Based on the 9 months follow-up, median duration was still not reached and median overall survival is estimated to be 11.9 months. In addition, DREAMM-1 supports the findings from the pivotal DREAMM-2 study.

Thank you. Dr. Abdullah will now present

the safety data.

Applicant Presentation - Hesham Abdullah

DR. ABDULLAH: Thank you.

I'm Hesham Abdullah, senior vice president, head of clinical development oncology at GSK. I will now review the safety data from the DREAMM-2 study. The safety profile of Belamaf has been systematically evaluated and it's considered to be manageable in the overall context of the benefit-risk.

Most patients reported an adverse event. While the AE rates were similar across doses, the 2.5 milligram dose demonstrated a more favorable safety profile with less need for dose reductions or interruptions and fewer SAEs. Three percent of patients experienced an AE leading to death in the 2.5-milligram group and 7 percent in the 3.4-milligram group.

Given the more favorable safety profile with comparable efficacy, we are recommending the 2.5-milligram dose in our indication. This will be our focus for the remainder of the safety

discussion.

In the DREAMM-2 study, the median number of the cycles administered was three and most patients receive their assigned dose intensity. The median time on treatment was about 9 weeks. Here I present the adverse events reported using standard CTCAE grading. In alignment with FDA, we also present adverse events grouped by related preferred terms.

It's important to note that whether we look at these AE data through the lens of the individual preferred terms or grouped preferred terms, similar conclusions are reached. Keratopathy was the most commonly reported adverse event occurring in 71 percent of patients. Dr. Colby will later present the corneal data as reported based on exam findings.

You'll note the rate of keratopathy remains the same between the two assessment methods. When looking more closely by grade, keratopathy was also the most commonly reported grade 3-4 AE.

Dose modifications were effective in

managing AEs and allowed patients to remain on treatment. Almost all dose delays were due to corneal events. Keratopathy accounted for 47 percent and the next most frequently reported was blurred vision at 5 percent. The median duration of dose delays was 42 days and 69 percent of patients restarted treatment.

Likewise, corneal adverse events led to almost all dose reductions. Twenty-nine percent of patients required these reductions overall; keratopathy accounted for 20 percent, thrombocytopenia for 5 percent, and an additional 2 percent for blurred vision. Dose modifications allowed patients to remain on treatment with few discontinuations.

Let me now share the discontinuation data. Eight percent of patients discontinued, 2 percent due to keratopathy. The remaining discontinuations occurred due to a single adverse event in each patient.

In conclusion, Belamaf has a manageable safety profile with low frequency of adverse events

other than corneal events. Few patients discontinued, attesting to the tolerability of treatment and utility of dose modifications. Based on the 9-month update, no new safety signals have been identified. Finally, corneal events will be monitored and managed through the proposed label and REMS with ETASU, which I will discuss after Dr. Colby's presentation on the corneal events. Thank you.

(No response.)

DR. GUPTA: Dr. Colby, we aren't able to hear you.

DR. COLBY: I'm sorry. Can you hear me now?

DR. GUPTA: Yes, we can. Thank you.

Applicant Presentation - Kathryn Colby

DR. COLBY: Sorry about the technology challenges.

Thank you. I'm Kathryn Colby, the Louis Block professor and chair of the Department of Ophthalmology and Visual Science at the University of Chicago. I'm the president of the Cornea Society and a practicing ophthalmologist,

specializing in diseases of the cornea and ocular surface.

As you heard, ocular events are common with Belamaf. These findings may be unfamiliar to oncologists or new in the myeloma space, but these are bread-and-butter findings for ophthalmologists that we manage on a daily basis. Such events from medications are not uncommon and occur with medications such as amiodarone and Ara-C.

The collaboration between the ophthalmologist and the oncologist, reflected in the sponsors clinical program and proposed REMS, allows the ophthalmologist to identify these findings in a timely fashion, while the oncologist will treat the myeloma with appropriate Belamaf dosing. First, let me briefly describe the anatomy of the eye so you can understand what is actually happening with these events.

Here is a schematic of the eye. The cornea, shown in yellow, is the clear front window to the eye. In this cross-section, you can see that the cornea is made up of multiple layers, each of which

has a different function. The events in this clinical program occurred in the most superficial layer of the cornea, the epithelium. The epithelium, like the skin, is a naturally regenerating tissue, and it's completely replaced every 7 to 10 days. Therefore, typically events in the epithelium are self-limiting. The literature is highly supportive of the conclusion that such events in the epithelium are reversible.

The characteristic corneal finding with Belamaf was a microcyst-like change in the epithelium. This is a subtle exam finding shown in the slit lamp image on the left. We can get a detailed view of the various parts of the cornea using an imaging technique called confocal microscopy. Shown in the top-right panel is a normal epithelium. In contrast, hyper-reflective deposits, likely apoptotic cells, are seen after Belamaf administration in the lower-right image.

These exam findings are a type of keratopathy, which is a nonspecific term for various disorders of the cornea. These findings

may appear only on exam and may not result in changes in vision, depending upon their severity and location.

Let me provide a schematic explanation that shows the microcyst-like findings greatly enlarged so you can see them. We've observed that the keratopathy with Belamaf originates in the peripheral corneal epithelium. Deposits in the center cornea can appear over time in some patients. Central deposits can affect visual acuity while peripheral deposits generally do not. The keratopathy recovers in reverse fashion, first resolving in the center and then outward. This explains why many patients have keratopathy but fewer patients have a change in visual acuity. It also explains why the visual acuity changes resolve prior to complete resolution of the keratopathy.

To ensure a comprehensive understanding of ocular events, various types of data were collected in DREAMM-2. Adverse events were collected based on subjective symptoms reported by patients and graded by investigators. In addition, ophthalmic

exams prior to every dose, with particular attention to visual acuity and changes in the cornea, were conducted..

Exam findings were graded by investigators based on protocol-defined criteria. The severity of these findings were used to determine dose modifications. The severity of the objective exam findings were graded in two ways, first using a protocol-specified keratopathy and visual acuity, or KVA scale, which graded events based on objective findings in the cornea and changes in visual acuity.

This is a rigorous method for identifying and grading events, and in agreement with the FDA, the KVA scale was used to determine dose modifications. Second, the changes seen in eye exams were created using standard CTCAE criteria. This took subjective patient experience into consideration.

The overall incidence of keratopathy is the same regardless of methodology used, but there were differences in the grades of events. Seventy-two

percent of patients experienced a keratopathy. Evaluation of the keratopathy was done by the ophthalmologist and takes into consideration the distribution of microscyst-like changes in the cornea. The more diffuse the microcysts, the higher the severity grade. A grade 3 event here is based on an exam finding, which may or may not have resulted in reduced vision or patients' symptoms.

Keratopathy takes time to resolve completely, at least 80 days in most cases. This is not surprising based on the timing of the natural regeneration of the corneal epithelium and Belamaf's long half-life. Seventy-five percent of patients recovered from their very first occurrence of keratopathy. Just under half of the patients had more than one occurrence of keratopathy.

Based on the last follow-up, 48 percent have documented recovery to grade 1 or better and 77 percent of patients with grade 3 or 4 events either recovered or were recovering. Of the patients with unresolved keratopathy, 27 percent are still on treatment or in follow-up. Those

still on treatment and those without sufficient follow-up time would not be expected to have complete recovery of the corneal changes.

Additionally, 25 percent of the patients were reported as not recovered when follow-up ended. This percentage includes patients who died, withdrew early, or who did not return for eye examinations. For those that were not recovered when follow-up ended, the median follow-up time was only 23 days, which is too short for complete recovery. Again, objective findings of keratopathy were reported in 72 percent of patients. Only 3 patients discontinued due to corneal events.

Keratopathy does not always lead to patient symptoms or meaningful changes in vision. In fact, 83 percent of patients in the study were without meaningful visual acuity changes. Fifty-two percent of patients were symptomatic and 16 out of 95 patients had a meaningful but temporary change to vision, which makes sense given how keratopathy recovers. If there is an event, it will be quickly identified with monitoring, and if that event is

severe, it will be managed.

Let me explain how visual changes are observed from the patient perspective. 20/20 vision using the Snellen scale is considered to be normal vision. As vision is reduced to 20/50, you can see here how an image would appear slightly blurry, however, this is still good enough vision to allow people to do most activities. When vision is reduced to 20/200, which is considered legal blindness in the United States, although the image is blurrier, people can still find their way around their homes, perform self-care, and read large print.

Sixteen patients experienced a decline in visual acuity to 20/50 or worse at least once during or after the treatment period. The median duration of this decline was 22 days and 94 percent of patients recovered by the last assessment. One patient experienced a worsening to 20/200, however, this was temporary, and vision recovered to baseline at the next assessment. No patient had complete vision loss.

Functional impact of reduced vision varies from patient to patient, however, overall, the negative effects on important activities of daily life like driving and reading were temporary. Functional impact of reduced vision was assessed using the standardized NEI-VFQ. This overall assessment is patient-reported outcomes as they relate to visual function.

Here are the worst post-baseline changes in driving and reading as assessed by the NEI-VFQ 25 for patients who reported little or no difficulty at baseline. Among the patients with little to no difficulty driving, 53 percent of patients experienced no change throughout the study.

Of the 23 percent who gave up driving due to eyesight, about half regained this function prior to the end of study. Among the patients with little to no difficulty reading, 42 percent experienced no change and 7 of 8 who stopped reading returned to reading by the end of the study.

It's also helpful to review the

visual-related, patient-reported outcomes in the context of overall quality of life. Here is the mean change in global health status based on patient-reported outcomes as measured by the EORTC. We observed that patients' quality of life remained stable that we acknowledge this sample size as limited. Thus, corneal adverse events and visual acuity changes don't always translate into changes in overall quality of life.

As an ophthalmologist, I am comfortable with these events. It's the myeloma that worries me. I can assure you that when keratopathy occurs, it will be identified and effectively managed with dose modifications. Keratopathy exam findings improve with time. Visual acuity changes can result from keratopathy, but these changes were temporary.

The ophthalmologist and the oncologist must work together to ensure patients receive the optimal dosing of Belamaf to control their life-threatening myeloma. Thank you. I'll return the presentation to Dr. Abdullah.

Applicant Presentation - Hesham Abdullah

DR. ABDULLAH: Thank you, Dr. Colby.

Belamaf associated corneal events are unique in the myeloma population. GSK acknowledges the importance of these events, and as such, we've addressed them in the proposed label and developed a formalized plan, including a REMS to manage these events and continue to closely monitor patients.

The proposed label will include a box warning to inform patients and physicians of corneal toxicity and potential changes in vision. The warning will highlight the need to conduct eye exams prior to each dose and to use dose modifications to manage events.

The goal of the REMS with ETASU is to ensure appropriate monitoring and management of corneal events. The central component of the REMS program is the requirement for an exam to be conducted by an eye care professional before a patient receives each dose of Belamaf. Next, the results of the exam will be shared to support timely management if needed. The prescriber uses these results to guide

dosing decisions, including dose modifications. Finally, automated systems would restrict access to Belamaf.

Now let me show you how the multiple controlled and recurring activities will maximize the early identification of corneal changes in order to enable timely management through dose modifications. Importantly, these activities help ensure that changes in the corneal epithelium or visual acuity are not missed.

Awareness in monitoring begins with education and training on the risk of corneal events and their management, along with guidance on implementation of and adherence to the ETASU components. This will include confirmation of prescriber knowledge and training on how to educate and enroll patients.

GSK will further support the patient with eye care resources and help them find and schedule appointments with an eye care professional. The completed ocular exam, including slit-lamp and visual acuity assessments, then help guide patient

treatment. Prescribers will document that they have reviewed the eye exam results and implement dose modifications as needed. These actions are part of a feedback loop between the patient, physician, and eye care professional.

The documented activities are used by the infusion center to verify patient eligibility prior to the administration of each dose. Upon confirmation, the center will issue an automated authorization that is required for Belamaf to be administered.

Importantly, GSK will receive automated notifications of all corneal events that result in a dose delay or reduction. As you can see, these multiple control points and systematic feedback loops help further optimize patient safety and Belamaf benefit-risk.

Thank you. Dr. Lonial will now conclude with his clinical perspective.

Applicant Presentation - Sagar Lonial

DR. LONIAL: Thank you. I'm Sagar Lonial, professor and chair in the Department of hematology

and Medical Oncology and the chief medical officer for The Winship Cancer Institute of Emory University. I also served as the global lead PI for the DREAMM-2 clinical study.

As you heard from Dr. Anderson, for patients with relapsed and refractory myeloma, there's no clear treatment consensus and really only one approved agent for these patients. Beyond that, we recycle agents that the patient has already used or combinations of cytotoxic chemotherapy. These lack durable benefit and are associated with significant toxicity. We need new drugs with new mechanisms of action.

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 corneal events on the patient? We also consider how the benefit-risk profile compares with other potential options, and in the case of refractory myeloma, they are often heavily weighted towards toxicity. Addressing these questions allow for a clear assessment of

risk and benefit and allows the physician the opportunity to have an open dialogue with patients regarding the risk and benefit as they decide to move forward.

Belamaf demonstrated deep and durable responses in a highly refractory patient population. This continued through the 9-month follow-up, and this is evidenced by the achievement of complete remissions despite the fact that these are heavily pretreated patients.

The median duration of response in my view is an amalgamation endpoint of both efficacy and safety. Achieving depth of response and having a durable duration of response in a refractory myeloma patient population speaks to the unique target and efficacy of Belamaf.

Additionally, we see that patients who respond experience a longer duration of overall survival. We also see that patients who don't respond have the expected overall survival for this patient population in general as described in the MAMMOTH study.

To further contextualize the Belamaf data, here is data Dr. Anderson showed earlier, but this time I add Belamaf next to selinexor. And while this is an indirect comparison, you can see that Belamaf overall response is at least in line with this agent that was granted accelerated approval. Most noticeably, however, is the durability of response, greater than 9 months for Belamaf compared to 4.4 months observed with the selinexor-dexamethasone combination.

Additionally, the safety profile for Belamaf compares favorably as well. Across all categories, in fact, Belamaf has fewer events reported in aggregate. I especially want to highlight the relatively low rate of adverse events resulting in treatment discontinuation for Belamaf.

The next question, then, is can the corneal events be managed because the benefit I've already demonstrated is really only meaningful if patients can remain on treatment and have a stable quality of life. As you heard from Dr. Colby, the corneal events are manageable, and from the treating

oncologist perspective, that is my view as well.

I acknowledge that these are unique findings. Initially, I didn't understand them myself, but as the trial progressed and in discussions with my patients I gained greater comfort with these symptoms and working closely with ophthalmology was able to give patients a chance to respond to therapy while minimizing the risk of significant keratopathy.

Keratopathy was frequent but did not result in significant changes in visual acuity in around 80 percent of patients, and only 3 patients discontinued due to these events. Those holds in modifications clearly allowed for continued therapy with close monitoring, and the clinical data demonstrate that patients still achieved meaningful response regardless of modifications.

Additionally, vision returned to baseline or near baseline in 94 percent of these cases, and this occurred because of a very strong partnership between ophthalmologists and the clinical investigators that allowed us together to determine

the optimal time to reinitiate dosing; and given the sponsor's REMS plan, I expect this same level of close partnership to continue post-approval. This will allow us to safely treat these patients who have few, if any, real treatment options.

The data presented today demonstrate that there's a positive benefit-risk profile for Belamaf. When patients are on therapy, they will likely experience some form of a corneal event, which can be managed in partnership with our ophthalmology colleagues. It is important to remember that keratopathy identified during an eye exam is not the same as a finding of vision loss. In fact, keratopathy does not often correlate with changes in vision, and in many patients doesn't result in symptoms.

Per the sponsor's REMS, patients will be routinely monitored regardless of symptoms as they were in the clinical program. Patients are also likely to experience a meaningful response, something they cannot get with most available therapies since their myeloma has already become

triple-class refractory.

The overall response rate demonstrates Belamaf's unique activity and the median duration of response exceeds background estimates of overall survival for this population, speaking both to safety and to efficacy as I described earlier. Perhaps the most impressive to me is that the efficacy continues to gain as we get longer follow-up on this trial.

I also add Belamaf's tolerable safety profile to its list of benefits. Eight percent of patients discontinued, and in the context of advanced disease with comorbidities, that is fairly low. Despite all the advances we've been able to enjoy in myeloma, the triple-class refractory patient does exist and is unfortunately growing in number, and options like Belamaf offer significant advance for our patients.

I want to leave you with two patient examples that I have personally cared for. Both patients are in their mid to upper 70s. Both have received 6 to 7 prior lines of therapy similar to

the DREAMM population. Both have basically exhausted available treatment options, and when we read about Belamaf compared to other potential options, decided to move forward with Belamaf.

Both achieved meaningful clinical responses, one without the development of visual changes or keratopathy and one with intermittent changes keratopathy requiring dose holds and dose modifications. Both patients have been on therapy for over 4 months and neither patients have regretted the decision to go on therapy, and in fact, given the risks we discussed prior to therapy, are gaining the benefit from receiving Belamaf as a treatment in this setting.

From my view, BCMA represents an important treatment target, and it doesn't make sense to wait an additional 2 to 3 years to have an off-the-shelf therapy for patients with triple-class refractory myeloma. The benefit far exceeds the potential risks of using Belamaf in the context of the currently described REMS program. Our patients should be afforded this treatment option to

determine an informed decision making with their oncologist if it is right for them.

Thank you again, and Dr. Gupta will return to take your questions.

FDA Presentation - Andrea Baines

DR. BAINES: Good afternoon. My name is Andrea Baines, and I'm a hematologist with the Division of Hematologic Malignancies 2 at the FDA. I am the clinical reviewer for the belantamab mafodotin application. Today I'll provide an overview of FDA's review of the major safety concern of ocular toxicity with belantamab mafodotin.

We would like the committee to discuss whether the risk of ocular toxicity has been adequately characterized in study 205678, or DREAMM-2, to allow for an assessment of the benefit-risk profile and to discuss the impact of ocular toxicity on the benefit-risk profile for belantamab mafodotin.

Considering the available information regarding the efficacy and safety of belantamab

mafodotin, which I will discuss further in the upcoming slides, our question to the committee will be, does the demonstrated benefit of belantamab mafodotin outweigh the risks in the proposed patient population with multiple myeloma?

Our review and presentation is primarily based on the phase 2 trial, DREAMM-2. Additional supportive data comes from the phase 1 first-in-human trial, DREAMM-1. DREAMM-2 is an open-label, multicenter study evaluating 2 doses of belantamab mafodotin in patients with relapsed/refractory multiple myeloma. Eligible patients had failed at least 3 prior lines of therapy, including an anti-CD38 monoclonal antibody and were refractory to a proteasome inhibitor and immunomodulatory agent.

Patients were randomized 1 to 1 to receive belantamab mafodotin 2.5 milligram per kilogram or 3.4 milligram per kilogram. However, the trial was not designed for formal comparison of the 2 doses from a statistical perspective. The trial initially only included evaluation of the 3.4

milligram per kilogram dose. However, following discussions with FDA regarding the instance of ocular toxicity and the frequency of dose modifications with the 3.4 milligram per kilogram dose in DREAMM-1, the DREAMM-2 trial was amended to include evaluation of the lower 2.5 milligram per kilogram dose.

Based on the occurrence of ocular toxicity in DREAMM-1 and with MMAF containing antibody drug conjugate in general, the trial also included an ocular substudy to address whether topical corticosteroids can mitigate the risk of ocular toxicity.

In addition, while most patients in DREAMM-2 received a frozen liquid solution of belantamab mafodotin, the trial was amended to also evaluate a presentation of belantamab mafodotin that is proposed for marketing that is lyophilized. However, the lyophilized presentation was only evaluated at the 3.4 milligrams per kilogram dose, whereas the 2.5 milligram per kilogram dose is proposed for marketing.

Treatment was continued every 3 weeks until disease progression or unacceptable toxicity. The primary endpoint was the overall response rate as assessed by an independent review committee and the secondary endpoints are shown here.

The trial demonstrated an overall response rate of 31 percent in the 2.5 milligram per kilogram cohort and 34 percent in the 3.4 milligram per kilogram cohort. With a median follow-up of 6.3 months and 6.9 months, respectively, the median duration of response was not reached for either cohort. However, among the patients who achieved a response, 70 percent had a duration of response of at least 6 months.

The data for overall survival was not mature at the time of data analysis, and although the data for median progression-free survival is shown, in general, the FDA does not rely on time-to-event analyses in single-arm trials because of the potential for lead-time bias and challenges associated with the use of historical controls.

Overall, the efficacy was similar between

the two dose levels and the response rate of 31 percent for the proposed 2.5 milligram per kilogram dose represents a treatment benefit in this heavily pretreated population of patients with relapsed/refractory multiple myeloma, especially considering that these patients had received a median of 7 prior lines of therapy.

The key safety issue with belantamab mafodotin is ocular toxicity, which is a unique toxicity that is not observed with the currently approved therapies for multiple myeloma. In the slides that follow, I will highlight the major issues regarding the ocular toxicity of belantamab mafodotin, which include the high incidence of ocular toxicity, including severe events; decreased visual acuity, including severe vision loss in some patients; and the absence of ocular symptoms in many patients despite findings on ophthalmic exam, which raises the concern that this could go undetected in the absence of close monitoring.

The frequent need for dose modification despite evaluation of the lower 2.5 milligram per

kilogram dose, and the fact that despite close monitoring and dose modifications, there were patients who had recurrent and unresolved events of ocular toxicity.

This table shows the most common adverse events in the DREAMM-2 trial. I apologize. My slides just disappeared from the screen.

Could one of our hosts let me know when I can proceed?

(Pause.)

DR. BAINES: I apologize for the technical difficulties. We're just waiting for the slides to get back up on the screen. I've got notice that our team is working on it. I was on slide number 7.

(Pause.)

DR. BAINES: Okay. I'm going to go ahead and advance the slides back to slide 7 where I was. I apologize for the delay. Hopefully everybody can see the slides again.

This table shows the most common adverse events in the DREAMM-2 trial. The ocular

toxicities observed included keratopathy and changes in visual acuity identified on exam, as well as symptoms of blurred vision and dry eye. Keratopathy was the most frequent ocular adverse event and also the most frequent adverse event overall, occurring in 71 percent of patients in the 2.5 milligram per kilogram cohort.

Unlike some of the other frequent adverse events such as thrombocytopenia and anemia, which had a lower incidence in the 2.5 milligram per kilogram cohort, there was not a substantial difference in the incidence of keratopathy between the two dose levels.

Although the mechanism by which belantamab mafodotin causes ocular toxicity is not completely understood, it's thought to be due to the monomethyl auristatin F, or MMAF payload. Ocular toxicity, including keratopathy, has been observed as a class effect with MMAF-containing antibody drug conjugates, including in animal toxicology studies, however, there are currently no approved antibody drug conjugates that contain MMAF.

Keratopathy is characterized by damage to the corneal epithelium. On the right is an example of the appearance of corneal punctate keratopathy. The fluorescent green staining highlights areas where the corneal epithelium is disrupted. Because the corneal epithelium normally serves as a protective barrier, patients with keratopathy are at risk of developing more severe corneal defects, including corneal ulcers, which in severe cases may require a corneal transplant.

Patients in the DREAMM-2 trial were monitored closely with ophthalmic exams at baseline and prior to each dose of the belantamab mafodotin. Dose modifications are the primary mitigation strategy for the toxicity, as no therapeutic interventions have been identified and topical corticosteroids failed to show an impact on the incidence or severity of keratopathy in the DREAMM-2 ocular substudy.

Two different scales were used to grade ocular toxicity in DREAMM-2, the study-specific scale termed the Keratopathy and Visual Acuity, or

KVA scale, which was developed with input from FDA, and CTCAE grading, which is primarily based on symptoms and impact on activities of daily living. Some of the key aspects of the grading are underlined. The overall grade for the KVA scale is based on the more severe finding in the most affected eye.

Because many clinically relevant and serious ocular toxicities such as keratopathy are not necessarily symptomatic, FDA's analysis of ocular toxicity in DREAMM-2 is primarily based on the KVA scale, which incorporates both corneal exam and visual acuity findings, allowing for a more granular assessment of this type of ocular toxicity.

This shows a comparison of the grading by the KVA scale and CTCAE in DREAMM-2 for the 2.5 milligram per kilogram cohort. The comparison is based on the corneal exam finding component of the KVA scale. Although not shown here, we do note that 2 patients in the 2.5 milligram per kilogram cohort had grade 4 events per the overall KVA scale

based on changes in visual acuity. There are some differences in the individual grades, particularly for grades 2 and 3, however, the overall rate of keratopathy is the same for both scales.

In addition, based on the CTCAE grading, we note that investigators assessed 31 percent of patients as having had a significant impact on their instrumental activities of daily living and 27 percent of patients as having had a significant impact on their activities of daily living due to keratopathy.

I'm going to pause for one moment because I'm getting a lot of notes from the committee members that they're not able to see the slides. Could our technical team assist?

(Pause.)

DR. BAINES: I'm going to keep going while we work out the technical difficulties for some of our members; so again I apologize for the delays.

Characteristics of the incidence and severity of keratopathy are shown here. In the proposed 2.5 milligram per kilogram dose level, 71

percent of patients had at least one treatment-emergent event of keratopathy and 44 percent had severe grade 3 or 4 keratopathy.

We note that there was only one event designated as serious that occurred in the lyophilized cohort. Adverse events are defined as serious if they result in death, are considered life-threatening, require hospitalization, or result in significant incapacity or disruption of normal life function. Although ocular toxicity may be clinically significant and meaningful to patients, in most cases it is unlikely to be life-threatening or require hospitalization.

In terms of the timing for onset of keratopathy, the median time to onset for grades 2 or higher events was approximately a month and the majority of patients developed keratopathy within 2 to 3 cycles, with a cumulative incidence of keratopathy of 66 percent by the end of cycle 3.

Patients also had recurrent events. Thirty-nine percent of patients in the 2.5 milligram per kilogram cohort had more than one

event of grade 2 or worse keratopathy. We also note the higher incidence of keratopathy as well as severe keratopathy in the small cohort of patients who received the 3.4 milligram per kilogram lyophilized presentation of belantamab mafodotin.

While the numbers are small and there are some differences in underlying baseline characteristics for this cohort, this observation raises some uncertainty about the safety of the proposed presentation for marketing given that we do not have data with lyophilized presentation at the 2.5 milligram per kilogram dose.

A substantial proportion of patients in DREAMM-2 did experience worsening of their vision. Fifty-three percent of patients experienced any worsening in visual acuity and 26 percent of patients had a severe worsening in visual acuity. In addition, 17 percent of patients in the 2.5 milligram per kilogram cohort had worsening to 20-50, or worse in the better seeing eye, which is a level at which they may not legally be able to drive, and one patient in this cohort had worsening

to 20-200 or worse in the better seeing eye, which is a level that meets the definition of legal blindness.

While this particular patient had complete vision loss in their other eye at baseline, there were 2 patients in the higher 3.4 milligram per kilogram dose level who developed severe vision loss in both eyes with bilateral worsening of visual acuity -- [inaudible - unmuted voice].

I apologize. Could everyone who is not speaking please mute their phone?

Do our hosts have the ability to mute individual speakers?

DR. HOFFMAN: I'm sorry. Can we make sure that everyone who is not speaking, mutes?

(Pause.)

DR. BAINES: Okay. I'm going to try to go ahead again.

While this particular patient had complete vision loss in their other eye at baseline, there were 2 patients in the higher 3.4 milligram per kilogram dose level who developed severe vision

loss in both eyes, with bilateral worsening of visual acuity to 20-200 or worse.

The time course for the 3 patients who experienced severe vision loss is depicted here. The blue shading indicates when the doses of belantamab mafodotin were received and the unshaded boxes in that same row indicate that no further doses were administered.

The middle rows indicate the visual acuity for the right and left eye over time. The red shading highlights the maximum worsening in visual acuity and the green shading highlights resolution to levels at or near the patient's baseline.

The main purpose of this slide is to demonstrate that in some cases it took several months for visual acuity changes to resolve despite early discontinuation of belantamab mafodotin.

This slide shows the relationship between keratopathy and ocular symptoms. Of the 67 patients with keratopathy, only 43 percent had any of the ocular symptoms listed here, therefore, 57 percent of patients with keratopathy did not

have any ocular symptoms. The absence of symptoms in the majority of patients, despite findings on ophthalmic exams, raises the concern that keratopathy could go undetected in the absence of close monitoring by an ophthalmologist.

Again, if keratopathy is not identified and managed appropriately, patients could go on to develop corneal ulcers, which in severe cases may require a corneal transplant.

As mentioned, dose modifications are the only mitigation strategy identified to date for the ocular toxicity with belantamab mafodotin. Dose modifications due to keratopathy were frequent in DREAMM-2 despite evaluation of the lower 2.5 milligram per kilogram dose. Nearly half of the patients in the 2.5 milligram per kilogram cohort had at least one dose modification due to keratopathy, including 47 percent of patients with at least one dose interruption and 23 percent of patients with a dose reduction.

The rates of dose modifications due to keratopathy were not significantly different

between the 2.5 milligram per kilogram and 3.4 milligram per kilogram dose levels; and even though the protocol only recommended discontinuation for grade 4 keratopathy, there were discontinuations due to grade 2 or 3 keratopathy.

Despite dose modifications, not all patients had resolution of keratopathy. The outcomes for patients with keratopathy in the 2.5 milligram per kilogram cohort are shown here. The data is shown for both the primary analysis, at which time the median follow-up was 6.3 months, and also for the 90-day safety update, at which time there was a median follow-up of 9 months. Based on the safety update, we note that there was a new grade 4 keratopathy event of bilateral corneal ulcers reported for a patient in the 2.5 milligram per kilogram cohort.

In the DREAMM-2 trial, resolution of keratopathy was defined as recovery to grade 1 or lower, therefore the recovery rates presented here are based on the patients who had grade 2 or higher events, which include 59 patients in the

2.5 milligram per kilogram cohort as of the 6-month data cutoff and 60 patients as of the 9-month data cutoff.

For the primary analysis, as of the last assessment, the recovery rate was 41 percent. This increased to 48 percent with the extended 9-month follow-up. Among the 52 percent of patients who had unresolved keratopathy, 27 percent remained on treatment or in active follow-up and 25 percent had keratopathy that was ongoing when follow-up ended. The median time to resolution for events that resolved was approximately 2 months.

Because information on resolution for 25 percent of the 60 patients with grade 2 or higher keratopathy will not be available, as these patients either died or were lost to follow-up with persistent keratopathy, there is incomplete information on the reversibility of these events.

A direct assessment of the patient experience with ocular toxicity in DREAMM-2, based on patient-reported outcomes, also showed that the ocular toxicity had a measurable impact both in

terms of the severity of symptoms and interference with usual or daily activities. This figure shows the PRO-CTCAE results for blurred vision symptom severity and interference for the 2.5 milligram per kilogram dose level. The colored bars represent the proportion of patients at each time point by degree of severity and extent of interference.

In terms of symptom severity after week 4, the majority of patients who responded to each time point reported some degree of blurred vision, and at week 13, over 80 percent of respondents reported at least mild blurred vision. Patients who had any blurred vision were asked the degree of interference with their usual or daily activities.

By week 7, among the patients who had blurred vision, approximately 50 percent reported that blurred vision was interfering somewhat with their usual daily activities, and at week 10, approximately 50 percent of respondents reported quite a bit or very much interference with usual activities due to blurred vision.

Limitations of the PRO assessments in

DREAMM-2 included the suboptimal completion rates and the fact that many patients did not have an opportunity to respond to PRO questions because of disease progression, death, or discontinuation due to adverse events. In addition, the trial was not designed or powered to assess the maintenance of quality of life.

Despite these limitations, a substantial proportion of patients reported severe visual symptoms with significant interference in their daily activities. According to the applicant's analysis, at any on-treatment time point, 33 percent of respondents reported severe or very severe blurred vision and 45 percent of respondents reported quite a bit or very much interference with their usual activities.

In addition to the major issues and impacts of the ocular toxicity with belantamab mafodotin as I have discussed, there are several additional issues that raise uncertainty. These include concerns whether the proposed 2.5 milligram per kilogram dose is acceptable given the high rate and

severity of ocular toxicity, which were similar to the rates and severity with the higher 3.4 milligram per kilogram dose, as well as the high rates of dose modifications despite this being the lower of the two doses evaluated. I will discuss this issue in more detail on the next slide.

Second, there are concerns regarding the efficacy and safety in older patients. The trial enrolled a younger population of patients with a median age of 65 among patients in the 2.5 milligram per kilogram cohort compared to the median age at diagnosis of 69 for patients with multiple myeloma in the U.S., and patients with relapsed/refractory multiple myeloma who have received multiple prior therapies are likely to be older compared to the median age at diagnosis.

We note that although the number of patients age 75 and above in the 2.5 milligram per kilogram cohort was small, only 1 out of 13 patients achieved a response. Additionally, there were higher rates of keratopathy and visual acuity

changes in patients age 65 and above compared to patients under the age of 65 enrolled in the trial.

Third, as mentioned, there was an increased incidence of keratopathy, including severe keratopathy, in patients who received a lyophilized presentation of belantamab mafodotin compared to the frozen presentation at the 3.4 point milligram per kilogram dose.

Although the number of patients is small and there were some underlying differences in baseline disease characteristics, this observation raises residual uncertainty about the safety of the proposed lyophilized presentation for marketing considering that we do not have data with the lyophilized product at 2.5 milligram per kilogram dose.

Regarding the uncertainty with the proposed 2.5 milligram per kilogram dosage regimen, this table shows the response rate and incidence of ocular toxicity for each of the dose levels evaluated in the phase 1, first-in-human DREAMM-1 trial. The data is limited, especially at doses

lower than 2.5 milligram per kilogram, due to enrollment of only 1 to 4 patients per dose level.

In the dose escalation phase of the trial, all three patients in the 3.4 milligram per kilogram cohort achieved a response compared to a response rate of 13 percent in the 2.5 milligram per kilogram cohort and 25 percent in the 1.92 milligram per kilogram cohort.

Although the 3.4 milligram per kilogram dose was selected for expansion, we note that the perceived difference in efficacy between the 2.5 and 3.4 milligram per kilogram dose levels was not observed in DREAMM-2.. In terms of safety, ocular toxicity was observed at dose levels as low as 0.12 milligram per kilogram with grade 2 ocular toxicity observe starting at the 0.96 dose and grade 3 ocular toxicity starting at the 1.92 milligram per kilogram dose.

Although the safety data for dose levels below 2.5 milligram per kilogram is very limited, exposure-response analysis of ocular toxicity in DREAMM-2, adjusted by baseline soluble BCMA and

history of dry eye, shows that increasing dose and increasing trough concentration of belantamab mafodotin is significantly associated with an increased probability of grade 2 or higher and grade 3 or higher events of ocular toxicity.

To summarize the key points, lower doses or alternative schedules of dosing for belantamab mafodotin have not been fully explored. An exposure-response relationship for ocular toxicity was observed with increasing trough concentrations of the belantamab mafodotin. Taken together, this data suggests that a lower dose, or possibly an alternative dosing schedule, may help minimize the risk of ocular toxicity without a clinically significant impact on efficacy.

I'd now like to summarize the major concerns regarding the ocular toxicity in DREAMM-2 with a focus on patients who receive the 2.5 milligram per kilogram dose. There was a high incidence of ocular toxicity, including severe events, and the rates and severity did not differ between the two dose levels. Patients experienced significant

changes in visual acuity, including severe vision loss in some patients.

The changes in vision also had a measurable impact based on patient-reported outcome. Many patients did not have ocular symptoms despite having keratopathy on exam, raising a concern that keratopathy may not be identified in the absence of close monitoring by an ophthalmologist.

The rates of dose modifications due to ocular toxicity were high despite this being the lower of the two starting doses. Despite close monitoring and dose modifications, patients have recurrent and unresolved events of ocular toxicity. Because information on resolution is not available for the patients who had ongoing keratopathy when the follow-up ended, the data regarding the reversibility of ocular toxicity is incomplete.

Lastly, there are additional uncertainties regarding the proposed 2.5 milligram per kilogram dosage regimen, the efficacy and safety in older patients, and the safety of the lyophilized presentation at this proposed 2.5 milligram per

kilogram dose.

I will now discuss some of the considerations for the overall benefit-risk profile of belantamab mafodotin. Despite recent advances in the treatment of multiple myeloma, there continues to be an unmet medical need in patients who have received multiple lines of therapy and are refractory to the major classes of available anti-myeloma therapies.

Belantamab mafodotin is a first-in-class anti-BCMA, antibody drug conjugate with a novel mechanism of action compared to the currently approved anti-myeloma therapies.

I've lost the slides again, but I think in the interest of time, I'll keep talking, and we'll try to get it back up to slide 23.

Belantamab mafodotin is a first-in-class anti-BCMA antibody drug conjugate with a novel mechanism of action compared to the currently approved anti-myeloma therapies, and the overall response rate of 31 percent in the 2.5 milligram per kilogram cohort represents a clinically

meaningful benefit in this heavily pretreated population.

It is notable that patients enrolled in the 2.5 milligram per kilogram cohort had a median of 7 prior lines of therapy, however, ocular toxicity associated with belantamab mafodotin remains a major safety concern. The incidence and severity of keratopathy observed in DREAMM-2 was high and associated with clinically relevant decreases in visual acuity, including severe vision loss in some patients and significant impact on patients' daily activities.

This is a unique toxicity that is not typically seen with anti-MM agents, and currently there is no other approved antibody drug conjugates that contain MMAF. Despite evaluation of the lower 2.5 milligram per kilogram starting dose, close monitoring and implementation of dose modifications, many patients have recurrent and unresolved ocular toxicity. Because many patients had keratopathy on ophthalmic exam in the absence of other ocular symptoms, there is a need for close

monitoring to ensure appropriate dose modifications are implemented to prevent severe keratopathy.

Overall, considering the rates and severity of ocular toxicity associated with belantamab mafodotin, the lack of clear mitigation strategies and incomplete data regarding reversibility, there is uncertainty whether the proposed modification strategy is sufficient to mitigate the risk.

Although the efficacy results from DREAMM-2 suggest a benefit with belantamab mafodotin and the proposed population of patients with relapsed refractory multiple myeloma, it is not clear whether the benefit outweighs the risk of ocular toxicity.

In light of the issues with ocular toxicity, a risk mitigation and evaluation strategy, or REMS program, with elements to assure safe use, or ETASU, has been proposed. The main reasons are twofold.

First, because many patients are asymptomatic and keratopathy may not be identified in the absence of close monitoring with ophthalmic

exam, risk mitigation measures are needed to prevent or reduce the risk or the severity of risk with ocular toxicity.

Second, because the risk is unique to this product and oncologists likely do not have significant experience managing ocular toxicities, labeling is unlikely to be sufficient to mitigate the risk. Therefore, if belantamab mafodotin were to be approved, a REMS with ETASU would be needed.

Given the information available at this time [indiscernible], we would like the committee to discuss whether the risk of ocular toxicity has been adequately characterized in DREAMM-2 to allow for an assessment of the benefit-risk profile and to discuss the impact of ocular toxicity on the benefit-risk profile for belantamab mafodotin.

While belantamab mafodotin appears to have a treatment benefit in the proposed population, given the available data regarding the risk of ocular toxicity, the incomplete characterization of this toxicity, and the residual uncertainties at this time, we ask the committee to vote on the question,

does the demonstrated benefit of belantamab mafodotin outweigh the risks in the proposed patient population with multiple myeloma?

Thank you. This concludes the FDA presentation. Thank you for bearing with us through the technical difficulties.

Clarifying Questions to Presenters

DR. HOFFMAN: Thank you very much. We're now going to take clarifying questions to the presenters. Please use your raised hand icon to indicate that you have a question, and please remember to put your hand down after you have asked your question. Please remember to state your name for the record before you speak. Please direct your question to a specific presenter if you can.

It will be helpful to acknowledge the end of your question with a thank you and end of any follow-up question with "that is all for my question" so we can move on to the next panel member. It also looks like we're posting a revised agenda for the meeting that you can see.

DR. WAPLES: Hi. This is Yvette Waples, the

acting DFO for ODAC. I just wanted to go quickly over the agenda for the remainder of the of the day, as some of the time has shifted.

For the next, about, 30 minutes, we'll be doing clarifying questions to the presenters, and we will need to take a 30-minute lunch break, which is different from the previous agenda, and then the OPH will start following the lunch break. Then we will have the questions to the committee followed by adjournment.

I apologize for the change of the agenda for today, and it is posted on the screen now. That ends my update. Thank you.

DR. HOFFMAN: Okay. We have a question from Dr. Sung.

(No response.)

DR. HOFFMAN: Please unmute yourself.

(No response.)

DR. HOFFMAN: Why don't we move for the moment on to Dr. Nowakowski, if you want to unmute yourself and ask a question.

DR. NOWAKOWSKI: Thank you. I have a couple

of questions to the sponsor, and maybe we'll start from the timing of the development of keratopathy and the response. What's the time to response in this study? How quickly do we see that patients are responding? Because as we see from the data, the chance of response is about 1 in 3 and the chance of developing keratopathy is about 2 in 3.

So I'm trying to understand the timing of those two events and is there a subgroup of patients which can stop treatment early without evidence of response before they develop keratopathy. And the reverse is true, that the majority of patients who are responding actually are developing keratopathy just because of duration of exposure.

This will be my first question. I can proceed to some other questions or maybe we can address this one, and then I can ask additional questions afterwards.

DR. GUPTA: Absolutely. This is Ira Gupta, and I'll begin by answering your question. The median time to onset of response is 1.4 months and

the median time to onset of keratopathy is 37 days. We have not identified any subgroup of patients who may or may not respond to keratopathy.

Given that this is a class effect of a disease, it is expected that most likely all patients will develop keratopathy, and that's the importance of educating these events as well as ensuring that all patients are enrolled in the REMS program and a patient will not be dosed unless seen by a eye care professional.

DR. NOWAKOWSKI: Thank you. In terms of visiting with the ophthalmologist, I understand that the ophthalmological examination was required prior to each administration of the drug. What was the compliance with that on the study? Was it pretty good? Because in our community or treatment centers, in our experience it's something that's very difficult to synchronize those.

DR. GUPTA: The events are designed with the patient safety in mind, and it aligns with what was done in the clinical trials. We've seen a compliance rate of 98 percent with eye care visits

in the clinical trial. We will also have patient support services to assist patients with scheduling eye care appointments in the time frame needed for dosing, and therefore we are confident that this will be effective in the real-world setting.

DR. NOWAKOWSKI: Maybe this would be more of a question to Dr. Colby but also to the sponsor. How specific are those findings in terms of the ability of regular community ophthalmologists, which many of our smaller oncology practices will have to work with, to assess those changes? Does it require a corneal specialist like Dr. Colby is, or can it be done by an ophthalmologist, a practicing ophthalmologist after some training?

DR. GUPTA: Keratopathy is an eye examination finding, and that could be identified on the slit-lamp examination. I'm going to request Dr. Colby to share her perspective on which eye care professionals can perform this examination and identify the keratopathy.

DR. COLBY: Thank you, Dr. Gupta. This is Kathryn Colby. The question is regarding whether

you need to be a cornea specialist to diagnose this condition, and the answer is no. The KVA scale requires measurement of visual acuity, which any eye care professional is trained to do as one of the first parts of their training.

Secondly, the keratopathy is a very characteristic although subtle finding, and this, too, although it seems unfamiliar to non-ophthalmologists, is readily visible on the slit-lamp exam. The sponsor has created grading systems to help the eye care professional be able to get the appropriate grade of the keratopathy, and in conjunction with the visual acuity, this will enable pretty much any trained eye care professional, ophthalmologist or optometrist, to correctly identify these events. Thank you.

DR. HOFFMAN: Okay.

DR. NOWAKOWSKI: Thank you. This is helpful; just two more small follow-up questions. Could you just remind us, in the study, what type of centers participated in the study? Were they mainly academic centers, and what proportion of

patients were coming from U.S. or international? Because the median age of the studies are different than what we'd expect for this patient population, and also raises the question that it's probably easier to monitor some of those patients in an academic setting versus in a community setting.

If you could give us a little bit of an idea about that, the centers which participated in the study.

DR. GUPTA: This was a global study in which 58 centers participated. It included mainly tertiary care and academic centers where patients with relapsed/refractory multiple myeloma are treated. Sixty percent of the patients were enrolled in the U.S.

DR. NOWAKOWSKI: So really, no community centers are experienced with this.

The last question is we often give a lot of toxicity, unfortunately, to our patients with myeloma as well, and some of this includes neuropathy from some other classes of drugs, which were used in the disease. In the elderly, the

visual acuity is very important for stability and risk of falls, particularly in a setting of neuropathy.

Do you have any data regarding the falls and the risk of falls in this study or other events, which could be associated with the combination of neuropathy and decreased visual acuity?

DR. GUPTA: We do not have any data on the number of falls that the patients might have because of changes in visual acuity, but I think what's important to remember is that keratopathy is an eye examination finding that does not always lead to changes in visual acuity. In fact, 17 percent of the patients had meaningful changes in visual acuity that led to difficulties in reading and writing.

I would request Dr. Pete Voorhees to share his perspective on the quality of life of the patients that he has treated with Belamaf.

DR. VOORHEES: Thank you. My name is Peter Voorhees. I'm a multiple myeloma physician at Levine Cancer Institute in Charlotte, North

Carolina, and I've been caring for myeloma patients for 16 years. I was a PI on the DREAMM-1 study, so I do have experience treating patients with belantamab mafodotin over a range of doses. I was also a PI on the DREAMM-2 study.

Between the DREAMM-1 and DREAMM-2 studies, as well as compassionate use, I've cared for 14 patients with belantamab, the majority of whom were under my direct longitudinal care, and I have actually treated patients up to the age of 89 with this particular product.

With regards to the potential impact of keratopathy on quality of life, I would make a few points. First off, as Dr. Gupta alluded to, the physical exam finding of keratopathy does not impact quality of life in the absence of symptoms.

The FDA has appropriately expressed concern about the lack of symptoms in some patients and risk of inappropriately dosing patients with clinically significant but asymptomatic keratopathy. However, in the DREAMM-2 study and in the proposed REMS program, belantamab mafodotin is

held and potentially dose reduced based on corneal physical exam findings and symptoms, not symptoms alone.

I would argue that for patients with grade 1 symptoms of keratopathy, that has minimal to no impact on quality of life. I would say that for patients with grade 3 symptoms, there is clearly an impact on quality of life. And for those with grade 2 symptoms, there can also be an impact on quality of life that varies depending on the number or the severity of the corneal symptoms; however, with dose holds and reductions, the impact on quality of life can be mitigated.

As outlined in the briefing document, resolution of symptoms that impact quality of life, such as impaired vision, occur more quickly than the resolution of the physical exam findings, and the fact that only 3 percent of patients discontinued treatment due to keratopathy supports the argument that it was successfully managed with those dose holds and reductions. If the severity of the keratopathy was of a sufficiently prolonged

duration or irreversible, would we not have seen more treatment discontinuations due to this adverse event?

So clearly this is a very important side effect, but I think with close management and appropriate guard rails in the form of a REMS program with ophthalmologic exams before each dose and appropriate informed consent and patient counseling, I do feel that this agent can be given safely. And considering the overall response rate of 31 percent and the median duration of response of 11 months with the 13-month follow-up that was presented at ASCO, I do believe that the benefit-risk profile does favor approval of this agent. Thank you.

DR. HOFFMAN: Thank you. Dr. Chodosh?

DR. CHODOSH: Can you hear me?

DR. HOFFMAN: Yes.

DR. CHODOSH: Okay, great.

I have two questions for the sponsor. One is I'm curious how these dose holds and modifications might have affected the outcomes of

therapy. This gets at the FDA's comment that lower doses have not really been thoroughly vetted.

I wonder if there's any data or suggestions because if the patients did fine with lower doses and less frequent therapy, and the corneal changes are directly related to the quantity of drug in the system, then I'm just wondering if there's any data on that.

DR. GUPTA: Dose modifications include both dose delays as well as dose reductions, and they were allowed to manage treatment-related toxicity. Patients were able to achieve clinically meaningful deep and durable responses in spite of these dose modifications, and the dose modifications did not preclude efficacy. In addition, the events appeared to be reversible over time.

I would like to request Dr. Sagar Lonial to provide his perspective on this.

DR. LONIAL: Thank you, Dr. Gupta. This is Sagar Lonial. I think the question about dose modifications and dose holding really is an important question because that is the primary

method by which we manage a lot of these patients.

What I can tell you is that when we went back and analyzed the patients who had dose holds, which was the predominant method that was used, we demonstrated that most patients actually maintained or continued to improve their response with a dose hold, and then when retreated either maintained that or continued to deepen their response. The typical concern we often have about dose holding in oncology is that you lose control. That only occurred in a minority of patients. The majority were able to stay on, and stay on for a longer period without necessarily a dose reduction.

DR. GUPTA: Thank you, Dr. Lonial.

DR. CHODOSH: My second question --

DR. GUPTA: If I could answer -- sorry. Please go ahead.

I just wanted to answer the second question that you had about the dose selection.

DR. CHODOSH: I only stated one question. I have a second question.

DR. GUPTA: Okay. Please go ahead.

DR. CHODOSH: The second question is really for Dr. Colby. I was wondering if there was any evidence by imaging of damage to the subbasal nerve plexus in treated patients, and given the short time of the study, whether, given the epitheliopathy, we might expect long-term changes to the corneal nerves that might predispose patients to neurotrophic keratopathy later on.

DR. GUPTA: Dr. Colby, could you answer the question?

DR. COLBY: Yes. Thank you for the question. This is Kathryn Colby. There was no evidence of reduction in the subbasal nerve plexus on confocal microscopy, but I do not think that that particular measure was specifically looked at. We did not see any in the patients that we evaluated in our center.

DR. CHODOSH: Thank you.

DR. COLBY: Thank you.

DR. HOFFMAN: Okay. Thank you. I'll just remind the people who are asking questions to state your name for the record.

Next, Dr. Garcia?

(No response.)

DR. HOFFMAN: Unmute, please.

DR. GARCIA: Thank you. Thank you, Dr. Hoffman.

Jorge Garcia. I have a couple comments and two questions for the sponsor mainly. When you look at DREAMM-1 and you look at the dose escalation, as alluded by one of the FDA physicians, at the dose of 1.92, a hundred percent of those patients experienced grade 2 ocular toxicity; yet when the dose was escalated to 2.5, only 38 percent of those patients on that cohort experienced the same degree of grade 2 ocular AEs, which leads me to believe that may be an underlying characteristic of the patient population that may have enrolled on those two cohorts.

It's somewhat disappointing to me that knowing DREAMM-1 and the ocular AEs observed in that study, that the sponsor only looked at 30 patients in the ocular substudy for DREAMM-2.

Do you guys have any data as to what

appeared to be a quarter, one quarter, of patients who did not experience any keratopathy in DREAMM-2? That's for the sponsor. And also maybe for Dr. Anderson and Dr. Lonial, if they could also comment as to if indeed Belamaf gets approved, then clinically we'll have two agents for that patient population, selinexor and Belamaf.

So although it's hard to compare across trials, and I think Dr. Lonial did an excellent job trying to actually tease out some of those differences with regards to efficacy and side effects, both agents appeared to be toxic, but their toxicities appeared to be different in nature and clearly uniquely different for Belamaf.

How will you as a clinician decide or define Belamaf over selinexor in that refractory space? Thank you.

DR. GUPTA: Thank you for the question. I'll answer your question about the data that was seen in those patients who did not have keratopathy, and then hand it over to Dr. Sagar Lonial to share his perspective on where Belamaf

would sit [indiscernible] for the management of relapsed/refractory multiple myeloma.

Keratopathy is exposure dependent, and consequently patients who stayed on treatment for a short period of time may not develop these events. These are those subgroup of patients that did not have keratopathy and likely progressed very quickly. We have not identified any patient disease characteristics which might point towards a subgroup of patients that may not have keratopathy.

It is therefore very important that we ensure that all patients and the treating physicians are educated about these programs. All patients will be enrolled in the REMS, and a patient cannot be dosed unless seen by an eye care professional.

Dr. Lonial, could you add your perspective on the second question?

DR. LONIAL: Thank you. Thank you very much, Dr. Gupta.

This is Sagar Lonial. From my view, as you try and think about what you're going to do with a

given patient, as you well know, you weigh both the known and unknown adverse events, you weigh what's in front of you with the patient, and you try and make the best reasonable decision that you can, guided by data.

I will tell you that, in my view, to me one of the most important factors I use is not just performance status and things along those lines, but I really think about the likelihood of gaining significant durable response; that if you look at the data that I presented at ASCO this year, which is a 13-month follow-up of the DREAMM-2 study that was not part of the FDA review, the median duration of response was 11 months for that group with a median overall survival of 13.7 months for the entire trial.

That to me speaks to safety and efficacy in balance and says that using the dose modifications and appropriate holds and partnering with ophthalmologists and the REMS program that's being described, you can safely keep responders on if they are responding and offer them significant

clinical benefit. An 11-month DOR is significantly longer than anything else that's out there. When you couple that with the adverse event profile as I showed during the core deck in that one slide, I think it does make Belamaf a pretty easy go-to option regardless of age.

DR. CHODOSH: Thank you.

Dr. Hoffman, if you allow me to have a final question --

DR. HOFFMAN: Yes.

DR. CHODOSH: -- for the sponsor as well, Dr. Colby from ophthalmology.

One of the questions that we're being asked as committee members relates to whether or not DREAMM-2 has fully characterized, to the extent of what we know, the AEs seen on therapy. In addition, or perhaps my question relates to what else one can do if you dose reduce or hold the therapy, dose modify -- I'm not sure that I have seen or heard yet what is the true management of keratopathy from therapy in addition to stopping therapy or modifying the dose of the treatment.

DR. GUPTA: Given that corneal events are better than expected, as was even the Belamaf, we've been working very closely with ophthalmologists to ensure that these events are correctly characterized.

Throughout our clinical development program, eye examination and visual function data have been collected in numerous ways, and the KVA scale is a regress [ph] scale that uses objective eye examination findings to identify and grade corneal events regardless of the patients symptoms. These objective exam findings will be used to inform dose modifications.

I'm going to now request. Dr. Colby to share her perspective on the approach we have taken to characterize corneal events across the program.

DR. COLBY: Thank you, Dr. Gupta.

This is Kathryn Colby. The question is regarding the management of keratopathy beyond the modification of Belamaf administration. A lot of this depended upon the specifics of an individual patient. For those patients who noted dry eye

symptoms, lubricating artificial tears were given with good success. Additionally, there are some other supportive measures including warm or cool compresses.

Then there were cases where ophthalmologists involved in the study used other management approaches, including things like bandage contact lenses and tears made from a patient's serum as a management. We have reviewed in the ocular no proven benefit to prophylactic administration of steroids, but for certain patients, especially if there's a component of inflammation, topical steroids were given as therapy. Thank you.

DR. HOFFMAN: Okay. Thank you.

Dr. Cristofanilli?

DR. CRISTOFANILLI: Hi. This is Dr. Cristofanilli. I have a question I think for Dr. Abdullah at GSK. This is regarding obviously the management. It seems like, as we just heard, that obviously this medication has side effects that we are not very commonly used to managing and to recognize as medical oncologists. This is going

to be a problem for community oncologists, but we do have data, obviously from your study, showing that dose modifications and dose delays seems to be effective.

But when you look at the data that was presented, a KVA grade 3 was recorded in 44 percent of the cases and a dose reduction was only 23 percent of the cases. I think, first of all, I would like an explanation that maybe the oncologist and the treating physician were given the opportunity to manage according to their judgment, but in the community, particularly given this REMS program, we need to be absolutely sure that when there is a grade 3 recognized, the patient would hold the treatment until grade 1, and then will have a dose reduction.

DR. GUPTA: In accordance with what was done in the DREAMM-2 protocol, all patients who meet the criteria for dose modification, depending on the severity of their events, we asked to either those delay or dose reduce.

DR. CRISTOFANILLI: Well, the dose delay was

for everyone who had the grade 2 or grade 3, but the dose reduction was for grade 2, and we have only 23 percent for dose reduction. So some of the patients were not reduced according to protocol guidelines.

DR. GUPTA: In this study, patients did follow the dose modification guidelines that have been specified in the protocol. Some patients did not restart the treatment and that was because they discontinued due to disease progression. A majority of the patients did actually follow the guidelines and were able to comply with the dose modifications that were required.

I'm going to request Dr. Kathryn Colby to share her perspective on the utility of dose modifications for the management of these events.

DR. COLBY: Thank you, Dr. Gupta.

This is Kathryn Colby. We did see in this study that as Belamaf was held, that there was a gradual reduction in the keratopathy and a more rapid improvement in the visual acuity back towards baseline. So it's clear that as the medication is

held, that there is a natural resolution of the keratopathy. Thank you.

DR. HOFFMAN: Thank you. This is Philip Hoffman. I had a question to just clarify. The presenter said that the median was 3 cycles over 9 weeks, and that's much less, of course -- if the duration of response was about 9 months, I'm confused. Why so few cycles or was that because of dose holds?

DR. GUPTA: Overall, the treatment was tolerated as is evidenced by the load discontinuation rate. A median of 3 cycles takes the overall patient population enrolled into the study in consideration, and it is likely driven by the quick progressors who discontinued treatment quickly. We have patients now who have been created for over a year as they continue to see meaningful responses. I would request Dr. Sagar Lonial to share his perspective.

DR. LONIAL: Thank you, Dr. Gupta.

This is Sagar Lonial. I think your question about the median number of cycles delivered really

speaks to the median PFS in a refractory myeloma patient population and whether you look at carfilzomib, daratumumab, selinexor, or Belamaf, all of them have response rates around 30 percent.

All of them have median PFS's of around 3 months, which is driven predominantly by the responders. But it's the ability to keep patients on longer that leads to the DOR.

The 11-month DOR that I referenced is with 13-month follow-up, and overall that is really being driven by the responders and is an amalgamation of both safety, meaning they can stay on, and efficacy, meaning we had enough patients to carry them forward for a longer period of time.

DR. HOFFMAN: Okay. Thank you.

Next is Dr. Feldman.

DR. FELDMAN: Thank you. This is Brad Feldman. My question is in regards to the keratopathy and visual. This is what we are using to determine dose modifications, and it's the way that we have been told in the REMS program the community, or ophthalmologists, or optometrists,

who may be following patients, are judging the patients in communicating to the oncologists.

My question is, has this scale been reassessed and are there plans for optimizing it? And I ask that question for two reasons. One is that it's clear that there's a big discrepancy between the grade level of the scale and quality-of-life changes or vision changes of the patients; and two, given what Dr. Colby described in her slide number 40, the way that patients develop visual changes appear to be from the keratopathy progressing peripheral cornea to the central cornea. And once the central cornea is involved, that's when patients develop visual acuity changes.

I'm not sure if we have data to back that up, but if we do, it would seem that central involvement of the keratopathy would probably be a better way to grade the keratopathy or to fuse words or terms that are used currently in the scale. This is similar to some other diseases that we manage in cornea such as diffuse or

neuro-keratopathy, which has a grading scale based on the involvement of peripheral and central cornea involvement, which is typically more likely to be clinically significant to the patients.

This is really critical in my mind because this is the scale that we're all going to be using to decide how the patient's doing and what needs to happen with their treatment, and this could have an effect on the efficacy of the treatment as well. Thank you.

DR. GUPTA: The KVA scale is the protocol-defined scale that was used in the DREAMM-2 study and it focused both on keratopathy as well as changes in visual acuity. You are correct that keratopathy and changes in visual acuity do not always correlate and they don't always lead to patient's symptoms. Therefore, from an abundance of caution, we suggest that dose modification be based on either the severity of eye examination findings or severity of visual acuity change.

The key is going to be, from a patient's safety, to ensure that this and the dose

modifications are implemented. Some of your perspective that you just shared, we will definitely take that into consideration as we continue to generate data in our clinical development program.

DR. HOFFMAN: Thank you.

Mr. Mitchell?

MR. MITCHELL: Thank you, Dr. Hoffman.

I'm David Mitchell. I'm the consumer representative. I'm also a multiple myeloma patient, and I'm currently using a 4-drug combination to keep my disease in check: daratumumab, bortezomib, pomalidomide, and dexamethasone, so I have a dog in this fight.

I want to disclose that Kenneth Anderson is my physician, but I haven't discussed the issues for the day with him. I'll note before I ask my question to the FDA that the only option stated for this population was selinexor with dex, but I think autologous stem cell transplant could also be an option for patients who have delayed taking that and shouldn't be ignored.

My question is for the FDA. Given the risks involved, I want to know if approval can be conditioned on several factors: continuation and completion of the phase 3 trial; testing other keratopathy mitigation strategies; obviously a black box warning; and REMS with ETASU. And the ETASU should include the engagement of qualified ophthalmologic care with close integration with the oncologist.

I think there needs to be a requirement that the physicians explain the risk of vision loss and the management necessary to deal with it to the patient. The patient should understand it and sign a document at testing that it's been explained to him or her.

Perhaps most importantly, can it be conditioned on postmarket research coordinated and funded by the drug manufacturer to ensure both the benefits and risks presented in all the research are borne out in practice to the real-world population, especially among more typical older patients, and at the same time test the mitigation

strategies for the keratopathy.

The manufacturer should conduct the research so the costs are not shifted to patients and payers in order to demonstrate what we haven't seen demonstrated yet in the manufacturer or sponsored clinical trials. Patients should be informed that they're going to participate in that research and consent be given.

So I'm wondering if the FDA can respond to can the condition improve based on the things [inaudible - unmuted voice]? Thank you.

DR. HOFFMAN: I don't know if Dr. Baines is on the call.

DR. KANAPURU: Hi. This is Bindu Kanapuru. I'm going to ask Dr. Nicole Gormley to answer that question.

(Pause.)

DR. KANAPURU: It looks like she might be having some audio difficulty.

MR. MITCHELL: It was three questions, but if the FDA can give me some guidance on whether those kinds of qualifiers can be placed on approval

or not.

DR. KANAPURU: Hi. This is Dr. Kanapuru. I think Dr. Gormley is having some audio issues. I just wanted to state that we appreciate the question that you have posed. We want to state that we will consider the benefit-risk profile, and we have to understand that while there are other types of approvals, as you have mentioned, the drug when approved will be used for the indication that it's approved and for the patient population that it's approved.

While there is always a requirement if it is given conditional approval that you will need a post marketing study, we have to understand that the postmarketing study is not always required to be done in the same patient population as the drug that's currently approved.

So at this present time, we are asking the committee to decide on the available data that we have and for the patient population, and based on the data from the DREAMM-2 trial, if the drug is approved, based on this data and for the proposed

indication that the applicant is requesting, this will be used with the current mitigation strategies as well as the dose modification.

Our question and what we would like the committee to decide is to evaluate the current data from the DREAMM-2 trial and also the risk of ocular toxicities and the other uncertainties we have mentioned, and to determine if the ocular toxicity has been adequately categorized and the data currently that's available supports the benefit-risk profile of belantamab mafodotin in the proposed patient population.

MR. MITCHELL: I would just state that the benefits of the drug are clear, especially for this population. It's the risks we're concerned about. And if there's a way to move forward to give patients access to the benefits of the drug, with informed consent, while we continue to explore ways to mitigate the risks of the keratopathy and the vision loss, that would seem to be a better outcome than simply making a decision, yes or no, based on -- yes or no, we should just approve it with no

further requirements.

A postmarketing study would certainly be helpful, especially because the population is not necessarily typical in these two studies we're looking at, especially with regard to age. So it would be in the interest of patients if there could be an approval that was given that required those steps so as not to take away the choice for patients. And I'm asking can the FDA do that, yes or no?

DR. KANAPURU: Again, thank you again. As you have seen, we have given conditional approval that act to mitigate approvals in the past. But I think, again, our question right now, again, we would want the committee members to discuss, regardless of the type of approval, what we have with the DREAMM-2 trial and whether this supports the approval at this time.

DR. HOFFMAN: This is Philip Hoffman. But does not the REMS designation address that basically by involving the patient in that consent process, clearly?

MR. MITCHELL: Well, the REMS is a safety program. I'm talking about a postmarketing study that will dig more deeply if we approve the drug or recommend approval of the drug today. Do it on the condition of a manufacturer-sponsored postmarket study that tries to dig more deeply in the mitigation strategy of vision loss and to ensure that the drug works. It seems to in the two DREAMM studies, but for a real-world population that is going to be older and have other [inaudible - audio breaks], undoubtedly. So I'm wondering if a conditional approval is possible.

DR. HOFFMAN: Philip Hoffman here --

DR. GUPTA: Thank you. This is Ira --

DR. HOFFMAN: -- oh, please go ahead.

DR. GUPTA: Sorry. This is Ira Gupta from GSK. I did want to clarify that the application is being considered under an accelerated approval and would be supportive of a REMS as well as the educational material, including the Med Guide in the label. We can ensure that the patients are educated and can make an informed decision while

keeping the benefit-risk in mind.

As a part of the accelerated program, there will be additional studies that will be done, including the patient populations that were mentioned, so that we can continue generating data on the unique ocular events that have been seen with Belamaf.

DR. THANARAJASINGAM: Dr. Hoffman, this is Dr. Thanarajasingam. May I ask a question? I'm not sure if you can see my raised hand due to some technical difficulties.

DR. HOFFMAN: Yes, go ahead. We have a few other people as well, but actually --

DR. THANARAJASINGAM: No, you can get to me. I just wasn't sure if you could see me.

DR. HOFFMAN: No. I got your email, but I was being asked if I could do Dr. Sung next because I think he has to leave.

DR. THANARAJASINGAM: Yes, please, go ahead. Thank you.

MR. MITCHELL: And I want to say thank you, Dr. Hoffman.

DR. HOFFMAN: Okay.

DR. SUNG: Hi. This is Anthony Sung, and thank you for accommodating me. I had a question. Much has been made of the benefit of a 31 percent response rate, but I would point out, as many of the investigators probably know from the CARTITUDE study of CAR-T therapy also directed against BCMA, there was a 100 percent response rate, a 56 percent complete response rate, and 90 percent of subjects remained progression-free after 9 months.

Two questions I have, one for Dr. Anderson and other experts. How would you compare this therapy to something like CAR-T? Then my second question is because these therapies are directed against BCMA, on subjects who are on this drug, what happens to BCMA expression and will they still be eligible for CAR-T or other therapy afterwards?

DR. GUPTA: Thank you for the question. Could I request Dr. Sagar Lonial to share his perspective on how the data with Belamaf compares with CAR-T?

DR. LONIAL: Thank you, Dr. Gupta.

This is Sagar Lonial. There are very different types of treatment and they're likely very different types of patients that may first go to a CAR-T cell or may first go to an antibody drug conjugate such as Belamaf. I think that certainly the overall response rates we've seen with CAR-T cells have been impressive. You've mentioned the CARTITUDE trial. There are other trials, including KarMMa or other ones that are out there that show equally high response rates.

The durability of those responses is still a question, and I think we need longer follow-up. But not every patient is going to be eligible or have the ability to wait the period of time that's needed for a CAR-T cell, and physically every patient may not be able to go through that process as well.

I think Belamaf to me represents a really important option, another way to target BCMA. What we know about patients that progress on BCMA-directed therapy is that they do not appear to lose expression of BCMA, which is different from

what we've seen with CD19 for instance in CAR-T cells.

So while many trials have limited the ability of patients who have seen BCMA-directed therapy to receive another agent on clinical trial, I suspect you will have the ability to re-respond, and I would anticipate that my patients will likely get multiple drugs that may target BCMA with different mechanisms, whether they be CAR-T cells, antibody drug conjugates, or bispecifics, or bio-based therapies.

I know you actually specifically mentioned Dr. Anderson, so I'm going to stop there and let him weigh in as well.

DR. ANDERSON: Thank you very much, Sagar. I do agree with what you've said. I do think one of the major advantages here is it's an off-the-shelf medication, so comparing it to something like CAR-T cells of which we're also excited, it's much more practical, and readily available, and likely to be able to be used more widely.

I do think if there is a concern with BCMA expression varying over time, we know now from clinical ongoing protocols with gamma secretase, for example, that we can upregulate BCMA should that be necessary in the future. But I think, excitingly, as you've heard from the myeloma treatment paradigm, patients now are utilizing the image, the proteasome inhibitors, and the CD38 antibodies earlier in their treatment course, so this would be the first BCMA-directed therapy, we hope of a series. But this is a new target and a novel mechanism, and herein lies the excitement.

DR. HOFFMAN: Okay. Thank you. We have a question from Dr. Uldrick, and then we'll go to Dr. Thanarajasingam's question.

Dr. Uldrick?

(No response.)

DR. HOFFMAN: I'm not sure -- Dr. Uldrick, are you still on the call?

(No response.)

DR. HOFFMAN: Okay. Dr. Thanarajasingam, would you like to ask your questions?

DR. THANARAJASINGAM: Yes, thank you.

DR. ULDRICK: Dr. --

DR. THANARAJASINGAM: Oh, go ahead. Is that you, Dr. Uldrick?

DR. ULDRICK: I apologize. I'm having technical difficulties. Can you hear me now?

DR. THANARAJASINGAM: Yes.

DR. HOFFMAN: Yes.

DR. ULDRICK: Sorry. Thank you, Dr. Hoffman.

I have two questions related to risk mitigation. For the first question, I was wondering if the sponsor could speak a little bit about the guidelines for dose reduction and also address Whether or not the 40 percent of participants who had recurrent keratopathy, whether those cases were dose dependent.

DR. GUPTA: This is a slide that summarizes the dose modification guidelines prespecified in the DREAMM-2 study. Depending upon the location and the intensity of the keratopathy as well as changes in the corrected visual acuity, patients

were allowed to either continue at current dose for grade 1, delay treatment and then resume for grade 2 patients, or leave treatment and then resume at a lower dose for grade 3 patients.

All patients that developed a grade 4 corneal event would be asked to communicate discontinued treatment. These guidelines have been developed in consultation and interactions with the FDA to ensure that patients' eye examination findings and changes in visual acuity, and not patient-reported symptoms, drive the decision for treatment with Belamaf.

DR. ULDRICK: Thank you.

DR. GUPTA: I think your question --

DR. HOFFMAN: Yes, go ahead.

DR. GUPTA: Those patients who developed a grade 3 or 4 event, they were allowed to restart treatment with a reduced dose once the event has resolved to a grade 1 or better, always keeping the patient's benefit-risk in mind.

DR. HOFFMAN: Okay. Dr. Thanarajasingam?

DR. ULDRICK: I'm sorry. Can I ask one more

question, please?

DR. HOFFMAN: Oh, I'm sorry.

DR. ULDRICK: Sorry, Dr. Hoffman. Thank you.

This is a question related to the sponsor's slide 54 presented by Dr. Colby about the NEI-VFQ25. In particular, there was a quite high rate of impact on driving and reading, and I was curious as to the timing to these moderate outcomes and whether this could be further mitigated with the proposed strategy.

DR. GUPTA: Slide 54 presented the worst baseline changes in driving and reading as assessed by the NEI-VFQ25 for patients who had reported little or no difficulty at baseline. I'm going to request Dr. Gorsh to share further perspective on this detail.

DR. GORSH: Hi. This is Boris Gorsh from GSK. I will just comment on the timing of the events. I can provide you information on timing of [indiscernible - audio breaks] -- mean time to onset of the first occurrence, there was about 63

days, and in terms of the reading, it was 85 days.

DR. ULDRICK: Thank you so much.

DR. HOFFMAN: [Inaudible - audio breaks.]

DR. THANARAJASINGAM: Thanks. Yes, I have two questions based on [indiscernible - audio breaks] and anticipate your answer. I think the first one is probably best answered by Dr. Abdullah, and it's come up numerous times that myeloma patients in this study were younger than most with relapsed/refractory myeloma and, additionally, normal renal function was required.

Do we have any evidence that the ocular toxicities that were seen might be worse in older patients or in those with renal insufficiency? I think this has a lot of ramifications of use on the drug in the real world.

So that is the first question, and the second question goes out to the GSK team in general. Tolerability is really the key issue here. In addition to that being informed by clinician reports and dose modifications and treatment discontinuations, it's substantially

informed by the patient-reported outcomes that evaluate the functional impact of vision change and quality of life.

You all used the ocular-specific indices, the PRO-CTCAE and the EORTC QLQ-C30. I'm not sure existing PRO data is expected due to attrition on the study or, by design, due to conditional branching in the survey administration of PRO-CTC, for example. However, there was some suboptimal completion in eligible patients.

For patients who reported visual changes that were still eligible to complete the PROs but did not, do we know why? For example, it would be helpful to know if there were patients who declined to complete the questionnaires because they had that 2050 blurriness in their eye that was nicely demonstrated and they couldn't see the questions well enough to answer them, either electronically or on paper, however you did it.

Those are my two questions. Thank you.

DR. GUPTA: Thank you for your questions. I'll begin by answering the first one around the

safety in the older patient population, including the incidence of keratopathy, as well as in those who might have renal functions, which is a poor prognostic factor for relapsed/refractory multiple myeloma.

For Belamaf, in the older patients, it's similar to the overall patient population. We've enrolled a total of 40 patients across both the monotherapy DREAMM-1 and DREAMM-2 study that are above the age of 65. When we look at specifically the subgroups for key safety measures, including keratopathy, there is no trend in either direction.

When you look, as the age group gets older, the overall incidence of keratopathy is 54 percent in [inaudible - audio echo.]

DR. HOFFMAN: We're losing you, Dr. Gupta.

DR. GUPTA: Yes, I'm sorry. I'm hearing an echo. Thank you.

The overall incidence of keratopathy is 54 percent in the 75 or older subgroup of patients. We have also not seen any differences in the incidence of keratopathy for patients who enrolled

in the study with renal impairment, and at this time no dose adjustment is required for patients with mild or moderate renal impairment that has been seen in the study.

I'm going to request Dr. Gorsh to answer the question around the PRO data.

DR. GORSH: This is Boris Gorsh from GSK. I'll answer the question around any changes or any differences in visual acuity or keratopathy among patients that completed versus those that did not complete the patient-reported outcomes measured. We had a very similar question. We assessed this, and we did not find any meaningful differences between patients that had visual acuity changes, neither by grade nor keratopathy between patients that had completed versus those that did not complete the patient-reported outcomes questionnaire.

DR. THANARAJASINGAM: Thank you. Was the reason for missingness of data recorded?

DR. GORSH: That was not recorded as part of this study.

DR. THANARAJASINGAM: Okay. Thank you.

DR. HOFFMAN: Okay. I think we'll go to lunch now, and if there are any additional important questions for the clarifying questions, we'll complete them after lunch before we go into the open public hearing part of the meeting. So let's try, in the interest of time, to regroup at 2:08. Enjoy your break.

(Whereupon, at 1:39 p.m., a lunch recess was taken.)

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

(2:19 p.m.)

Clarifying Questions to Presenters (con't)

DR. HOFFMAN: Good afternoon, everyone. This is Philip Hoffman. We're going to reconvene the meeting. Let's start with a couple of remaining clarifying questions. I see two hands up, Dr. Klepin and Dr. Feldman.

Dr. Klepin, do you want to proceed?

DR. KLEPIN: Yes, thank you. This is Heidi Klepin. I have two questions for the sponsor. I'll go ahead and ask both of my questions and then just await the response.

The first gets back to the question around any potential risk factors for developing visual impairment specifically that could be gleaned from the data that you have. So we've talked a bit about whether or not age is associated with increased toxicity or renal dysfunction but we haven't heard more broadly if there were any other risk factors, other than duration on treatment, and specifically comorbid conditions, things like

diabetes or other ocular conditions that are more common in the older adults.

So that's one question, and any information I think that could be gleaned from these data would be helpful in the informed consent process, and I'm specifically interested in clinically significant visual changes, so not just the keratopathy itself.

The second question relates to the low response rate that was seen in the patients who are 75 and older with the dose in question. As I recall, I think there were only 8 patients, so this is a very small sample of older adults, so obviously the response rate may simply be due to chance, but it would be helpful to have a better understanding.

It's certainly notable that it was quite low, so is this possibly related to toxicity? These patients didn't stay on therapy long enough to see a benefit? Was there something different about their myeloma that could be gleaned from the data, or are there any data that might suggest that there might be an aging-related biological reason

that response rates could be lower in that older adult population?

So those are my two questions. Thank you.

DR. GUPTA: Thank you. This is Ira Gupta from GSK. To answer the first question around risk factors that might be associated with clinically significant changes in visual acuity, we've done multiple covariate analysis to see if there was any association looking at baseline disease characteristics, demographics, including prior medical history, history of intraocular surgery, cataracts, et cetera, and have not been able to identify any association between the baseline disease characteristic.

The one significant factor that was seen in a logistic regression analysis was the history of dry eye. Patients who have a history of dry eyes tend to have more superior keratopathy in eye examination finding.

Moving on to the second question around the efficacy that has been seen in the older patient population, there were a total of 13 patients that

have been enrolled in the 2.5 milligram per kilogram dose, and as you rightly mentioned, one patient of those had a response rate.

We cannot identify any reason why the others have not responded. We do see similar responses in the 3.4 milligram in the same patient population, so this is likely more a reflection of the smaller sample size, and we continue to generate more data on the efficacy and safety in the older patient population and establish the benefit-risk with Belamaf for this group of patients.

DR. KLEPIN: Okay. Thank you.

DR. HOFFMAN: Dr. Feldman?

DR. FELDMAN: Thank you. I have two questions as well. Assuming that we've adequately characterized the toxicity, ocular toxicity, with Belamaf, one practical question that comes up is the access to appropriate eye care providers for the patients who will be receiving this drug. I appreciate what Dr. Abdullah laid out in the REMS presentation that he gave, but my first question is, is there any precedent for oncologists

collaborating to this degree with a specialty like ophthalmology that is primarily outpatient based?

In ophthalmology, over 85 percent of ophthalmologists are not working in hospitals or in academic centers, so is there any precedent for that? Do we anticipate any trouble finding ophthalmologists? And as a corollary to that, in this slide deck presented by GSK, there was a mention of ophthalmology but are we including optometry as well?

Then the second question is, in the study -- and this was kind of falling over from the last question -- patients were allowed to enroll if they had mild dry eye symptoms, and mild I think they said SPK or punctate epithelial erosion. Is the thought to exclude anyone from receiving this drug if they have more severe pre-existing corneal condition? Thank you.

DR. GUPTA: Thank you for your questions. The treating oncologist as well as the [indiscernible] are used to taking a multispecialty approach for managing their patients, especially if

there have been any pretreated relapsed/refractory multiple myeloma patient populations. Therefore, there should be a collaboration already established between the eye care professionals as well as the multiple myeloma expert.

As for the REMS, as was presented by Dr. Colby, eye care professionals, including optometrists and ophthalmologists, are qualified to perform the examinations that would be required for identification of the keratopathy as well as the changes in best-corrected visual equity. Therefore, we feel quite confident with the REMS program and GSK ensuring that we facilitate and manage and help with these eye examination appointments, et cetera, and that this would be feasible in the real-world setting.

To answer your second question around patients with mild superficial contact [indiscernible] keratopathy -- do we have Dr. Jeng on the call? Maybe he can add his perspective.

DR. JENG: Yes, this is Bennie Jeng. Thank you, Dr. Gupta.

In my practice, we've seen a lot of these patients, and as Dr. Gupta's alluded to, the analysis has shown that patients who start out with dry eyes may end up with more keratopathy. I've seen that as well, but I haven't noticed any significant response rate in terms of whether they want to stop the drugs, for example. I do not see a difference in how they do. Thank you.

DR. FELDMAN: Can I make a follow-up question here?

The follow-up question would be when we have these multispecialty monitoring of patients who are on oncology drugs, are there any access issues for patients in terms of the cost of the visits or for providers and being able to bill these visits as something that would be a pretty high frequency, more than what we're used to in monitoring medicines in ophthalmology typically?

Also, is there a thought to, again, changing the KVA grading scale to better reflect primarily the clinically significant components of it so we can potentially decrease the number of unnecessary

visits for patients and decrease the dose modification? I know, especially in the current environment, we're trying to decrease the number of visits patients have to outpatient facilities. Thank you.

DR. GUPTA: Thank you, Dr. Feldman. We will definitely take your feedback in terms of optimizing the KVA scale and its use in the real-world settings as we continue to understand these better in our clinical development program.

I'm going to request Dr. Pete Voorhees to answer your question around a multi-specialty approach for treating patients and some of the issues they might face with these visits.

DR. VOORHEES: Sure. This is Peter Voorhees from Levine Cancer Institute. We certainly are used to dealing with oncology drug-related toxicity in a multidisciplinary fashion, but your point is well taken. We know that the frequency of co-management with the ophthalmologists in this particular situation is higher than a typical drug-related side effect. At least in the DREAMM-2

study, adherence to the ophthalmology visits was very high. It was in the high 90 percent range.

At Levine Cancer Institute, we actually partnered with a small private ophthalmology practice, and once the patients were in, it was actually very easy to manage these patients with that particular group. We had access to each other's numbers. We had access to each other's emails. The forms that they're required to fill out are very easy to interpret from the oncology side of things as far as whether you need to hold the dose or not.

In those situations, what the patient may be experiencing symptomatically doesn't necessarily gel with what we're seeing on the eye exam, and that's the situation where we can talk with the ophthalmologist to better understand what direction the keratopathy is headed and what we should do with the drug in that situation. So I think it's definitely manageable not only in an academic setting but also in a community-based ophthalmology practice setting as well.

DR. HOFFMAN: Okay. Thank you.

The last comment, Dr. Chambers?

DR. CHAMBERS: This is Wiley Chambers. I just wanted to go back and make a couple of comments about the topic that Dr. Feldman had brought up. The scale and the dose reductions that were done for the DREAMM-2 were obviously done before that trial was started.

I don't think there is an expectation that we couldn't do a better job now with the information that we know, but what you're presented with is the data that we had based on a best guess of a scale and a dose modification that was done prior to DREAMM-2 being run.

There is a clear delay or an extended period of time from when the drug is on board to the corneal changes that occur, and the hope at the beginning of DREAMM-2 was that there would be a treatment with the steroids that would help mitigate the corneal findings. That didn't turn out to be true, but we didn't know that until the trial was run. Thank you.

Open Public Hearing

DR. HOFFMAN: Okay. Thank you.

We're now going to move to the open public forum section.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your participation in this 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 today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect, therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, your audio is now connected. Will speaker number 1 begin and

introduce yourself? Please state your name and any organization you're representing for the record.

MS. AHLSTROM: Yes. Hi. My name is Jenny Ahlstrom, and I am the founder of the Myeloma Crowd. I'm also a multiple myeloma patient who was diagnosed in 2010, and I believe you have a video presentation for me. And I have not received anything from GSK to participate in today's meeting.

(Video played.)

"My name's Jenny Ahlstrom, and I'm a myeloma patient diagnosed in 2010. [inaudible - audio breaks] --"

(Video stopped.)

MS. AHLSTROM: -- so I created a patient advocacy organization called -- [inaudible - audio breaks] -- many times I feel like I have to constantly -- so far I've had a good outcome with my treatment, but I talk to thousands of myeloma patients every year who are my friends, and the hardest conversations I have are those who go through standard-of-care therapies in a short

period of time.

I had a friend, Michael, like that, and in less than 5 years, he had Revlimid, Velcade, dex, Pomalyst, Kyprolis, transplants, thera-elo [ph], Cytoxan, cisplatin, and selinexor, and he was not well enough to join a clinical trial though he wanted to try. So what does someone like that do?

I've spoken to friends who were on effective standard-of-care therapies, but because of the side effect profile, they had to stop. In some cases that eliminated the whole class of drugs for them, further reducing our options. So what do they do?

What do you do as a patient if you're out of standard-of-care treatments and you can't join a clinical trial? You hope for new options and combinations, which is why I hope you will approve belantamab mafodotin. Myeloma patients need more options, especially those with new approaches and targets.

Now, when it comes to safety and side effects, I've heard Dr. Robert Kyle of the Mayo Clinic say that there is no drug on the market

today, any drug, that doesn't have a side effect. Now, we've gotten used to dealing with certain side effects in myeloma, like neuropathy with Velcade, or feeling really OCD on dex, or having GI issues or rash on Revlimid. Sometimes they can be very severe.

Patients stop treatment today because they're on these therapies that become so bad. Patients hate side effects but they really hate dying of myeloma and running out of options even more. So as a patient, I make a benefit decision every day about which side effects I can tolerate and which I can't, and I do that with the help of my doctor who lays out my options and helps guide me, choosing the right combination, and I ultimately choose what I can tolerate.

Although there might be a learning curve with the ocular side effects for physicians and patients with Belamaf, eventually we will all gain experience. It was hopeful to see that in the DREAMM-2 study a few patients stopped therapy because of eye issues and they were able to modify

or hold the dose, or even patients who did that deepened their response during that time.

When you're managing a cancer diagnosis, in many ways you feel like your freedoms have been taken away, and this is an easy way to let patients decide their own future. In addition, there are many therapies targeting BCMA, and they're coming in myeloma, each with their own technologies and impact. Which of them will best work for me or my myeloma friends? We just don't know yet.

If all myeloma were the same, we could bring them all to market quickly to quickly determine which one was superior, but that's not likely to happen in myeloma any time soon because while myeloma is different, there are unique genetic subsets, and those change over time. So we don't get to that level of insight without approved therapies that can be used in all patient types, standard, high risk, or otherwise, and we should let the physicians and patients discover that broader use outside of a clinical trial.

I think it's fascinating that selinexor went

through a similar [indiscernible] by Drs. Keith Stewart and Leif Bergsagel. We now know that selinexor has great impact for patients that later relapse and those who have more aggressive myeloma like patients before 14 translocation or deletion 17p, which we didn't know during the approval process. So I believe we don't get to cure myeloma unless we have a broad set of options that can be used in studies.

In the summer of 2018, my family canvassed the United States, and that was over 850 myeloma patients, remote patients of all ages, races, and in all areas of the country like rural Nebraska and New York City. And it wasn't until we met them face to face that we understood the true challenges of myeloma care. We need more options that can be administered everywhere.

CAR-T will likely not be that option because of just the way that it's administered. This is one such off-the-shelf choice that doesn't require you to be in the clinic for long periods of time, and it's given every 3 weeks, so it's a good choice

for patients regardless of their proximity to an academic center, which I think is an important point.

So for the sake of myeloma patients everywhere, I hope you'll decide to approve this first-in-class antibody drug conjugate, belantamab mafodotin for multiple myeloma patients. Thank you.

DR. HOFFMAN: Okay. Thank you.

Speaker number 2, your audio is connected now. Will speaker number 2 begin and introduce yourself? Please state your name and any organization that you're representing for the record.

MR. GREKLEK: Hello. My name is Chris Greklek. I'm not representing any organization, just myself today. I'm a multiple myeloma patient diagnosed in January of '08, and I have not received any compensation from GSK regarding this meeting. I did send in an audio pre-recording with some slides. I don't know if that is able to be brought up.

Perhaps you --

DR. WAPLES: Yes. Hi. This is Yvette, the DFO. The videos will not be shown. Everyone will need to present live for the OPH session. Thank you.

MR. GREKLEK: Alright. I can read that, sir. Please go ahead. Thank you.

Hello, members of the committee. Thank you for the opportunity to speak to you about my cancer journey and experience with belantamab mafodotin. My name is Chris Greklek, and I'm a multiple myeloma survivor. I was diagnosed in January of 2008 when I was 39 years old, the father of three young children, an Ironman triathlete, and having a very successful work career.

All of that changed overnight. My disease had progressed so far, my local oncologist gave me less than a 5 percent chance to make it out of the hospital that first weekend. It was the worst and most advanced case of multiple myeloma he had ever seen in his experience. But I did make it out of the hospital in that first faithful weekend, only

after having 9 liters of plasmapheresis and having a steeled resolve to live so my children would be able to grow up with a father. I was determined that I was going to walk both of my daughters down the aisles someday.

I then started on thalidomide and dexamethasone, while later that year adding Velcade. This prepared me for my autologous stem-cell transplant, which put me into a complete remission for 6 months. I then relapsed into a very good partial remission but had to go back on thalidomide and dex maintenance therapy for the next 2 years. After breaking through again, I began treatment with the then new therapy Revlimid and dex. This kept me in a very good partial remission again for 4 years.

All these therapies worked very well for me, but also came at a price. There were many side effects with every one of them, some more severe than others and some that still affect me to this day. After another relapse and then failure with pomalidomide, something more seriously needed to be

done.

I came to Dana-Farber in 2014. I started in the trial with melflufen. While efficacious and giving me a minimal response, it had come with some challenges and side effects as well. That needed to be discontinued. During most of the first 6 years of my disease, I was also treated with Zometa. This resulted in severe osteonecrosis of the jaw. I've had numerous smaller surgeries plus 3 major surgeries to rebuild my jaw.

I've endured so many physical side effects from so many efficacious therapies that they are too long to list. However, I'm grateful for all of them because they have given me life and have helped me to conquer this disease over and over again.

This all brings me to May of 2016 when I started in the DREAMM-1 trial with belantamab mafodotin. Being a phase 1 trial, the correct human dose needed to be determined and the correct human dose was found by treatment 3. Having experienced excellent results right from dose 1, I

was prepared to have to endure several more side effects again, especially as quickly as the medication was working; however, no substantial side effects ever came. In fact, the only physical side effect I experienced through all of my 16 doses was some minor ocular changes, which I usually addressed with a slightly stronger glasses prescription. In addition, my vision corrected itself back to baseline within 30 days of ending the trial.

I ended the trial in June of 2017 with an excellent partial remission and have needed no maintenance therapy of any kind. I've been in excellent health ever since. Belantamab mafodotin treatment was extremely tolerable, has been very durable, and most importantly sustainable.

The care and treatment I received at Dana-Farber under the care of Paul Richardson, Kathy Colson, and the entire team has been second to none. It has been and continues to be very comprehensive cancer care with knowledgeable professionals and excellent in every way.

I'm a single dad with three older children now. My son is 23; my daughters are 20 and 18. They have seen me through the last 12-plus years of this disease and the last 4 thanks to belantamab mafodotin.

Here is where I would be showing several pictures of the last 3 to 4 years, where we've been able to experience beautiful milestones together and create lasting memories. And the most recent was just last month with my youngest daughter's graduation from high school, and I'll be able to drive her to college in the fall where she'll be going to Siena, my alma mater.

I was determined to stay here for all of my children thanks to belantamab mafodotin, and I will walk both of my girls down the aisle one day. Thank you all for listening, and thank you for your consideration.

DR. HOFFMAN: Thank you.

Speaker number 3, your audio is connected now. Will speaker number 3 begin and introduce yourself? Please state your name and any

organization you're representing for the record.

MS. DEROME: Hello? This is Mary Derome. I am director of Medical Communications and Education at the Multiple Myeloma Research Foundation. Today I'll be making MMRF's statement on behalf of Anne Quinn Young. I have no financial disclosures.

"Good afternoon. I am Anne Quinn Young, chief marketing and development officer of the Multiple Myeloma Research Foundation, where I have worked for nearly 18 years. The MMRF is a national 501(c)(3) nonprofit organization, and our mission is to accelerate the development of new more effective treatments and a cure for every patient. We have raised nearly $500 million dollars in support of this mission over the past 20 years.

"I'm here today to speak on behalf of the hundreds of thousands of patients, family members, and friends that the MMRF represents. Most everyone at this meeting is aware of the remarkable progress this community has seen since myeloma patient Kathy Giusti and her twin sister founded the MMRF in 1998. The gains in new treatment

options and survival are truly stunning and nearly unprecedented in any other cancer. This is the result of an extraordinarily committed and collaborative community working tirelessly together.

"The MMRF not only works with the community to accelerate drug discovery and development but also to provide the education required for every patient to maximize his or her outcome On any given treatment. This means we place a significant focus on helping them and their clinicians learn to manage potential and actual side effects to enjoy the full benefits of each and every treatment.

"Despite decades of progress, the 5-year survival rate for multiple myeloma is only 53.9 percent. Myeloma is a disease of remission and relapse with some patients cycling rapidly through many lines of therapy until their treatment options are exhausted. Clinical trial after clinical trial has shown that response rates, duration of response, and progression-free survival decrease with every line of therapy.

"Furthermore, myeloma not only differs from patient to patient but within patient. As we have seen from our own CoMMpass study data, there was a median of 5 different myeloma clones within a single patient. The result is that the hardiest clones survived many treatments, leading to an increased incidence of high-risk features the more lines of therapy a patient receives.

"Nearly half of the patients in the DREAMM-2 trial had high-risk features, and they had seen a median of at least 6 prior therapies. I cannot emphasize enough that these patients have very few options available. Belantamab mafodotin, or Belamaf, can make a difference for these patients who are particularly hard to treat. The most important advance for patients in later stages of their disease is an off-the-shelf novel therapy that can offer significant survival benefit with manageable toxicities, and that is Belamaf.

"The incidence and severity of the keratopathy observed with Belamaf was not insignificant. In our view, the company has

indicated a strong commitment to mitigate and manage toxicities through dose reductions, supportive care, and physician and patient education, which will allow patients to take full advantage of the potential benefit of this agent. The MMRF is also happy to partner with the company on these important educational endeavors.

"Every day we speak to patients who have run out of commercially available treatments for multiple myeloma, and in too many cases, they are not eligible for clinical trials due to low counts or concomitant cancers. It's heartbreaking and underscores the need for additional options that have proven efficacy in this heavily pretreated population.

"It is important to appreciate that patients in this situation have much higher risk tolerance of side effects than less heavily pretreated patients, and we strongly believe that they deserve that choice. If there is an option that could potentially extend their lives, let them and their care team determine if the risk-benefit ratio is

acceptable, especially if the side effects could be managed with appropriate supportive care.

"It is our hope that the committee will appreciate that despite the significant progress made in the last 20 years, more options are urgently needed, particularly in this heavily relapsed and highly refractory population. We believe that the potential benefits of Belamaf outweigh the risks for many patients and believe patients and their doctors should evaluate this question for each individual patient.

"As you have heard, there remains a significant unmet need for relapsed/refractory patients, and making Belamaf widely available can help to address that need. Thank you."

DR. HOFFMAN: Alright. Thank you.

Speaker number 4, your audio is connected now. Will speaker number 4 begin and introduce yourself? Please state your name and any organization you're representing for the record.

MS. MOSCARITOLO: My name is Edwina Moscaritolo. I'm speaking on my journey with

multiple myeloma, and I have no affiliation with any institute regarding any monetary amount. I do have a recorded statement. I don't know if that plays or not.

DR. HOFFMAN: I think we're probably not going to be able to play the recorded pieces.

MS. MOSCARITOLO: Okay. So I'll just read it now.

DR. HOFFMAN: Please.

MS. MOSCARITOLO: Okay. My name is Edwina Moscaritolo, and I am a patient of Dr. Paul Richardson at Dana-Farber Institute in Boston. I'm going to tell you what I have been on and when.

I was diagnosed with smoldering multiple myeloma in 1993. My initial treatment was radiation therapy due to a plasmacytoma. I did have low-grade anemia that required procrit support. I was on pamidronate, a bone strengthener, for approximately one year. That was in May of 1999 to 2000. The myeloma smoldered until 2002.

When I appeared to have the disease most

consistent with very early-stage myeloma, from 2000 until 2014, I remained on observation alone. From 2014 until 2015, there was a slow increase in the anemia, which required an additional amount of progress, raising the concern that the myeloma may have been becoming more active. In fact, I was stable until 2015 when I progressed as my bone marrow revealed 90 percent plasma cell involvement.

I underwent lenalidomide and dexamethasone based therapy initially, but did not tolerate lenalidomide because of a rash. I was subsequently placed on Velcade and dexamethasone for one year with cyclophosphamide added in 2016. I still continued to have an increase in light-chain myeloma and was referred to Dr. Paul Richardson in 2017 at Dana-Farber Cancer Institute, who recommended the addition of daratumumab to Velcade and dexamethasone.

In July 2017, I was in therapy, and on August 22, 2018, pomalidomide was added. Pomalidomide was discontinued on 8/25 due to rash and swelling of face. Due to the treatment of

Velcade, daratumumab, and dexamethasone not being effective any longer, my last treatment was in November 2018.

In January of 2019, I became a participant in the research study of GSK 2857916. On February 26, 2019, my ophthalmologist noted corneal events which consisted of blurry vision, dry eyes, and light sensitivity, and I continued to have some issues with my eyes. I am on 5 eye drops daily to help with these conditions. I have some difficulty reading and have to find large-print books to read, but I am able to function normally otherwise.

Compared to other drugs I have received, the side effects have really been minimal by comparison. I wish to especially acknowledge Dr. Paul Richardson along with Kathy Colson, RN, and his team for monitoring my multiple myeloma and for encouraging me all along the way. They have been right on top of any issue I might have, and at the moment I am feeling very good.

My kappa light chains have come down significantly since I've been on this GSK drug, and

everyone seems very pleased with the results, including me and my family. I appreciate the opportunity to speak to this advisory board and hope that this GSK drug will be approved so that it will be able to help other multiple myeloma patients.

DR. HOFFMAN: Okay. Thank you.

MS. MOSCARITOLO: Okay.

DR. HOFFMAN: Oh, I'm sorry. I thought you were finished.

MS. MOSCARITOLO: I am finished.

DR. HOFFMAN: Okay. Thank you.

Speaker number 5, your audio is connected now. Will speaker number 5 begin and introduce yourself? And please state your name and any organization you're representing for the record.

(No response.)

DR. SEYMOUR: I'm speaker number 6 if there's no 5 coming.

DR. HOFFMAN: Okay. I guess why don't we go ahead with number 6, and we can go back to number 5 if he or she comes.

DR. SEYMOUR: Okay. Alright. That sounds good. Thank you.

Thank you for the opportunity to speak today on behalf the National Center for Health Research. I'm Dr. Meg Seymour, a senior fellow at the center. Our center analyzes scientific and medical data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

Today the committee is asked to discuss whether the benefits of belantamab mafodotin outweighs risks for patients with relapsed or refractory multiple myeloma who received at least 4 prior therapies.

While patients clearly need new and better treatments for RRMM, these treatments need to also have meaningful benefits to patients, especially if they are associated with serious risks.

There's a reason why this drug is only being considered as a fifth-line treatment for patients who have received at least 4 different types of

prior therapies. Some people might think this is just a Hail Mary pass, and therefore we're considering this better than nothing, but we know what will happen.

If FDA approves this drug, it will be heavily promoted and inappropriately used as a second- or third-line, and fourth-line treatment as well, as has happened with other drugs in the past.

So let's look at the data starting with the risks. The known risks are substantial. This is true particularly in regard to ocular toxicity, however, there are other risks associated with the treatment such as gastrointestinal toxicity.

Seventy-one percent of patients in the proposed dosage group of 2.5 milligrams per kilogram experienced keratopathy. This is alarming. Furthermore, one-fifth of the patients who completed vision assessment and who had little to no baseline symptoms, had to give up driving and had difficulty with or gave up reading. The applicant did not identify therapeutic strategies that would mitigate the risk of ocular toxicity and

the data are not sufficient to say whether delaying or lowering doses mitigates the risks.

While this loss of vision disrupted patients' lives, limiting their freedom, it might be a risk that is acceptable to some patients, but such a risk should be acceptable only if there's a reasonable chance of meaningful benefit such as longer life or improved quality of life; however, the benefits of this treatment are not clear.

What about the benefits? The benefits are questionable because the DREAMM-2 study is an open-label, single-arm, phase 2 clinical trial comparing 2 doses of the same drug with no other active comparison group. This is completely inadequate for a cancer drug. Although the applicant met its primary endpoint with an overall response rate of 31 percent, there's a lack of crucial data regarding overall survival and quality of life.

Given the available data and the study design, we agree with the FDA's assessment that the applicant is unable to claim that patients were

satisfied with the treatment and maintain a stable quality of life. If patients do not receive a benefit in terms of overall survival, they may be taking on unnecessary risks and complications that make their final days miserable.

Moreover, replication is the key to science. Because differences in the patients enrolled, medical practice, and even chance can affect the results, interpretation of the study is further complicated by comparison to a historical control, which may have very different study populations, timing of assessments, and changes in treatment options. These limitations make it difficult to evaluate the benefits and risks and determine generalizability.

There is a need for new treatments for RRMM. Patients may be willing to accept more uncertainty and more risk for new treatments, but their need should not be the basis for approving treatments whose benefits do not outweigh the risks. Based on the data discussed today, it is difficult to determine how well the treatment in question works

and whether its effect is clinically meaningful.

To approve a treatment for which the benefits do not clearly outweigh the risks creates additional risks for those who are already suffering. At the same time, FDA would have lowered their standards for cancer drugs, so FDA will no longer be the gold standard that patients and their physicians can rely on. Thank you.

DR. HOFFMAN: Thank you.

Speaker number 7, your audio is connected now. Will speaker number 7 begin and introduce yourself? And please state your name and any organization you're representing for the record.

(No response.)

DR. HOFFMAN: Do we have speaker number 7?

(No response.)

DR. HOFFMAN: Okay. Well, let's move on to speaker number 8. Your audio is connected now. Will speaker number 8 begin and introduce yourself? Please state your name and any organization you're representing for the record.

(No response.)

DR. HOFFMAN: Speaker number 8?

(No response.)

DR. HOFFMAN: Okay. Speaker number 9, your audio is connected now. Will speaker number 9 begin and introduce yourself? Please state your name and any organization you're representing for the record.

(No response.)

DR. HOFFMAN: Okay. I'm told there is no number 9.

Number 10? Speaker number 10, your audio is connected now. Will speaker number 10 begin and introduce yourself? And please state your name and any organization that you're representing for the record.

DR. RICHARDSON: Hello?

DR. HOFFMAN: Yes, are you number 10?

DR. RICHARDSON: No. I apologize. No. This is Dr. Paul Richardson. I'm speaking for Dr. Ola Landgren and myself. We're speakers numbers 6 -- sorry, 7 and 8.

DR. HOFFMAN: Okay. Well, just a minute

because I just called on speaker number 10.

DR. RICHARDSON: I'm totally fine waiting, not a problem at all.

DR. HOFFMAN: I'm sorry. Just tell me what number you were.

DR. RICHARDSON: I'm speaking for speaker number 7, Dr. Ola Landgren on his behalf, and I am speaker number 8, Dr. Paul Richardson.

DR. HOFFMAN: Okay. Please go ahead.

DR. RICHARDSON: Lovely.

Good afternoon, everyone, and a pleasure to present to the committee this afternoon. I'm speaking on behalf of Dr. Ola Landgren first. Unfortunately because of the technical difficulties, his prerecorded statement could not be uploaded. So on behalf of Ola, who's the professor of medicine and chief of the myeloma program at Memorial Sloan Kettering Cancer Center in New York, he would like to convey his opinion on the matter of belantamab mafodotin for the approval for the treatment of relapsed and refractory myeloma.

To give you background for Ola's program, he states, "We last saw over 10,000 outpatient visits for myeloma, and therefore we do have patients in all different stages of disease." He oversees the program and he states that he can offer our patients very many different treatment options, but unfortunately, because there is no cure yet established for multiple myeloma, eventually patients become triple-class refractory. "Many of these patients can be very difficult to treat, unfortunately, and eventually we run out of therapeutic options that are viable."

"For all these reasons, we continue to urgently need new drugs that are based on new mechanisms of action where there is efficacy, and in that context, we have been using belantamab mafodotin in a variety of clinical trials --"

(Automated voice interruption.)

DR. RICHARDSON: I'm sorry, Dr. Hoffman. I don't know what that was, but I'll carry on.

"I can attest that the drug clearly has efficacy. I'm also aware, similar to all other

drugs, that there is a toxicity profile."

Specifically, Dr. Landgren does think that the focus has been on keratopathy, and that has been recognized both at meetings and in publications, but I also do think that clinically it's not every patient that suffers from this. In his experience, about a quarter of patients could have blurred vision, and this for the most part is reversible in the Memorial Sloan Kettering Cancer Center experience when the drug is stopped after some weeks or even after several months. But nonetheless, the toxicity is, in his experience, manageable.

He would again like to emphasize that when patients become triple-class refractory, there may not be other options, so having options and letting the patients have the option to choose whether he or she is interested in going on to try a new regimen is of paramount importance.

He thinks this is a modern way of offering patients treatment in the future. He hopes that you find his testimony useful, and he asks that you

kindly take this into account for today's meeting. Thank you very much, Dr. Hoffman.

DR. HOFFMAN: Okay. Do you want to proceed now as number 8?

DR. RICHARDSON: If you wouldn't mind, I would love to, thank you; just to echo some of the excellent comments made earlier and the very important discussion that we've already had. You've heard very nicely from two of my patients, Chris first and then Edwina, but I think they crystallized -- both at one end of the age spectrum and of the other, Edwina being older than Chris -- the importance of this agent to their management.

I think that critically what we see here is a new class of drug in terms of the mechanism of action and that it targets BCMA, as you heard so nicely before. This is a key target for us in the relapsed/refractory space, which obviously there are a number of strategies currently pursuing, but none of which are yet approved.

Most importantly, as an off-the-shelf

option, this antibody drug conjugate platform provides us with a very viable and user-friendly approach in the sense of being reliable and available to patients in both the community and academic setting, which is tremendously important as we think about the current environment as we deal with the consequences of COVID and beyond.

I think in that same spirit, the toxicity that you've heard about is clearly manageable in our experience, and Edwina and Christopher were very gracious in acknowledging how carefully my research nursing team in particular has managed the toxicity. But very important to share that this has been actually very practical.

We've used ophthalmic consultants of Boston who are off site, so in a sense, that's provided us with a kind of real-world experience where our patients have gone to an office practice that's separate to Dana-Farber, been evaluated, and come to us. We've liaised with their ophthalmologists and then being able to go on and treat them.

I think what's particularly important about

Christopher's experience, to illustrate from DREAMM-1, is the longevity of his clinical benefit and the fact that in terms of long-term toxicities, by far and away, the bigger problem he's been dealing with has unfortunately been the consequences of bisphosphonate exposure and certainly none of the residual minimal toxicities, in fact, that he encountered with belantamab mafodotin.

In a similar vein, Edwina's had a more challenging course in terms of her ocular issues. As she so nicely framed it, these have proved manageable, and her triple-class resistant refractory disease has been controllable now for 18 months, which is quite remarkable in the setting of such aggressive disease.

So I think they both in different ways exemplify the toxicology of this drug being manageable, most importantly with appropriate real-world considerations and ophthalmic collaboration. I think the REMS program that you heard so nicely from the sponsor team, from our

perspective, would be a very practical approach to managing this.

So in conclusion, I would simply echo the comments made earlier by previous speakers but to emphasize a real-world experience from both DREAMM-1 and DREAMM-2, emphasizing the clinical benefit we've seen of this approach for our patients. And reflective of that, our expanded access program is enrolling very rapidly such that at our center we have over 20 patients worth of experience now, including both DREAMM-1, DREAMM-2, and now very rapid enrollment in the expanded access program, reflecting the importance of this approach.

I just want to thank you very much for your kind attention.

DR. HOFFMAN: Okay.

DR. RICHARDSON: I do want to add one last comment. I have no relevant financial disclosures and have not obviously been compensated in any way for today's discussion.

DR. HOFFMAN: Okay. Thank you.

Open public hearing speaker number 5 is on

the line. Your audio is connected. Will you please introduce yourself? State your name and any organization you're representing.

DR. McDONALD: Yes. Good afternoon. I'm Marguerite McDonald. I'm an MD. I'm a clinical professor of ophthalmology at both NYU in New York and Tulane in New Orleans. I'm a cornea specialist with OCLI Vision on Long Island and director of their clinical Dry Eye Center of Excellence. I'm also a consultant to GSK.

I want to thank FDA and the ODAC for permission to address you today. It's my pleasure to speak to you about the need for regular eye exams in patients with relapsed or refractory multiple myeloma, who will be treated with belantamab mafodotin. Any ophthalmologist or optometrist can perform the slit-lamp exam and an assessment of best corrected vision; any change from last exam; and the grading of corneal changes attributed to the medicine and the change from the last exam.

The elements of these assessments are not

unique to patients on belantamab mafodotin; they're routine for an eye care professional. We note any corneal changes at the slit-lamp. In other words, these tests are the standard of care for any office visit on any patient, and we in the eye care community are all qualified to perform them.

We eye care professionals are located in private practice, clinics, and major retailers and malls across the country, so nearly all Americans have easy access to our services. It's very important to note two things. One, the exams are routine and shouldn't be considered a hindrance for an effective therapy, and keratopathy is a common, manageable eye condition; and two, the timely collaborations between the oncologist and eye care practitioner, MD or OD, is essential as it is with other treatments.

I hope this has been helpful. Please let me know if I can provide further information.

DR. HOFFMAN: Alright. Thank you.

Also speaker number 10 is now connected. Will you please begin and introduce yourself? And

state your name and any organization that you may represent.

MR. GREKLEK: Hello again. This is Chris Greklek speaking again on behalf of Sue Glick. She cannot be here today.

Can you hear me alright?

DR. HOFFMAN: Yes.

MR. GREKLEK: Oh, great. Sue Glick is not affiliated or having any -- she is not being compensated by anyone regarding this. She would just be representing herself.

"Hello. My name is Sue Glick. I'm 69 years old with two children and two grandchildren. Thank you so much for this opportunity to testify on behalf of belantamab. I was diagnosed with smoldering multiple myeloma late in January 2014. I then began therapy in May of 2014, and since that time have been on many different types of drugs, including a stem-cell therapy three years ago in September, and then also CAR-T cell therapy two years ago.

"As you well know, all these therapies cause

different side effects and I have experienced them all. But each drug has its merits, and I am grateful, and I think it was worth my while to try them. I am also happy to have the opportunity to be with doctors who are looking out for me and giving me those opportunities.

"In addition, belantamab has been my latest drug, and I am taping this the day after my fourth infusion of belantamab. My last infusion was on hold because I was experiencing the main side effects of this drug, which are eye issues and low platelets. Both of these issues resolved somewhat, and I was then eligible to then get the infusion yesterday.

"For me, my quality of life is still one of the happiest and I am happy with it. I get to walk every day, do my workouts, even with the side effects. I don't like them. I haven't liked any of the side effects I've had, but I want to continue to live for my children, my grandchildren, and myself. So I feel very fortunate, and the drug has definitely been worth my while to this point.

It is working. The doctors are very pleased, and if they're pleased, I'm pleased. Thank you very much."

That was on behalf of Sue Glick.

Questions to the Committee and Discussion

DR. HOFFMAN: Okay. Thank you.

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

We'll now proceed with the questions to the committee and panel discussions. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

So let's move to the first question. The first question for discussion is for us to discuss Whether the risk of ocular toxicity has been adequately characterized in study 205678 to allow

for an assessment of the benefit-risk profile.

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

(No response.)

DR. HOFFMAN: Okay. We can open this question for discussion. Please indicate by raising your hand if you want to make a comment. Obviously, the questions that we have are somewhat similar. Any specific comments, particularly perhaps from our ophthalmology members of the committee?

Dr. Feldman, you have a comment?

DR. FELDMAN: Yes. I think that the sponsor did a good job in characterizing the ocular toxicity of the patients in the trial during the trial period. The one question that remains is for the responders who go on to remain on drug for a longer period of time, what the ocular toxicity is as time goes on and if those patients take longer to recover from subsequent grade 3 or grade 4 toxicity incidences. We don't really have clear data looking at a longer time frame. Thank you.

DR. HOFFMAN: Thank you. Are there any other comments regarding this question before we move to the second question? Not ready to vote yet.

DR. GARCIA: I've raised my hand.

DR. HOFFMAN: I'm sorry. Dr. Garcia?

DR. GARCIA: Thank you, Dr. Hoffman.

Obviously, I think one of my concerns is I don't think DREAMM-2 really is able to characterize the ocular toxicities noted on trials, but I do believe there is already existing data with these sort of unique toxicities across other malignancies. I'm a GU medical oncologist specifically, and although with some of the agents now FDA approved for bladder cancer, we wrestle with the same concerns of ocular toxicity.

I think that there is a precedent that oncologists have the ability to work with ophthalmologists to try to learn and understand these unique side effects in a heavily pretreated patient population. I just wish, with the DREAMM-1 data, that the sponsor would have been more

careful, perhaps, in their approach for DREAMM-2 and be able to, actually, instead of doing a small ocular substudy, if you will, of 17 and 13 patients, that they could have actually expanded that to the entire patient population on trial and really try to tease out medical management as they went on trial, prospectively, if you will.

DR. HOFFMAN: Thank you.

Dr. Chodosh, did you have a comment?

DR. CHODOSH: Yes. This is Jim Chodosh. The question to adequately characterize, that's where the rub is. I don't think that the risk of ocular toxicity has been fully characterized; I'll just put it that way. Whether it's adequate to recommend approval is a different question.

I think it's always easy in retrospect to say, well, it could have been looked at more closely, and I'd certainly like to know more about it. But I guess I come down thinking that the odds that there's going to be huge unforeseen events regarding corneal toxicity are relatively low. I'd like to know more about it, but I'm less concerned

maybe than I was when I started reading the document.

DR. HOFFMAN: Mr. Mitchell?

MR. MITCHELL: Yes, Dr. Hoffman, thank you. I want to just say I agree with the previous speaker, fully versus adequately. I don't think we have fully explored the toxicity profile. And one thing I wish I knew more about, especially given the similarity of the results from the 3.4 milligram and the 2.5, in terms of effecting the cancer, if even a lower dose would be effective and produce lower toxicity.

But again, this key goes directly to the idea has it been fully explored versus adequately explored. I wish I knew that the lower dose would help with the toxicity, but at the moment we don't.

DR. HOFFMAN: Okay. Thank you for your comment.

Are there any other comments about this question before we move to discuss the second question?

(No response.)

DR. HOFFMAN: Okay. Let's move to the second question, discuss the impact of ocular toxicity on the benefit-risk profile for belantamab mafodotin. I think this is sort of the meat of the matter, if you will. I'm happy to hear comments from the group.

DR. THANARAJASINGAM: Dr. Hoffman, this is Gita Thanarajasingam. I don't think you could see my hand raised, but I have comments when it's my turn.

DR. HOFFMAN: Please go ahead.

DR. THANARAJASINGAM: My research expertise lies in improved evaluations of adverse events and understanding treatment tolerability from the patient perspective, which I think is a really central issue in this ODAC. We're talking about a novel ocular AE related to Belamaf, and it's substantial and requires monitoring.

In my opinion, the level of reversibility, as evidenced by 52 percent of patients who had not recovered as of the 9 months of follow-up, and the ability to mitigate with dose modification

strategies is uncertain. I have, like many other members here, concerns about the feasibility of broad, consistent access to the ocular specialists who are aware of this drug and need it for monitoring of the AE in community settings, but I think the big question here is how tolerable was this AE to patients and was it worth it to them; so I wanted to flush out that discussion a little bit more.

Tolerability is a degree to which symptomatic and non-symptomatic AEs affect the ability or the desire of a patient to adhere to therapy. It's informed by clinician-reported AE data, dose modifications, and treatment discontinuations. And I'll pause to say that it's meaningful that only 2 of 95 patients on this dose level discontinued treatment due to keratopathy.

Tolerability is also informed by patient-reported outcomes, and the investigators here did a good job of incorporating several PRO assessments to evaluate the functional impact of ocular AEs on patients to help us understand what

the true tolerability was.

Despite some limitations, I do think the PRO data provided are interpretable, and they're meaningful, and they demonstrate some concerning trends. For example, via NEI-VFQ, 21 percent of patients gave up night driving, and by the PRO-CTCAE, 45 percent of patients who experienced blurry vision reported quite a bit or very much interference in their lives.

From the meeting materials that were provided, the study also conducted an embedded interview substudy asking patients about their satisfaction with the treatment, and I think this would have been more valuable if it was done earlier than cycle 4, as most patients were off study by then, so this was selecting for patients who are responding.

That all being said, in the heavily pretreated triple-class relapsed/refractory population, the calculus of whether treatment is tolerable or worth it is different than in the front line. I was struck by one of the patient's

comments on the submitted material that patients hate side effects, but they hate dying of myeloma and running out of options even more. But even in a population with limited options, adverse effects that cause pain; or ones that cause intractable fatigue; or inflict the need for frequent visits; or numerous supportive care interventions; or monitoring are substantial, and they may be worse than the disease for most.

Here, the symptoms reported in the trial are primarily dry eyes, blurry vision, decreased visual acuity affecting the ability to drive or read, and even severe vision loss. Are these AEs ones patients are willing to tolerate? Is it worth it when there aren't alternate options? I wish we had some rigorous PROs that asked patients, "Is it worth it?"

At this juncture, based on the treatment discontinuations, the PRO data, and what the patients here are telling us, it seems like the ocular AES may be worth it to some or most refractory patients and that we have characterized

this toxicity adequately but not fully, as was just discussed. So I do think that talking about the risk-benefit discussion between patients and clinicians for this drug is very reasonable. Thank you.

DR. HOFFMAN: Alright. Thank you.

Are there any additional comments about this? Raise your hand or speak if I'm not seeing your hand here.

DR. CHODOSH: This is Jim Chodosh.

DR. HOFFMAN: Oh, please, go ahead. Yes?

DR. CHODOSH: My hand is raised. I'm not sure that the hand raising is working properly.

DR. HOFFMAN: Well, it raises, but it doesn't go down in my experience, so that's why I thought maybe you --

DR. CHODOSH: Well, it goes down if you could just make it go down. Okay.

So I agree. I think it comes down to what I saw in the written statements and then heard in the open statements, public statements, which were, for the most part, it's worth it because these folks

are out of options with regard to extending their life, and they show it's worth taking this chance.

I think a very great majority of patients, unless they're just tired of living, would opt for the possibility that they might have some visual problems and not be able to read and drive for some time, or maybe indefinitely, over dying. I think when you put it in that context, I think the great majority of people would choose it.

I would love to see a study asking that specific question of patients in the trial. I think that would be very worthwhile in a situation where you're nearing an earlier demise to loss of some independence. Thank you.

DR. HOFFMAN: Thank you.

Dr. Klepin?

DR. KLEPIN: Hi. This is Heidi Klepin. I agree with the prior speakers. I think it was all very eloquently stated. I did just want to hear again from the ophthalmologists on our committee today about the question with regard to feasibility

of developing these collaborative relationships, sort of larger scale, from their perspective in the community oncology setting. In academic centers, it's probably easier for us to do and maybe a little more challenging when your patients already have varied optometrists and ophthalmologists, but not impossible.

I'm just curious about their perspective, and particularly about whether or not -- and I might have misunderstood this, but it sounded like the grading system would be one that many providers would need to be educated on, if I'm correct on that. Does that seem like something where the onus would then be on the oncologist to provide to the ophthalmologist, or did I misinterpret that?

I'm just trying to get a sense of the feasibility of the monitoring process working. Obviously, it will take some time to get it set up in a lot of practices, but curious about your thoughts.

DR. HOFFMAN: Dr. Feldman, do you want to make a comment on that? I see your hand up. I

know that's probably not why it is up, but would you want to make a comment as an ophthalmologist?

DR. FELDMAN: Yes. Thank you, Dr. Hoffman.

Yes. To clarify, my criticism of the scale wasn't intended to mean that any eye care provider could follow that grading system. It actually is pretty simple to follow. So I think it would be very feasible to have an optometrist or an ophthalmologist be able to interpret the grading scale.

I do think there would need to be some education put out either by FDA, industry, or perhaps our national organization about this particular medicine so there can be a deeper understanding of how the ophthalmologists partner with the oncologists, and is so critical because it is very different from any other medicine that I'm aware of that we're monitoring ocular toxicity for in ophthalmology. It doesn't mean it can't be done; I just think it will be an educational process about the importance of these visits among several key stakeholders. I do think that

ophthalmologists in the community can work with oncologists successfully, though, in this regard. Thank you.

DR. HOFFMAN: Okay. Thank you.

Dr. Garcia, did you have your hand up?

DR. GARCIA: Yes, Dr. Hoffman.

I just want to comment, just to echo Dr. Feldman's comments, that one of the concerns when I was reading the docket was the percentage of patients with asymptomatic ocular AEs. But it appears that in the REMS program that the company has put forward, not only are they going to actually tackle people, those who have symptoms, but they're going to actually capture those with asymptomatic disease, which means that the eye exams appear to be mandated now regardless of having symptoms and no symptoms, which I think would allow to capture those patients who may be developing ocular toxicities, yet they don't have symptomatology.

I also think that when you look at -- and I'm not a myeloma expert, but I would argue that

when you're going to fourth- and fifth-line therapy, most of the patients in America may be actually already seen at major ophthalmic institutions. So it's hard for me to believe that a person who has gone to fourth- or fifth-line therapy is still sitting in the community oncologists. I would argue most of those patients probably have already been referred early on for clinical trials and may even stay at large practices.

Also, I think with one of the comments, I want to pick on a comment that I heard in the open presentations, which is questioning the transparency and/or the reliability of the FDA should this agent get approved. I disagree with that.

I think that regardless of the approval or not of this agent, we all have to recognize that clinical cancer research would require adaptability, and it is quite important for us to embrace new endpoints outside survival benefit, especially in patient populations that are heavily

pretreated, as is the case for multiple myeloma and among many other tumors.

DR. HOFFMAN: Okay. Thank you.

Dr. Gupta, did you want to make a comment?

DR. GUPTA: Yes. Thank you. This is Ira Gupta from GSK. I did just want to acknowledge and reiterate that as a part of the REMS, the education, as well as ensuring that the patients are seen by an eye care professional before the patient is dosed, as well as the fact that irrespective of patient symptoms, all eye examination findings, including changes in visual acuity, will be captured.

The comments made from Dr. Feldman will all be taken into consideration with the proposed REMS data in the real-world setting. Thank you.

DR. HOFFMAN: Okay. Thank you.

Dr. DeFlice?

DR. CHODOSH: Dr. Hoffman?

DR. HOFFMAN: Yes?

DR. CHODOSH: This is Dr. Chodosh again. In responding to whether it's feasible for eye care

providers to do this exam, we already do exams for Plaquenil toxicity, which is only annual. We also do diabetic eye exams, and in some medical record systems that's built into the system as a warning and is a common quality measure for ophthalmologists to have done an annual diabetic dilated eye exam.

I don't think it's a very heavy list to get there if it's required to have an eye care provider do the testing. I don't think that this examination is particularly complicated, and certainly less complicated to do this than what we typically do and what comprehensive ophthalmologists do to test for Plaquenil toxicity. So I just wanted to add that.

DR. HOFFMAN: Alright. That's a good point.

Dr. DeFlice, do you have a comment?

(No response.)

DR. HOFFMAN: You're on.

(No response.)

DR. HOFFMAN: You probably need to unmute if you're muted.

DR. DeFLICE: Can you hear me now?

DR. HOFFMAN: Now I can, yes.

DR. DeFLICE: Yes. As a myeloma patient, I know hundreds of myeloma patients, and some with refractory/relapsed disease that would be very willing to try this new drug given the option, where there's not many options. I think with the ocular toxicity and the ability to follow this with ophthalmology, I think it would be truly a benefit for these patients. So I would be in favor of tolerating the possible ocular toxicity and using this new drug. Thank you.

DR. HOFFMAN: Alright.

Dr. Uldrick?

(No response.)

DR. HOFFMAN: Dr. Uldrick, are you able to get on?

DR. ULDRICK: Dr. Hoffman?

DR. HOFFMAN: Yes?

DR. ULDRICK: This is Tom Uldrick. Sorry about the technical difficulties. Most of my comments have been addressed.

Are we still on question 1 or are we on question 2?

DR. HOFFMAN: Well, on question 2, but you can make a comment.

DR. ULDRICK: The one thing that I would say is that I think BCMA is an important target, and the efficacy data, although limited and still coming out, suggest an interesting durability of response that needs to be taken into consideration. I agree with the speaker who said that the very low number of participants discontinuing due to use of drug suggests that patients will accept this risk-benefit.

DR. HOFFMAN: Okay. Thank you.

Dr. Feldman, did you have another comment?

DR. FELDMAN: Yes. Thank you. I have just a quick comment, and then I'll counter my own comment. There likely is, or was, a selection bias in the patients willing to participate in the trial. We see in clinical practice that there are patients who are terrified of their side effects and who are terrified of losing any vision. I'm

assuming those patients wouldn't have filled out the informed consent to do the DREAMM-2 trial. But the same is going to happen in clinical practice, and there are patients who really would rather suffer from the disease than take on the risk of ocular toxicity, will self-select, and not be given this drug.

So the patients, as long as they are informed of the risks, I think will be active participants in making this decision, and that makes me feel comfortable about the risk-benefit profile for this drug.

DR. HOFFMAN: Okay.

Dr. Garcia, did you have one final comment?

DR. GARCIA: Yes. Thank you, Dr. Hoffman. I have wrestled with where I'm going to be with this vote. I put myself in the position as a medical oncologist to try to understand the uniqueness of this set of novel ocular toxicity, if you will, because we're accustomed in medical oncology to see grade 3's and grade 4's, neutropenias, leukopenias, anemias, and

thrombocytopenia.

One has to wonder if the AE profile of this agent was similar to the AE profile from selinexor, hypothetically, with regard to hematologic toxicities, for instance, we would actually be hesitant with benefit-risk ratios in the context of DREAMM-2. I think the novelty of the ocular toxicity is what puts the pressure, perhaps, on the group. But the fact that it's a novel ocular toxicity doesn't make it, in my opinion, any different than having a grade 3 or 4 with hematologic toxicity when you become transition dependent, and still patients continue therapy and actually have a pretty decent quality of life, however, you define those PROs.

DR. HOFFMAN: Okay. That's helpful. Thank you. I agree.

Let's talk about our voting now. We're going to be using email to submit our vote for this meeting. After everyone has submitted their vote, the vote will be compiled while we take a brief break. The vote will then be displayed on the

screen. The DFO will read the vote from the screen into the record.

Next, I will go down the roster, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you want to. We will continue in the same manner until all questions have been answered or discussed.

The question for voting is, does the demonstrated benefit of belantamab mafodotin outweigh the risks in the proposed patient population with multiple myeloma?

Any concerns or any questions about the wording? I think Mr. Mitchell expressed some earlier this morning, but this is the question at hand. Any comments about the wording of it?

(No response.)

DR. HOFFMAN: Okay. I think in many ways the discussion we've had regarding questions 1 and 2 have touched on most of the aspects of question 3. Are there additional comments, short of saying how you're going to vote, regarding this question?

Or else if there are, we'll take them, and if not, we will proceed to vote.

Raise your hand if you have additional comments or questions. There are a couple people who, for some reason, I don't get to see their hand up. I don't see Dr. Waples flagging me on that.

(No response.)

DR. HOFFMAN: Okay. So we're now going to begin the voting. You will have received an email yesterday from Yvette Waples with the voting instructions. The instructions are to reply "all" to that message. She sent it at 3:55 p.m. central time if you're looking for it.

When you respond, state your name, that it is question 3, and you're voting yes or no, or I suppose abstain is a possible vote as well. So let's go ahead and respond to that message, and then we'll take a few minutes break while our folks at the FDA compile the votes.

(Voting.)

DR. HOFFMAN: Okay. I understand that we're ready to show the vote. We have two members who

did not vote because they had to leave early, Dr. Hinrichs and Dr. Sung.

DR. WAPLES: Hi. Good afternoon. For the record, for question number 3, we have 12 yes, zero no, zero abstain, and 2 no votes.

DR. HOFFMAN: Okay. So everyone has voted; well, except Dr. Hinrichs and Dr. Sung, who we knew had to leave early, so they did not vote. We have the vote now read into the record. Now that the vote is complete, we'll go down the list, briefly, and have everyone who voted state their name, vote, and if you wish, you can state the reason why you voted as you did.

Dr. Cristofanilli?

DR. CRISTOFANILLI: This is Dr. Cristofanilli, and I voted yes because I think the data showed that the drug is effective in spite of dose reductions and interruptions. I think this tells a lot on the efficacy of this drug itself and the toxicity. The ocular toxicity has been clearly described, and there is a monitoring plan treatment that will come eventually. So I think these

early-treated patients deserve to have access to this drug.

DR. HOFFMAN: Thank you.

Dr. Garcia?

DR. GARCIA: I voted yes, and I voted yes for multiple reasons; one, the lack of therapeutic options for patients with refractory multiple myeloma in the context of the patient population for DREAMM-2. The benefits in the context of that patient population are consistent and to some extent similar to what we have seen with other agents in the same space.

Although I don't believe we were able to really discern really well the ocular toxicities as we described before, I do think they are already present for collaboration between ophthalmologists and medical oncologists for the management of these novel toxicities. And as I alluded to in my statement, if this was the typical AE that we tend to see in our clinical research protocols, we may be actually facing a different discussion, but it is the novelty of this toxicity.

I think the data, although imperfect to some extent, clearly demonstrated to me that they are very unlikely significant toxicities for patients to experience, and to the extent of what the data will look like, the side effects, at least the ocular side effects, appeared to be managed appropriately with a good, very close ophthalmologic follow-up.

DR. HOFFMAN: Okay. And for the record, that was Dr. Garcia. Please state your name when you start to speak.

Dr. Halabi?

DR. HALABI: Yes. Susan Halabi. I voted yes. There is obviously an unmet need in this group of heavily-treated patients, and I think personally it's really difficult in a single and non-competitive trial to assess clearly the benefits. But overall, even though I was a little bit concerned with the risk, I think after today's presentation, I like the sponsor's approach in terms of the management plan and the ability for medical oncologists to work with ophthalmologists.

Thank you.

DR. HOFFMAN: Thank you. Dr. Hinrichs did not vote.

Mr. Mitchell? Oh, I'm sorry. My own vote.

This is Philip Hoffman. I voted yes. I think for reasons that we've pretty much heard, I think it seems clear that this is an active agent. The toxicity is certainly not life-threatening. In many instances, it isn't even comfort threatening, though evident on examinations. I do think patients are probably willing to take this risk, and I think that the mitigation strategy that the company has outlined for exams before each dosing and a grading system and so on is reasonable and addresses the concerns.

Mr. Mitchell?

MR. MITCHELL: I'm David Mitchell, and I voted yes. I think the answer to the question posed objectively is yes. We need a BCMA drug in multiple myeloma, and I think relapsed and refractory multiple myeloma patients should make the choice here. It will be important for a whole

lot of people to have that choice and to have this drug out there with the REMS and risk mitigation strategies that everyone has referred to. Thank you.

DR. HOFFMAN: Okay. Thank you.

Dr. Sung did not vote. Dr. Cheng is a non-voting member of the committee.

Dr. Chodosh?

DR. CHODOSH: Yes. You can hear me?

DR. HOFFMAN: Yes.

DR. CHODOSH: Okay. I'm so sorry.

So I voted yes for the statements I made earlier and explained why. Thank you.

DR. HOFFMAN: Okay.

Dr. DeFlice?

DR. DeFLICE: John DeFlice. I voted yes. It's a new drug, a new class of drug for refractory/relapsed multiple myeloma with a positive benefit-risk profile, and a drug that can be taken off the shelf. So I wholeheartedly voted yes.

DR. HOFFMAN: Thank you.

Dr. Feldman? State your name, please.

(No response.)

DR. HOFFMAN: Dr. Feldman, are you on?

(No response.)

DR. HOFFMAN: Okay. Well, we see his vote is yes.

Dr. Klepin?

DR. KLEPIN: Yes. This is Heidi Klepin. I voted yes. I think the efficacy and the toxicity remains favorable in the highly pretreated patient population that was studied with a REMS plan in place. I think the informed consent process will allow patients to choose whether this trade-off is worth it to them.

I would encourage the sponsor to really try to put some additional effort into enrolling and reporting on a representative number of patients age 75 and older since that particular subgroup was poorly represented and is a large and growing group of patients who may potentially have this choice; and at present we don't have enough evidence on the benefit-to-risk ratio in that patient population.

So I would just put that bug in their ear to really try and focus on that group in ongoing and future studies.

DR. HOFFMAN: Okay. I'll go back to Dr. Feldman.

DR. FELDMAN: Can you hear me now?

DR. HOFFMAN: Yes.

DR. FELDMAN: Thank you.

This is Brad Feldman. I voted yes. I do think that we need to better characterize the ocular toxicity and optimize our monitoring and grading systems and protocols for managing these patients. But I'm very comfortable and reassured by the REMS and ETASU proposed by the sponsor, and with that we can learn together and safely monitor these patients over time.

I believe that the sponsor, the patient advocates, and the physicians in the public hearing made a very convincing case that this fills a critical unmet need and that we can let the patients decide if they would like to be on this drug. Thank you.

DR. HOFFMAN: Okay. Thanks.

Dr. Nowakowski?

DR. NOWAKOWSKI: Can you hear me?

DR. HOFFMAN: Yes.

DR. NOWAKOWSKI: Thanks.

This is Greg Nowakowski. I voted yes. I think we've clearly seen evidence of efficacy both in terms of overall response rate and also of duration of response, which is meaningful in this group of patients with very relapsed/refractory disease. I think that oncologists are quick learners. We are used to unusual toxicities with some of the novel and targeted agents, and I think the REMS program that was put in place is very reassuring that the safety of administration of this drug will be adequate when it is available to the community. So for these reasons, I supported the approval.

DR. HOFFMAN: Okay. Thank you.

Dr. Thanarajasingam?

DR. THANARAJASINGAM: Yes. This is Gita Thanarajasingam. Can you hear me?

DR. HOFFMAN: Yes.

DR. THANARAJASINGAM: So I voted yes. In a clinical situation like this where few options exist, this discussion was an off-the-shelf antibody drug conjugate, which to me seemed well tolerated other than this unique ocular toxicity, which we should acknowledge can be severe in some cases and may not be mitigable or reversible in all patients. But the drug is efficacious, and it may be more tolerable in the perspective of some patients and physicians than other treatments that are currently available in this clinical setting.

I think it's reasonable to leave open the option for decision making to patients. They can express their values and preferences to clinicians who understand the unique circumstances of each of their patients. I do think there's adequate, albeit not complete, information to guide this risk-benefit discussion, and a REMS program, as my other colleagues on this ODAC, will help.

I hope the sponsor will work with organizations that represent ophthalmologists to

educate them on the need for their involvement and collaboration in the care of patients on this drug. It will also be really helpful if the PRO data, despite its limitations, was made publicly available such as via the FDA's Project Patient Voice. This would be very helpful to inform the risk-benefit discussion between a patient and a clinician.

I strongly encourage the sponsor to ensure rigorous systematic collection and analysis of PROs over time in the ongoing clinical studies and in the postmarketing setting for this drug. Thank you.

DR. HOFFMAN: Thank you.

Dr. Uldrick?

DR. ULDRICK: Hi. This is Thomas. I voted yes. Belantamab mafodotin is a targeted, first-in-class agent with a very interesting response rate compared to other options for people who have relapsed multiple myeloma, and in particular the potential durability of response and overall survival seen in DREAMM-2 was promising,

although it needs to be verified in a randomized clinical trial.

I think that the toxicity, although unique to this agent, has been characterized adequately to inform a thoughtful REMS program, and I'm hopeful that with patient education and great partnerships between ophthalmologists and treating oncologists that the risk could be mitigated by early detection, and follow-up through the REMS program should further inform this approach.

DR. HOFFMAN: Okay. Thank you.

Before we adjourn, are there any last comments from the FDA?

DR. GORMLEY: No. This is Nicole Gormley. Thank you very much to the committee for the discussion and the comments that were made, and we'll take this into consideration. Thank you.

Adjournment

DR. HOFFMAN: Okay. Thank you.

There was a question raised at a prior meeting a few months ago about the way the materials are presented and were combined from the

sponsor and the FDA, and I want to applaud that method of presentation. I think it is clearer, and briefer, and very pointed. So I think that was very well done.

So thank you, everyone, for your time today. We will now adjourn the meeting and see you next time.

(Whereupon, at 4:12 p.m., the meeting was adjourned.)