FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Virtual Meeting

Afternoon Session

Thursday, September 22, 2022

1:50 p.m. to 6:05 p.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

She-Chia Chen, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Jorge A. Garcia, MD, FACP

(Chairperson)

Chief, Division of Solid Tumor Oncology

George & Edith Richman Distinguished

Scientist Chair

Professor of Medicine and Urology

GU Medical Oncology Program

University Hospitals Seidman Cancer Center

Case Comprehensive Cancer Center

Case Western Reserve University

Cleveland, Ohio

Pamela L. Kunz, MD

(September 22 only)

Associate Professor of Medicine (Oncology)

Division Chief, GI Oncology

Vice Chief

Diversity Equity and Inclusion, Medical Oncology

Yale School of Medicine and Yale Cancer Center

New Haven, Connecticut

Christopher H. Lieu, MD

Associate Professor of Medicine

Associate Director for Clinical Research

co-Director, Gastrointestinal Medical Oncology

University of Colorado Cancer Center

Aurora, Colorado

Ravi A. Madan, MD

Senior Clinician, Genitourinary Malignancies Branch

Head, Prostate Cancer Clinical Research Section

Program Director, Physician-Scientist Early Investigator Program

Center for Cancer Research

National Cancer Institute, National Institutes of Health

Bethesda, Maryland

David E. Mitchell

(Consumer Representative)

Founder, Patients for Affordable Drugs

Bethesda, Maryland

Jorge J. Nieva, MD

(September 22 PM session and September 23 only)

Associate Professor of Clinical Medicine

Section Head, Solid Tumors

University of Southern California (USC) Norris Comprehensive Cancer Center

Keck School of Medicine of USC

Los Angeles, California

Anthony D. Sung, MD

(September 22 only)

Associate Professor of Medicine

Duke University School of Medicine

Duke Adult Blood and Marrow Transplant Clinic

Durham, North Carolina

ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE

(Non-Voting)

Albert L. Kraus, PhD

(Acting Industry Representative)

Global Regulatory Portfolio Lead – Oncology

Pfizer, Inc.

Guilford, Connecticut

TEMPORARY MEMBERS (Voting)

Andy I. Chen MD, PhD

(September 22 PM session and September 23 only)

Associate Professor, Center for Hematologic Malignancies

Oregon Health & Science University

Portland, Oregon

Stephanie Y. Crawford, PhD, MPH

(September 22 PM session and September 23 only)

Executive Associate Dean for Faculty Affairs & Strategic Initiatives

Professor, Department of Pharmacy Systems, Outcomes and Policy

University of Illinois Chicago (UIC) College of Pharmacy

Chicago, Illinois

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(Patient Representative for September 22 PM session only)

Albuquerque, New Mexico

Boris Freidlin, PhD, MS

(September 22 PM session and September 23 only)

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Professor of Biostatistics (Emeritus)

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(September 22 PM session only)

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Division of Hematology

University of Washington, Seattle, WA

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(September 22 PM session only)

Professor of Medicine and Oncology

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Mayo Clinic Comprehensive Cancer Center

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Mikkael A. Sekeres, MD, MS

(September 22 PM session and September 23 only)

Professor of Medicine

Sylvester Cancer Center

University of Miami

Miami, Florida

Scott A. Waldman, MD, PhD, FCP, FAHA, FNAI, FASPET

(September 22 only)

Chair, Department of Pharmacology, Physiology, & Cancer Biology

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Director, Oncology Center of Excellence (OCE)

Director (Acting)

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Marc R. Theoret, MD

(September 22 PM session and September 23 only)

Deputy Center Director, OCE

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Nicole Gormley, MD

(September 22 PM session and September 23 only)

Director

Division of Hematologic Malignancies II (DHM II)

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(1:50 p.m.)

Call to Order

DR. GARCIA: Good afternoon and welcome. I would first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is April Grant. Her email and phone number are currently displayed.

My name is Jorge Garcia, and I will be chairing today's meeting. I will now call the next session of the September 22-23, 2022 meeting of the Oncologic Drug Advisory Committee to order. Dr. She-Chia Chen is the designated federal officer for this meeting, and she will begin with introductions.

Introduction of Committee

DR. S. CHEN: Good afternoon. My name is She-Chia Chen, and I'm the designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation. We'll first start with ODAC members.

Dr. Garcia?

DR. GARCIA: Jorge Garcia, GU medical oncologist and the current chair of the Solid Tumor Oncology Program at University Hospital Seidman Cancer Center, Case Western Reserve University in Cleveland, Ohio.

DR. S. CHEN: Dr. Kunz?

DR. KUNZ: Hi. My name is Pamela Kunz. I'm a GI medical oncologist and director of the GI cancer program at Yale Cancer Center in New Haven, Connecticut.

DR. S. CHEN: Dr. Lieu?

DR. LIEU: Hi, everybody. My name is Chris Lieu. I'm a GI medical oncologist and associate director for clinical research at the University of Colorado Cancer Center.

DR. S. CHEN: Dr. Madan?

DR. MADAN: Good afternoon. My name is Ravi Madan. I'm a medical oncologist at the National Cancer Institute, with a focus on prostate cancer.

DR. S. CHEN: Mr. Mitchell?

MR. MITCHELL: Good afternoon. I'm David Mitchell. I am the consumer representative to the

ODAC. I'm the founder of Patients for Affordable Drugs, and I'm a multiple myeloma patient.

DR. S. CHEN: Dr. Nieva?

DR. NIEVA: Hello. I'm Jorge Nieva. I'm the section head of solid tumors at the University of Southern California Norris Comprehensive Cancer Center and the Keck School of Medicine of USC.

DR. S. CHEN: And Dr. Sung?

DR. SUNG: Anthony Sung. I'm an associate professor of medicine in the Division of Hematologic Malignancies and Cellular Therapy, Duke University. Thank you.

DR. S. CHEN: Now we'll move on to temporary voting members.

Dr. Chen?

DR. A. CHEN: Hi. I'm Andy Chen. I'm at Oregon Health & Science University, where I focus on lymphoma.

DR. S. CHEN: Dr. Crawford?

DR. CRAWFORD: Good afternoon. My name is Stephanie Crawford. I'm professor in the Department of Pharmacy Systems, Outcomes and Policy

at the University of Illinois Chicago, and executive associate dean for Faculty Affairs & Strategic Initiatives for the College of Pharmacy. My expertise is drug safety and health equity in the medication-use process.

DR. S. CHEN: Dr. DeFlice?

DR. DeFLICE: Good afternoon. I'm a gastroenterologist and patient advocate with multiple myeloma.

DR. S. CHEN: Dr. Freidlin?

DR. FREIDLIN: Good afternoon. I'm Boris Freidlin. I'm chief of the biostatistical branch in the Division of Cancer Treatment & Diagnosis, National Cancer Institute.

DR. S. CHEN: Dr. Harrington?

DR. HARRINGTON: Good afternoon. I'm David Harrington, biostatistician, Dana-Farber Cancer Institute, Harvard School of Public Health.

DR. S. CHEN: Dr. Kwok?

DR. KWOK: Hi. My name is Mary Kwok. I'm a clinical associate professor in the Division of Hematology at the University of Washington. I'm a

clinician in the myeloma service at the Fred Hutchinson Cancer Center.

DR. S. CHEN: Nowakowski?

DR. NOWAKOWSKI: Good afternoon. I'm Greg Nowakowski. I'm a malignant hematologist at Mayo Clinic Rochester, where I also serve as a deputy director of Mayo Clinic Cancer Center for clinical research.

DR. S. CHEN: Dr. Sekeres?

DR. SEKERES: Good afternoon, everyone. I'm Mikkael Sekeres, professor of medicine and chief of the Division of Hematology at the Sylvester Cancer Center, University of Miami, and also former standing member and chair of ODAC.

DR. S. CHEN: And Dr. Waldman?

DR. WALDMAN: Good afternoon, everybody. My name is Scott Waldman. I am the chair of the Department of Pharmacology, Physiology & Cancer Biology at Thomas Jefferson University. I'm an internist. The subspecialty boards are in clinical pharmacology, and my area of research is GI oncology.

DR. S. CHEN: Thank you.

Next is acting industry representative to the committee. Dr. Kraus?

DR. KRAUS: Yes. Hi, everyone. Albert Kraus. I work for Pfizer, and I've been involved with many companies over the last few decades doing drug discovery and development work. I'm particularly focused in oncology and a lot of different developments in various tumor areas. I look forward to today's discussion.

DR. S. CHEN: Lastly, we'll introduce FDA participants.

Dr. Pazdur?

DR. PAZDUR: Hi. Richard Pazdur, and I'm the director of the Oncology Center of Excellence at the FDA.

DR. S. CHEN: Dr. Theoret?

DR. THEORET: Yes. Hi. My name is Marc Theoret, and I'm the center director of the Oncology Center of Excellence.

DR. S. CHEN: Dr. Gormley?

DR. GORMLEY: Hi. I'm Dr. Nicole Gormley.

I'm the director of the Division of Hematologic Malignancies II here at the FDA. Thank you.

DR. S. CHEN: Dr. Kanapuru?

DR. KANAPURU: Hi. I'm Bindu Kanapuru. I'm a hematologist/oncologist physician and the team lead in the Division of Hematologic Malignancies II at the FDA.

DR. S. CHEN: And Dr. Schwarsin?

DR. SCHWARSIN: Hi. I'm Alexandria Schwarsin, a clinical reviewer in the Division of Hematologic Malignancies II at the FDA.

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

Thus, 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 the break. Thank you.

Dr. She-Chia Chen will now read the Conflict of Interest Statement for the meeting.

Dr. Chen?

Conflict of Interest Statement

DR. S. CHEN: Thank you, Dr. Garcia.

The Food and Drug Administration, FDA, is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations. The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs 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 the discussions of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purpose 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 receiving updates on new drug application, NDA, 214383, for Pepaxto, melphalan flufenamide, for injection, submitted by Oncopeptides A.B. This product was approved under 21 CFR 314.500, subpart H, accelerated approval regulations, for use in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who

have received at least 4 prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody.

The confirmatory trial demonstrated a worse overall survival and failed to verify clinical benefit. Confirmatory studies are postmarketing studies to verify and describe the clinical benefit of a drug after it received accelerated approval. Based on the updates provided, the committee will have a general discussion focused on next steps for the product.

This is a particular matters meeting during which specific matters related to Oncopeptides A.B.'s NDA, approved under 21 CFR 314.500, subpart H, accelerated approval regulations will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208 (b)(3) to Drs. Mary Kwok and Greg Nowakowski.

Dr. Kwok's waiver involves her employer's research contract for four studies funded by competing firms. One study is funded by Harpoon Therapeutics, and Dr. Kwok's employer received between $250,000 and $300,000 per year. The second study is funded by Celgene, and Dr. Kwok's employer received between $200,000 and $250,000 per year. The third study is funded by Nektar Therapeutics, and Dr. Kwok's employer received between $300,000 and $350,000 per year. The fourth study is funded by Janssen, and Dr. Kwok's employer received between $250,000 and $300,000 per year.

Dr. Nowakowski's waiver involves his employer's research contract for four studies funded by competing firms. One study is funded by Amgen, and Dr. Nowakowski's employer receives between $250,000 and $300,000 per year. The third [sic - second] study is funded by Novartis, and Dr. Nowakowski's employer receives between $0 and $25,000 per year. The third study is funded by a competing firm, and Dr. Nowakowski is not aware of the funding amount being provided to his

institution for the study. The fourth study is funded by Celgene, and Dr. Nowakowski's employer receives between $0 and $25,000 per year.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website at www.fda.gov/advisory-committees/committees-and-meeting-materials/human-drug-advisory-committees.

Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Division, 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267. To ensure transparency, we encourage all standing 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 will like to disclose that Dr. Albert Kraus is participating in this meeting

as a non-voting industry representative acting on behalf of a regulated industry. Dr. Kraus' role at this meeting is to represent industry in general and not any particular company. Dr. Kraus is employed by Pfizer.

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. GARCIA: Thank you, Dr. Chen.

We will now proceed with the FDA introductory comments from Dr. Nicole Gormley.

Dr. Gormley?

FDA Introductory Comments – Nicole Gormley

DR. GORMLEY: Great. Thank you.

Good afternoon. I'm Nicole Gormley, a hematologist and the director of the FDA's Division of Hematologic Malignancies II. I will provide a brief introduction to the issues presented by the melphalan flufenamide application, which I will hereafter referred to as melflufen.

I'd like to briefly review the evidentiary criteria for approval. It is important to note that drugs granted accelerated approval or traditional approval must meet the same statutory requirements for safety and effectiveness. For safety, there must be sufficient information to determine that the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling. For effectiveness, there must be substantial evidence of effectiveness based on adequate and well-controlled investigations that allow for the conclusion that the drug will have the effect it is represented to have in the proposed labeling.

There are two approval pathways available in the U.S., regular approval and accelerated

approval. Accelerated approval is available for drugs or biologics that are intended to treat a serious or life-threatening illness. The product should provide a meaningful therapeutic benefit over available therapy, and approval is based on an endpoint reasonably likely to predict clinical benefit or an intermediate endpoint. For products granted accelerated approval, there is a requirement to conduct post-approval trials to verify the anticipated clinical benefit.

The sponsor has highlighted in the briefing document the regulatory decisions of the EMA. The regulatory actions of other agencies are not relevant to the discussions at today's ODAC or any FDA regulatory decisions. The FDA must make regulatory decisions that adhere to U.S. laws and regulations. The information discussed at the ODAC should be viewed independently to inform decisions regarding the benefit-risk of melflufen for the indicated U.S. patient population. Also of note, the U.S. FDA is the only regulatory agency that reviews the primary source data, conducting our own

analyses to inform the benefit-risk profile of a given product.

This table shows the drug and biologic regimens approved for the treatment of relapsed/refractory multiple myeloma, with the approval specifically for patients who have received at least 4 prior lines, shown in red. Of note, many of the other therapies not in red can be used to treat patients who have received 4 prior lines of therapy or those with refractory disease; but those in red are specifically approved for these later-line populations. Unlike solid tumors, in some cases patients with multiple myeloma may be retreated with the same agent or the same agent in combination with different combination partners.

Melflufen was granted accelerated approval in February 2021, but the confirmatory trial failed to confirm the clinical benefit. Physically, the overall survival result was worse than that observed in a comparator arm, pomalidomide-dexamethasone, and there was not a demonstration of PFS superiority.

With regards to the regulatory history, as mentioned, melflufen was granted accelerated approval in 2021 based on the results of the single-arm trial, HORIZON. Melflufen is an alkylating drug indicated in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody, typically referred to as triple-class refractory disease.

The top-line results shared with the FDA showed that the OCEAN trial failed to demonstrate PFS superiority and suggested worse survival results. After the FDA expressed concerns with the results, the sponsor submitted a reanalysis of PFS based on reassessment of 29 patients, which indicated nominal superiority. The FDA concerns were not allayed with this reassessment, and the IND was placed on clinical hold, and a CDER safety

alert was issued.

The agency planned to present this information at an ODAC scheduled for October 28, 2021. After receipt of the FDA briefing document, an Oncopeptides board member requested a meeting with the FDA, which was held on October 19th, in which the FDA expressed concerns with the application and presented options and recommendations to the board member and sponsor.

A second meeting was held with the company on October 20th in which the sponsor stated that they planned to voluntarily withdraw the NDA and requested the FDA to cancel the ODAC meeting, and requested that the FDA briefing document not be made public.

On October 22nd, the NDA withdrawal request was received and the ODAC was canceled. The FDA initiated the administrative processes to withdraw the NDA. During this time, there were no additional analyses conducted by the FDA and there was no communication from the sponsor regarding marketing of the product until the receipt of the

notice from the sponsor to rescind the withdrawal request in January 2022.

The sponsor has not submitted new clinical data with melflufen, but rather post hoc, exploratory, subgroup analyses from existing trials and analyses of IMiD trials external to the OCEAN trial. The FDA is reconvening an ODAC now to discuss the benefit-risk profile of melflufen. Most recently, on October [sic - September] 12, 2022, the sponsor proposed postponing this ODAC to allow for consideration of results with a separate external trial that does not include melflufen but includes an IMiD in the control arm.

With regards to the top-line results, the original IRC-assessed progression-free survival results submitted to the agency showed a PFS hazard ratio of 0.8 and failed to meet statistical significance for superiority. The sponsor conducted a readjudication of 29 patients and subsequently claimed that statistical significance was met. The FDA did not agree that PFS statistical significance has been met. The PFS

results and subsequent readjudications will be discussed later in the FDA presentation.

While the PFS results are important, the FDA's primary concerns lie with the overall survival results. Shown here are the original overall survival results. Notably, the OS analysis showed a hazard ratio of 1.1 with a median OS of 19.7 months in the melflufen arm compared with 25 months in the pomalidomide arm. While this is not a statistically significant result, and this is a trial against an active comparator, the available data suggest that patients who received melflufen-dex have unfavorable outcomes compared to those receiving pomalidomide-dex.

Previously, the sponsor proposed that the detriment observed in OS may be due to prior transplant and subsequent therapies received by these populations. However, it should be noted that there were multiple subgroups that had a worse overall survival, including those age less than 65, those with 3 or 4 prior lines of therapy, those with better creatinine clearance, and those with

extramedullary disease, among others.

Most recently, the sponsor has proposed that the potential detriment observed in OS is due to those that received a transplant previously and had a time to progression after transplant less than 36 months, and that melflufen is safe in patients who have never been transplanted and those who have been transplanted but had a time to progression of 36 months or more.

However, when looking at the forest plot, we see that while patients with the time to progression of 36 months or more had a point estimate of 0.79, the confidence interval crosses 1, and the subgroup is small, with only a total of 43 patients, so we cannot say that this group is without harm. The confidence interval for those who have never received a transplant also crosses 1.

The FDA analysis does not support that the overall survival results are due to worse outcomes only in those that received a transplant and had a time to progression after transplant less than

36 months. Furthermore, this is a post hoc, exploratory, subgroup analysis, and there are multiple challenges with post hoc, subgroup analyses, that limit their utility beyond serving as the basis for hypothesis generation for subsequent study.

One of the fundamental underpinnings of clinical trial research is control of type 1 error probability. Type 1 error probability is the chance of finding a difference when there is none. Conventionally, the type 1 error is set at 5 percent or less. Stated another way, you assume no difference between the arms. If you perform the test 100 times, 5 times you will observe a difference as large as the one observed, but it would be a false positive. We accept this level of risk, but this is the significance level for one test. There are statistical methods to control the type 1 error when there are multiple analyses, but these must be prespecified.

So when thinking about subgroup analyses, there is often interest in comparing treatments

among subsets of patients using recognized prognostic factors such as age, gender, stage, histology, among others. If there were only 3 binary factors, 8 subsets could be formed. If you compare the treatments among these 8 subsets, there will be a 33 percent probability to observe a statistically significant treatment effect, even if there were no true difference between the treatments.

To illustrate this point a little further, I would like to share with you an example from the field of cardiology. The ISIS-2 trial randomized more than 17,000 patients who were suspected of having an MI to either streptokinase, aspirin, both, or neither, in a placebo-controlled fashion. Streptokinase alone, aspirin alone, and the combination significantly reduced the rate of 5-week vascular mortality compared with placebo alone. In reporting the results in the Lancet, the editors urged the authors to include nearly 40 subgroup analyses. The authors agreed on the condition that they also include an analysis based

on astrological sign.

The result: Geminis and Libras had an adverse effect from aspirin, a 9 percent increase in mortality, compared to patients in other astrological signs who had a 28 percent reduction, with the p-value shown there. The authors mentioned that even in a trial as large as ISIS-2, with over 17,000 patients, subgroup analyses are unreliable and potentially misleading. Instead, more weight should be given to the overall result than to data from subgroups of interest.

Given these concerns, the FDA and other regulatory bodies, through the International Council for Harmonisation, or ICH, provided regulatory guidance on the use of subgroup analyses in the ICH E9 guidance document. Specifically, the ICH E9 states that any conclusions of treatment efficacy or safety, based solely on exploratory subgroup analyses, is unlikely to be accepted. Additionally, only results from analyses envisaged in the protocol can be regarded as confirmatory.

This table shows the post hoc analyses

submitted to the FDA by the sponsor to explain the observed OS results. While prior transplant, yes or no, was included as an exploratory analysis in the statistical analysis plan, it was without type 1 error control. The analyses shown in the table were not included in the original statistical analysis plan and did not have a type 1 error plan established. We also do not know what other post hoc analyses the sponsor conducted but did not submit to the FDA.

Additionally, the sponsor also asserts that there is an age interaction with overall survival and the IMiD, as observed in the OCEAN trial and other trials of IMiDs, and that these interactions significantly confound the overall survival results. There are several flaws in the sponsor's argument, which will be discussed in more detail later in the FDA presentation. But suffice it to say that the sponsor's analyses so not support this assertion.

Additionally, FDA conducted their own analysis of data with IMiDs and did not find

evidence of an age OS interaction with the IMiDs. But even if there were an interaction, the preponderance of evidence from the prespecified analysis on the ITT population demonstrates a hazard ratio greater than 1 in the melflufen arm compared to the pomalidomide arm, and the data from the OCEAN trial does not provide substantial evidence of the safety and effectiveness of melflufen.

One factor which may be contributing to the overall survival finding is the dose. The 40-milligram fixed dose is poorly tolerated, and there are multiple safety events associated with higher exposure. As we will hear later in the FDA presentation, there were high rates of dose modification in the OCEAN trial; 78 percent of patients experienced at least one adverse event leading to dose modification; 47 percent of patients experienced at least one adverse event leading to dose reduction; and 26 percent of patients experienced at least one adverse event leading to drug discontinuation. These rates were

significantly higher in the melflufen arm as compared to pomalidomide arm.

PK exposure-response analyses suggest that weight or body-size based dosing may be more appropriate than the currently approved flat dose, and analyses suggest that the current 40-milligram dose may not be the correct exposure target. A lower dose may be more tolerable and may have similar efficacy.

So in conclusion, there are several issues presented by the melflufen application, but there are three central issues. First, in the confirmatory trial OCEAN, melflufen-dex demonstrated a potential document and overall survival compared to pomalidomide-dex. Several subgroups have been identified that performed worse in the trial, but as previously stated, these post hoc exploratory analyses should only be used to inform future trial design and cannot be relied upon to provide substantial evidence of safety and effectiveness.

Second, the trial failed to meet the primary

endpoint of a statistically significant improvement in PFS. The PSS reassessment by the sponsor and concerns regarding the censoring rule used will be discussed later in the FDA presentation. Third, there remains significant concern regarding the dose of melflufen.

From a regulatory perspective, we are in a situation where the randomized-controlled trial has shown a potentially worse overall survival compared to an active comparator. We cannot adequately assess overall survival from single-arm trials, so we cannot rely on the initial single-arm trial HORIZON to assess the overall survival. With the available data, we are unable to assess if melflufen is causing harm in the currently indicated patient population. The toxicity, dose modifications, and subgroup analyses suggest the potential for harm.

Lastly, accelerated approval requires that the drug provide a meaningful advantage over available therapies. Given what is currently known, we would not have granted accelerated

approval to melflufen, as the concerns and issues outlined above would preclude a conclusion that melflufen provides a meaningful advantage over available therapy.

Given these major concerns, we would like for the committee to discuss the benefit-risk profile of melflufen for the currently indicated patient population, considering the results of the confirmatory OCEAN trial. The voting question is, given the potential detriment in overall survival, failure to demonstrate a progression-free survival benefit, and lack of an appropriate dose, is the benefit-risk profile of melflufen favorable for the currently indicated patient population? Please note that we are asking for the committee members to use your clinical and scientific expertise to assess the benefit-risk profile of the product, based on data and discussion presented at this meeting.

I'd like to make a comment in closing. You will hear in the sponsor's presentation and the open public hearing about the need for additional

therapies. Please note that at the FDA, we strongly agree with that sentiment. Many of us have had family members affected by cancer or cancer ourselves, so when applications are submitted for new therapies that are effective, we do all that we can to expedite the regulatory decision for these therapies, but the need for new therapies must be balanced with the fact that we must first do no harm.

The sponsor has proposed a new indication based on a subgroup and a different dosing strategy for select patients. Any indication granted must meet the same clinical and statistical rigor as would be expected for a new application. You can't carve out a new population without studying it. The product should be studied prospectively and demonstrate in a rigorous manner that it is safe and effective in this new population at the proposed dose. Please bear this in mind during the remaining presentations and discussions today. Thank you very much.

DR. GARCIA: Thank you, Dr. Gormley.

Both the Food and Drug Administration, FDA, 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 applicants, including Oncopeptides A.B.'s non-employee presenters, to advise the committee of any financial relationships that they may have with the sponsor such as consulting fees, travel expenses, honoraria, and interest in the sponsor, 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 Oncopeptides A.B.

Applicant Presentation – Jakob Lindberg

MR. LINDBERG: Good afternoon. My name is Jakob Lindberg with Oncopeptides. We are here today to give a different perspective to the FDA's voting question. Rather than waiting to hear your independent ODAC assessment, they have asked the leading voting question that has already determined that there's a survival detriment when compared to well-established, active therapy; that the primary PFS endpoint, based on blinded IRC review, was not met, and that the dosing for this cytotoxic agent is inappropriate.

We are here because we strongly believe that patients need to understand the implications from the newly identified interactions that affect interpretation of OCEAN, one for Pepaxto that can lessen potential risk, and then unexpected independent agent reaction for immunomodulators. And this is important. The median patient on IMiD therapy in the U.S. right now is 74 years old.

This information is too important for patients to already predetermine the interpretation.

In the upcoming months, as independent experts assess these data, I personally believe that OCEAN will be remembered as the canary in the coal mine regarding this key interaction between IMiDs and age, and I hope it will help guide the assessment of heterogeneous studies with an active comparator. We only asked you to keep an open mind.

We assert that OCEAN met its primary endpoint of superior PFS, based on prespecified, independent review committee evaluation using IMWG response criteria and the prespecified statistical analysis plan. In the docket, you can see a letter from the chairman of the IRC stating that the IRC followed IMWG guidelines for disease progression, and was completely blinded throughout the process to assess the primary endpoint.

We agree that OCEAN demonstrates an overall survival hazard ratio of 1.14 in the full analysis population as of the latest update, however, the

hazard ratio in comparison to an active comparator doesn't tell the full story given the significant survival heterogeneity for both study drugs. Because the primary endpoint was confirmed in accordance with the prespecified analysis plan, this allows for assessment for homogeneity of treatment effect across prespecified subgroups, and it is here that OCEAN has a lot to teach us.

OCEAN identified significant PSF and OS differences for Pepaxto, based on patients' prior exposure to an autologous stem cell transplant. These data merit the limitations of use that I will review shortly. For pomalidomide, OCEAN identified unexpected significant survival differences, based on patients' age that was not reflected in the surrogate endpoint of PFS, and which has not been properly discussed in the literature.

This is the major confounder for the OS interpretation in OCEAN. Given this data and the recommended patient population, the confirmatory study OCEAN fulfilled accelerated approval obligations to confirm benefit-risk in a population

that desperately need access to product with novel mechanisms of action.

Let us further review the heterogeneity that confounds the OS interpretation in OCEAN. Here you see that PFS for pomalidomide treatment across prespecified age subgroups is identical, however, OS differs significantly. The hazard ratio between old and young patients is 2 to 3X. In relapsed/refractory myeloma, FDA's own analysis on age in 2019 shows that the survival should be very similar across these age groups at this stage of the disease.

In OCEAN, there was a clear deterioration in survival benefit with increasing age for pomalidomide. This phenomenon is replicated across studies that isolate pomalidomide or other immunomodulatory drugs that allow for detailed survival analysis with consistency. Further details regarding this data can be found in the appendix of your briefing book, as well as in the public docket. The forthcoming DREAMM-3 study will corroborate this phenomenon. To the left, you see

the heterogeneity for both PFS and OS for Pepaxto, based on prior ASCT. For Pepaxto, this reveals an identified subgroup risk which should be addressed in labeling.

As per the ICH guidelines for clinical studies that meet the primary endpoint, a review of prespecified subgroups should be conducted to assess homogeneity of treatment effect since ITT may not adequately characterize treatment effects across patient subgroups. This assessment is intended to identify patients that may be at increased risk.

Treatment effect differences need to be considered prognostic or predicted. This requires the filing to be in line with the mode of action and biological rationale, along with precedent in other trials, and the finding needs to be supported by other endpoints in the trial. Prior ASCT was a prespecified subgroup in OCEAN and is regularly used for treatment decisions in myeloma.

An ASCT interaction for Pepaxto aligns with biology and mechanism of action. Patients receive

conditioning therapy in conjunction with ASCT that typically consists of high-dose melphalan treatment. This likely induces partial or complete drug resistance to further alkylate the base therapy. On the prespecified subgroup level, prior ASCT is the patient group that would be excluded from treatment with Pepaxto, however, albeit the post hoc analysis, the patient group with real increased risk with Pepaxto treatment are those patients with a less successful ASCT in line with treatment guidelines. They describe tumors relapsing early after ASCT are more resistant to further alkylated based therapy.

Considering the OCEAN data, we are recommending a limitation of use that aligns with clinical treatment guidelines and published recommendations regarding ASCT. Pepaxto should not be used in patients with post-ASCT progression less than 3 years after transplant. We propose to include this in the prescribing information and adequately inform physicians of this update.

Let me summarize the important

considerations that address the three FDA concerns. First, Pepaxto met its primary endpoint with statistically significant superior PFS, based on blinded IRC review. The chair of the IRC has submitted written verification of this outcome, therefore, it's appropriate to look further into subgroups to identify potential heterogeneity of treatment effect.

We found that the OS risk with Pepaxto in comparison with pomalidomide is driven by patients with prior ASCT. Removal of this subgroup at risk improves both efficacy and safety for Pepaxto, and this is a biologically plausible risk, which is why we propose to update the label to include the limitations of use.

Additionally, Pepaxto is an alkylating cytotoxic drug being used in a severely ill patient population with very aggressive disease. As such, it is appropriate to administer at the maximum tolerated dose to establish tumor control. And when looking at the recommended population, there were less dose modifications, higher response

rates, and patients were able to remain on treatment longer.

With this information in mind, here is the agenda for the remainder of the presentation. We also have additional experts to answer your questions. Thank you. I'll now turn the presentation to Dr. Richardson.

Applicant Presentation – Paul Richardson

DR. RICHARDSON: Thank you very much, Dr. Lindberg.

Good afternoon, ladies and gentlemen. It is my privilege to provide a discussion on the unmet medical needs in relapse and refractory multiple myeloma. My name is Paul Richardson, and I serve as the R.J. Corman Professor of Medicine at Harvard Medical School, as well as clinical program leader and director of clinical research at our center. I was principal investigator on the HORIZON study on our site, as well as the largest enrollers. Moreover, subsequent to its accelerated approval last year, we at our center prescribed Pepaxto according to the label prior to the suspension of

that last year.

It's important to add that I've been treating patients with relapsed and relapsed/refractory myeloma for more than 20 years. We currently have a busy clinical practice with up to four clinics a week, where we see patients for both participation in clinical trials, as well as for receiving treatment as standard of care; and please note, I am not being compensated for my time in today's meeting.

Now, the treatment of multiple myeloma is truly a marathon and not a sprint, and strategic and practical considerations are absolutely key, particularly in the relapse and refractory setting. Very importantly, this can improve long-term outcome, and in our practice, we run out of options, unfortunately, every week as myeloma progresses rapidly once the disease becomes increasingly resistant and refractory. At this stage of the disease course, the goal of treatment is to stop further progression and maintain disease control, preserve quality of life, and recognize

that these patients are unfortunately past cure.

From my clinical experience with Pepaxto, this has been a generally well tolerated drug that is easy to administer in the outpatient setting, and meaningfully adds, in our experience, to the treatment paradigm. Not having Pepaxto readily available over the past 9 months has been a real loss, in my view, for both our patients and for us as providers.

Now let's turn to the evolving role of autologous stem cell transplant in the management of multiple myeloma. It's important to outline that outside of triple or quadruple treatment combinations we now typically use to newly diagnose disease, we also have autologous stem cell transplant as a first-line treatment in younger, fit, eligible patients. And it's important to also know that outcomes have previously improved with the inductor option of autologous transplant over 25 years ago, which at that time improved median survival between 2 to 5 years.

However, currently only about half of

patients with multiple myeloma are eligible for ASCT, typically due to advanced age and frailty, and of those eligible, only about a third currently undergo transplant. For those not eligible or after initial treatment fails, they can quickly cycle through other current available options and need newer and more abundant options urgently.

Now, very importantly, novel therapies have been critical in improving long-term outcomes, regardless of whether a patient has had a transplant or not. In fact, we've seen its effect, especially in younger patients, as shown in recent randomized practice-changing studies of early use of transplant versus delayed or deferred ASCT.

Now, in terms of the current treatment landscape for relapsed/refractory myeloma, we heard very nicely from this from a moment ago from Dr. Gormley. There are three primary classes of drugs, and these consist of proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies, and generally when one progresses on a particular regimen, we try to switch classes of agents and/or

utilize a next-generation drug; and as disease continues to progress and become refractory, these options rapidly become exhausted.

Now, if one of our three go-to novel agents targeting BCMA and other newer targets is not improving outcomes, and especially in the elderly, the need for additional therapies with novel mechanisms of action are absolutely vital for continued successful salvage. Whilst, specifically, anti-BCMA therapies have clearly improved outcomes for some patients, they do, however, come with their own challenges regarding both ease of administration and tolerability. These issues are not mutually exclusive.

We need all of these therapies, and more, in particular for our older patients, and this, in my view, is where Pepaxto fits nicely, adding meaningfully to the treatment landscape, where its novel mechanism of action is a peptide drug conjugate, and its use important as an outpatient can add benefit.

Now, the challenges for the efficacy of

current treatments in relapsed/refractory myeloma are several, but to understand patient need and treatment selection in the current era, and especially as these evolve, we also need to address the challenges with the efficacy of current treatments; and this is why the OCEAN results have caused experts to re-examine the data and reassess decision making in this context.

As one of the three cornerstones of our combination treatments, IMiDs are extensively used to treat myeloma, and it is estimated that about 80 percent of our patients who receive IMiD therapy are indeed over the age of 65. And as you heard, a very important implausible, age-related interaction has been identified in OCEAN, and now in other studies.

Whilst it's not a specific question in today's discussion, this IMiD interaction is a concerning finding, but in my view needs further evaluation and also needs to be communicated. We are leading the development of a forthcoming paper, with colleagues, to share the data, and hopefully

prompt additional investigation, as well as careful consideration of the implications in our treatment paradigm. In sum, you can see this interaction that was unexpected since IMiDs have been used widely for over 15 years, however, a retrospective evaluation of the data in the literature has found little information regarding efficacy by age, especially on our older patients.

So I share with you on this slide new data derived from myeloma studies that show that overall survival hazard ratios worsened with older age for IMiDs consistently across the studies we examined, with younger patients doing better on IMiDs than their older counterparts.

You can see the studies included on the right and the hazard ratios separated by age within those studies, with each reflected by the colored dots. This negative interaction with advancing age should be considered when making treatment decisions in my view; yet importantly, the current pomalidomide label doesn't provide this subgroup information. Patients and, of course, providers

should have full transparency of data, in my opinion, so we can adequately communicate the benefit-risk of therapies and determine the most appropriate therapeutic option for our patients during their treatment course.

Now, it's also important to emphasize that other recently approved therapies for refractory disease have challenges. As mentioned, we essentially have three viable choices: XPO1 inhibition, the use of antibody drug conjugates, and cellular therapies.

Selinexor has considerable GI toxicity and asthenia, which can be especially challenging with upwards of 40 patients discontinuing their prescribed dosing during clinical trials to date. Belantamab mafadotin provides similar efficacy as Pepaxto, but comes with significant ocular toxicity, which can be poorly tolerated and leads to discontinuation, particularly in older patients; and although manageable with dose reduction schedule change, it occurs in over 60 percent of patients treated. It also requires sophisticated

input with expert ophthalmic care, as well as frequent monitoring.

Finally, CAR-T therapies are very effective when attainable, however, it lacks, really, effects of accessibility, and many patients have had to wait almost 6 months in real-world experiences to receive treatment, according to a recent ASCO abstract. That's not at all practical for patients with relapsed/refractory disease, who are of course in immediate need of therapy.

Toxicities can be substantial, with almost all patients experiencing cytokine release syndrome and a significant number encountering complex CNS issues, some of which can be very serious. Hospitalizations are, of course, a routine and required part of management, which further stretches resources, especially in the COVID era.

Now, as we think about overall survival in relapsed/refractory multiple myeloma, it's clear that given the short survival in triple-class refractory patients, that we heard defined so nicely earlier by Dr. Gormley, it's key to

understand in that group that multiple options are absolutely needed. I also want to be clear, as we start our conversation today, that the OS seen with Pepaxto is promising and meaningful, in my view, compared to current historical norms.

For example, for triple-class refractory patients, as an example, median overall survival has been reported to be, at best, 9.2 months, and in penta-refractory patients, just 5.6 months, with double refractory patient outcomes estimated at a median of 11.2 months.

For Pepaxto, consistent improvements in overall survival compared to these contemporary historical controls are seen, reflecting on the one hand, in my view, its novel mechanism of action in the context of current therapies and is replicated across phase 1/2, and now phase 3 studies, in these specific patient populations.

When we consider special considerations for patients with relapsed/refractory disease -- I've summarized them here -- in addition to the clinical benefits, Pepaxto offers many practical advantages

for patients with relapsed disease that shouldn't be dismissed. As noted, multiple myeloma is predominantly a disease of the elderly and highly heterogeneous. We'll need to be particularly mindful that not all patients can tolerate current options, and yet drugs with new mechanisms of action are essential to improving outcome, and especially in the relapsed setting.

In this context, data from our HORIZON study support that Pepaxto can be used in patients with extramedullary disease, a key and very ominous feature of relapsed myeloma, especially after the failure of monoclonal antibody treatments. In fact, HORIZON is one of the few studies in which we included a significant number of relapsed/ refractory patients with extramedullary involvement, where they made up more than 40 percent of the population. We saw a remarkable single-agent activity in this advanced setting, with approximately 25 percent of patients responding, further supporting a role for Pepaxto for this important subgroup of unmet medical need.

Of course, no conversations about myeloma patient care in 2022 is complete without discussing the implications of COVID, from which our patients remain uniquely vulnerable. We now, more than ever, must consider the frequency of visits needed for patients to be treated and the rates of COVID infection, morbidity, and mortality seen. Patients and providers alike are turning to easier-to-administer outpatient based treatments whenever possible, with the lowest rates of COVID mortality seen.

Pepaxto has this attribute, and is given monthly, which is a real advantage, both reducing the risk of infection and providing additional convenience for our patients, as well as a mechanism of action which doesn't increase the risk of COVID mortality in this exquisitely vulnerable population.

To conclude, Pepaxto in its current indication is, in my opinion, meeting an important unmet medical need with patients with triple-class refractory myeloma, which remains incurable and

should be accessible to patients to meaningfully improve outcome. Patients with triple-class refractory myeloma urgently need additional treatment options that provide efficacy in an outpatient setting and that are also meaningfully different to the current BCMA-targeted treatment paradigm. The practical advantages of Pepaxto cannot be overlooked; that these patients are often older and frailer, and cannot readily tolerate the currently available treatment options.

The presentation of data you will hear will demonstrate clinically meaningful efficacy and a manageable safety profile, with importantly minimal non-hematologic side effects, in our experience, that critically reflect our own real-world experience in this setting and the unique features specific to older patients regarding its efficacy and value. I thank you very much for your kind attention, and I'll now turn the presentation to Dr. Bakker.

Applicant Presentation – Klaas Bakker

DR. BAKKER: Thank you, Dr. Richardson.

I am Klaas Bakker, and I'm the chief medical officer at Oncopeptides. I will review the results from our OCEAN study and share our learnings related to Pepaxto's benefit-risk.

This study provides important data for both the efficacy and safety of Pepaxto. I will first review the study design of OCEAN and share the efficacy results in the overall population. Then I will share the data demonstrating a clear interaction for Pepaxto, based on prior autologous stem cell transplant.

The identified heterogeneity of response in this prespecified subgroup is biologically plausible and compelling, and will guide future use and development of Pepaxto. I will not elaborate on the age interaction with IMiDs. This material can be found in your briefing document and the public docket. Lastly, I will review the safety data supporting Pepaxto.

OCEAN was a phase 3 randomized, active-control study, comparing Pepaxto plus dexamethasone to pomalidomide plus dexamethasone.

Treatment was continued until disease progression or unacceptable toxicity. This study enrolled patients who had received 2 to 4 prior lines of therapy other than pomalidomide and were refractory to lenalidomide, as well as their last line of therapy. Patients were also required to have an equal performance status of less than or equal to 2. In comparison, patients in HORIZON, the study that supported the accelerated approval, had an average of 5 lines of prior treatment over mostly triple-class refractory.

The primary endpoint was progression-free survival as assessed by an independent review committee. Key secondary endpoints included overall response rate and overall survival. As per the statistical analysis plan, because this was a head-to-head study with an active comparator, the prespecified anticipated difference to resolve the superiority was a median PSF advantage of 1.54 months.

The prespecified censoring rules also included in this set follow IMWG guidelines.

Progressive disease required confirmation of a secondary measurement with two exceptions. If the first assessment was progression of EMD or showed a progression with rapid subsequent treatment initiation, prohibiting a second measurement, it was also considered progressive disease. Clinically, this makes sense, as patients are often put on a subsequent treatment before there is time for a confirmatory assessment.

Now, let's look at demographics. Baseline demographics and characteristics were well balanced between both groups. Of note, median age was 68 years, and about half of the patients in both arms had a prior ASCT. If we look at the patient disposition, a total of 495 patients were randomized. Eighteen patients randomized to Pepaxto were not treated compared to three in the pomalidomide arm. With that, 228 patients received at least one dose of Pepaxto and 246 received pomalidomide. A similar percentage of patients who were dosed discontinued the study, mostly for progressive disease. Of those treated with study

drug, a similar number went on to receive subsequent therapy post-progression. This means that treatment with Pepaxto did not impact the probability of receiving subsequent therapy.

I will look to the OCEAN efficacy results. The OCEAN study met its primary endpoint as defined per the statistical analysis plan, demonstrating superiority compared to pomalidomide, with a median PFS of 6.8 versus 4.9 months, and a hazard ratio of 0.79, and a p-value of 0.03. Here you see Pepaxto in blue and pomalidomide in gray.

Again, I would like to emphasize that the IRC agreed with these findings, as described in their letter, which was submitted to the public docket. Additionally in that letter, in contrast to what the FDA states, the IRC confirmed that no re- or post hoc analysis was performed with only one final analysis, and that they were blinded throughout the full review process. The 2-month difference in median PFS is meaningful and translates to more than 40 percent improvement above the active comparator, which is in itself

already a very efficacious drug. This is an important improvement in a study comparing two different mechanisms of actions.

The OCEAN trial demonstrated a meaningful overall response rate of 33 percent for the Pepaxto arm and the clinical benefit rate was 50 percent, both numerically higher than the pomalidomide arm. Additionally, responses were equally durable in both treatment arms.

Here are the Kaplan-Meier curves for overall survival. As noted earlier, the updated overall survival hazard ratio from the OCEAN trial was 1.14 in the intent-to-treat population. While this was not statistically significant, it suggests the potential worsening of survival, which of course deserves careful analysis.

From a safety perspective, the survival curve is compounded by 18 patients assigned to Pepaxto and three assigned to pomalidomide, who were never treated. When looking at patients who actually received study drug, the early separation through the first year, as seen in the

intent-to-treat population, is eliminated. This means that all the events impacting the numerically worse overall survival occurred after completing the assigned study treatment.

Here are the overall survival results by prespecified subgroups to explore the homogeneity of the overall survival hazard ratio. As you can see, as mentioned also by Dr. Gormley, there are clear large differences in various subgroups. Careful and systematic evaluation led us to identify ASCT as the interaction driving the potential detriment for Pepaxto. It is important to note that other subgroups like age, prior lines of therapy, and creatinine clearance are reliable and strongly associated with ASCT.

Now let me review the impact of these biologically plausible interactions within the prespecified subgroup of patients with and without ASCT. Here is the PFS in patients with no ASCT. You can see early and sustained separation between the curves and an improved PFS for Pepaxto, while the PFS for pomalidomide remains the same as the

overall population. As such, removal of the subgroup with identified risk further enhances the PFS benefit, now providing 4.7 additional months over pomalidomide. Other endpoints, including ORR, CBR, and median duration of response also improved in patients with no prior ASCT. When looking at overall survival results in the group of patients with no ASCT, the median overall survival improves to 22.2 months compared to 17.5 months with pomalidomide.

Now, because of the interaction with ASCT, the sponsor further investigated the finding. IMWG criteria states that an ASCT with a time to progression of less than 24 to 36 months should be considered a failed transplant. Based on the guideline, the sponsor investigated the ASCT group by time to progression, which shows a clear, linear relation with efficacy results. This is in line with available biology as an ASCT and reliably accompanied with induction therapy with high-dose melphalan. For this reason, we established 36 months as the threshold for the limitations of

use.

The response to high-dose melphalan can be predicted based on the time to progression following ASCT. We investigated the optimal time since transplant to better isolate the subgroup at risk. We found that the risk appears to be removed for patients that do not have progression until more than 36 months post-ASCT, as shown on this table. We detect a clear risk for potential harm for progression less than 24 months from progression.

Here we show a PFS when we implemented proposed limitation of use. We've seen statistically significant almost doubling of PFS with 9.3 months on Pepaxto compared to 4.6 months on pomalidomide. The curves separate early and are sustained throughout the study.

Here we show the median survival in patients with either no transplant or who progressed more than 36 months after ASCT. These are the patients that should be treated with Pepaxto, providing improved survival over pomalidomide in comparison

to patients with early post-transplant progression at lower survival. For this reason, we aim to communicate the potential risk as a limitation of use, and patients with a time to progression of less than 36 months after an ASCT should be treated with an alternative drug.

When looking at the overall survival curve for the recommended population, we see separation from pomalidomide at 3 months that continues through the duration of the study, and here is the forest plot looking at the recommended patient population, based on the ASCT interaction. You see the improved point estimates favor Pepaxto with no increased risk for potential detrimental survival anymore.

Here we give context to the limitation of use, showing why we recommend to be more specific about time to progression since transplant rather than by patients with no ASCT. This change shown at the bottom now clearly separates the risk with separate non-overlapping confidence intervals.

Let me now share the safety data, which

demonstrated consistent and manageable safety profile of Pepaxto. Here is an overview of the adverse event profile across OCEAN. Grade 3/4 adverse events were primarily of hematologic nature and occurred at higher rates compared to pomalidomide. These events are well known and managed for dose modifications in clinical practice. Serious adverse events were comparable between groups. As noted, given the number of hematologic adverse events, there were more dose modifications for Pepaxto compared to pomalidomide, but with comparable adverse events leading to discontinuation. The dexes were also comparable between arms.

Now here we are showing grade 3 and 4 adverse events of special interest. Thrombocytopenia and neutropenia occurred most frequently and at higher rates in the Pepaxto group compared to pomalidomide. It is important to point out that these events can be quickly identified and are effectively managed, seldom resulting in chemical sequelae such as concomitant bleeding or

infection.

Now let me show how the limitation of use to avoid treatment in the at-risk population further enhances the safety profile and reduces fatal events. Data will now be shown based on the recommended limitations of use, thus showing the recommended patient population.

This safety risk and improved adverse event profile from the restriction of use is most clearly communicated when looking at the event rate, based on time to progression following ASCT. As we increase the time to progression, we see that patients at least 36 months out from ASCT have the best profile and the least fatal adverse events. This supports the identified safety risk, as we see that fatal adverse events are significantly reduced.

The first thing to note is that for Pepaxto, the recommended patient population stays on therapy more than twice as long as the group with a time to progression less than 36 months after ASCT. The median treatment exposure is 8.1 compared to

3.7 months. As a consequence, one would expect more dose modifications from longer treatment; instead, we see less adverse events leading to discontinuation and less fatal events.

Here we are showing the same table again now in events per patient here, but it even more clearly demonstrates the safety benefit in the recommended population across all parameters. This also applies to dex, where we see fewer in the recommended population. Importantly, we also see a reduction in dex more than 30 days after last dose.

Now let's discuss dosing. As Pepaxto is a cytotoxic agent, using the maximum tolerated dose is the appropriate strategy to define the dose, and dose modifications are used to manage hematologic adverse events. Forty milligram is the recommended dose for most patients, however, to lessen the risk of thrombocytopenia, we proposed a 30-milligram starting dose in patients with a body weight of less than or equal to 60 kilograms. This was based on PK data and the occurrence of cytopenia. In addition, we've revised the dose modification

guidance with earlier dose reductions.

To conclude, the data confirms a favorable benefit-risk for Pepaxto when a limitation of use is applied to exclude patients with a time to progression of less than 36 months after ASCT. In this population, tolerability is improved with more patients remaining on therapy and less need for dose modifications. We intend to clearly communicate the risk associated with Pepaxto in patients with progression from transplant less than 36 months. We will exclude these patients from future use and clinical trials.

Thank you. It's now my pleasure to hand the presentation to Dr. Efebera to share her clinical perspective.

Applicant Presentation – Yvonne Efebera

DR. EFEBERA: Thank you so very much.

I am Yvonne Efebera, professor and medical director of the Blood and Marrow Transplant program at OhioHealth. It is truly a pleasure to be with you today to share my clinical perspective on the importance of Pepaxto in the late-line setting. I

have been treating patients with relapsed/refractory myeloma for almost 20 years, and our site was part of the Pepaxto study program. My research entails participation in clinical trials in newly diagnosed multiple myeloma, relapsed myeloma, autologous and allotransplants, cellular therapy, and amyloidosis. Like Dr. Richardson, I am not being compensated for my time in today's meeting.

To recap from Dr. Richardson's presentation, relapsed/refractory myeloma is incurable, and patients with triple-class refractory disease continue to need options despite even recent approvals. Once a disease becomes multirefractory, survival quickly diminishes, as there become few successful or tolerated options for our patients. Pepaxto's mechanism of action acts on a different pathway, allowing for continued response with improved outcomes compared to the MAMMOTH study, which has been widely referenced. In my own clinical experience, Pepaxto supports the clinical trial findings.

As some of you may know, myeloma is a disease of the elderly, with more than 80 percent of patients being 65 years or older. These older patients with relapsed/refractory myeloma are perhaps most in need of novel agents. Let me provide a narrative of a patient who was in the HORIZON trial, and who reflects a very good example of the type of patient who continues to need Pepaxto as an option.

The patient is a 74-year-old Caucasian woman who was first diagnosed in 2005. Her disease progressed to 4 lines of therapy, and due to comorbidities, she was not eligible for transplant. She entered into HORIZON and fared very well on Pepaxto. She stayed on Pepaxto for 2 years, with a very good partial response before progression. She tolerated Pepaxto very well, with no hospitalization, and experienced only expected hematologic adverse event.

Her dose was reduced 2 times for moderate leukopenia and thrombocytopenia. The first dose happened 6 months after she started treatment, from

40 milligram to 30 milligram. She continued on 30 milligram for another 6 months before it was dosed reduced to 20 milligram, and she stayed on that dose for another 12 months. Dose reduction was an effective management tool, as she never reported bleeding or neutropenic fever, only mild to moderate fatigue, and was able to stay on treatment until the disease inevitably progressed.

This is one of many examples of patients who needed Pepaxto as an option, and I continue to feel comfortable prescribing Pepaxto to the right patient population. It is worth noting that in the CARTITUDE-1 trial with cilta-cel, for which approval was obtained, the oldest patient was 68 years old, and patients were required to have an ECOG of 0 to 1, a stricter criteria for even patients undergoing autologous transplant, and would definitely have excluded this patient and many patients included in the HORIZON study.

Additionally, important and informative from the HORIZON data and my experience, Pepaxto is used in patients with extramedullary disease, EMD. As

you know, EMD is associated with very poor patient outcomes, and yet it is not well studied, and patients are typically excluded from clinical trials despite the high unmet need. HORIZON represents the largest cohort of patients, with EMD evaluated to date in a prospective clinical trial; so positive outcomes with 24 percent of the EMD patients experiencing response. Importantly, the safety profile for this subgroup is consistent with the overall population.

Turning to the data from OCEAN, from my point of view, the OCEAN study is an important trial in relapsed/refractory myeloma, in the area of relapse and as to our previous understanding from the HORIZON study. The data in patients without stem cell transplant or having progression after 36 months from transplant is compelling and should be considered a key learning from OCEAN. It is a clear biological rationale supporting this subgroup, and these are the patients with high unmet need in the clinical setting. These patients are typically elderly and frail, and cannot always

tolerate all treatment options. Patients without prior transplant were able to stay on drug longer and reported less thrombocytopenia on a drug that actually demonstrates favorable activity in a difficult-to-treat group of patients.

The early Pepaxto data is particularly reassuring since we observe this level of efficacy with limited non-hematologic toxicity associated with many other agents. Certainly, from my clinical perspective, the absence of alopecia, cardiac toxicity, and neuropathy that we see with other agents, this agent with the lack of these, and as well as only minimal mucositis and low rates of infection, are particularly valuable aspects to its use. Patients tolerate drug well, and adverse events were effectively manage with methods such as dose modification and supportive medications.

This is apparent when looking at the comparable discontinuation rate across the program. When my patients see the disease responding to treatment after being on 3 or 4 lines of prior therapy, they do feel good about the regimen, and

they do not want to stop treatment. Additionally, the ease and infrequency of administration cannot be underscored. A monthly infusion is particularly important for this elderly patient population who have difficulty coming to the infusion centers. I have personally heard from my patients that this is a much added benefit of Pepaxto.

I want to conclude by stating that patients with relapsed/refractory myeloma should have Pepaxto as a late-line option. Our patients with triple-class refractory myeloma are in urgent medical need of salvage therapy with different mechanisms of action. These patients do not have many remaining options. Many have been treated with combination therapy at onset, and many cannot tolerate other treatments that have significant toxicities.

Multiple studies demonstrate Pepaxto's benefit in this setting. Importantly, that benefit is observed in the context of a consistent and manageable safety profile, where patients are able to remain on therapy. When patients get to time to

progression of less than 36 months after transplant is excluded, the remaining recommended population experiences an improved safety profile in addition to meaningful progression-free survival. Importantly, these are often elderly patients who continue to need alternative treatment options the most.

Our patients urgently need therapy, and I hope to be able to continue to provide my patients this additional line of effective therapy. Thank you so very much for your kind attention. I will return to Dr. Bakker now.

MR. LINDBERG: This concludes our presentation.

DR. GARCIA: Thank you to Oncopeptides A.B. and team.

We will now proceed with the FDA presentation from Dr. Alexandria Schwarsin.

Dr. Schwarsin?

FDA Presentation – Alexandria Schwarsin

DR. SCHWARSIN: Thank you.

Good afternoon. I am Alexandria Schwarsin,

a hematologist/oncologist in the Division of Hematologic Malignancies II at the FDA. I will be presenting the FDA's discussion on melphalan flufenamide, referred to as melflufen in the presentation. The members of the FDA review team are listed here. My presentation represents their collective input.

The central issues we would like to focus on today are: 1) the potential detriment in overall survival seen in the melflufen-dexamethasone arm of the phase 3 confirmatory trial, OCEAN, as compared to the control arm of pomalidomide-dexamethasone; 2) the failure to demonstrate a progression-free survival benefit; and 3) the lack of an appropriate dose.

To highlight where melflufen resides in the current treatment landscape of multiple myeloma, I would like to begin with an overview of the current treatment landscape. The table presented on the slide represents the treatment options for patients with relapsed/refractory multiple myeloma. The treatment landscape has changed dramatically over

the last decade, including multiple novel therapies approved since 2015. Highlighted in red are the four currently approved regimens indicated for patients who have been treated with 4 or more prior lines of therapy, including a proteasome inhibitor, immunomodulatory agent, and a CD38 monoclonal antibody.

While many of the other agents listed can also be used for this highly pretreated population, and repeated, those in red are specifically only approved for later lines. Selinexor in combination with dexamethasone was granted accelerated approval in July 2019. The clinical benefit of Selinexor was subsequently confirmed in a phase 3, randomized-controlled trial, BOSTON, and Selinexor's accelerated approval was converted to regular approval in December 2020. Belantamab mafadotin received accelerated approval in August 2020, and the confirmatory trial is currently underway. Two CAR-T cell therapies have received regular approval, idecabtagene vicleucel in 2021 and ciltacabtagene autoleucel in 2022.

Also, not on the slide, melphalan is an oral drug approved for use in patients with multiple myeloma.

Now I'll turn to the presentation today, which will focus on melflufen. Melflufen is a peptide conjugated alkylator with the same alkylating moiety as melphalan. Melflufen is passively distributed into cells, then enzymatically hydrolyzed to melphalan. Like melphalan and other nitrogen mustard drugs, DNA cross-linking is involved in the anti-tumor activity of melflufen.

As you have heard previously, melflufen was granted accelerated approval on February 26, 2021, in combination with dexamethasone for patients with relapsed/refractory multiple myeloma who have received at least 4 prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory drug, and one CD38-directed monoclonal antibody. A 40-milligram flat dose administered intravenously via a central venous line was approved based on the phase 2 study. However, at the time of accelerated

approval, there were residual uncertainties about the dose, and two postmarketing requirements related to dosing where issued, which I will discuss further in the upcoming slides.

Efficacy of melflufen in combination with dexamethasone was evaluated in the HORIZON trial, or OP-106, a single-arm, open-label, phase 2, multicenter trial. The accelerated approval was based on 97 patients with relapsed or refractory multiple myeloma, who were treated with four or more lines of therapy and whose disease was refractory to at least one proteasome inhibitor, one immunomodulatory drug, and one CD38-directed monoclonal antibody, which I'll refer to as triple-class refractory disease, indicated as TCR on the slide.

Seventy percent of patients had received a prior autologous stem cell transplant. The major efficacy outcome was overall response rate and duration of response, assessed by the International Myeloma Working Group response criteria. The overall response rate in the 97 triple-class

refractory patients was 23.7 percent, with a median duration of response of 4.2 months.

Myelosuppression was the major safety concern for melflufen. Approximately 75 percent of patients had severe neutropenia and thrombocytopenia. Nearly half of subjects had severe anemia. The melflufen USPI includes warnings and precautions for thrombocytopenia, neutropenia, and anemia.

In addition, a warning and precaution was included in the label to alert prescribers of an increased risk of mortality with melflufen at dosages higher than the recommended dosage. This was based on results from a nonclinical safety study in dogs, which examined melflufen against equimolar doses of melphalan. There was increased mortality in dogs receiving melflufen at dosages exceeding the recommended dose. Also, subsequent clinical studies did not investigate doses higher than 55 milligrams. Therefore, a limitation of use was added to the label, stating that melflufen should not be used as a conditioning regimen.

At the time of accelerated approval, several postmarketing requirements were issued. Since accelerated approval was based upon a single-arm trial with an intermediate endpoint of overall response rate, continued approval was contingent upon verification and description of clinical benefit in a phase 3 randomized trial. OP-103, henceforth referred to as the OCEAN trial, was the proposed confirmatory trial we will discuss in the upcoming slides. Due to the concerns of dosing, two postmarketing requirements were issued to further evaluate the acceptability of the fixed 40-milligram dose. In the next slide, I will briefly review the OCEAN trial.

This slide shows the trial design for the OCEAN trial. OCEAN was a randomized-controlled, open-label, phase 3 study of melphalan flufenamide and dexamethasone, henceforth referred to as the melflufen arm, compared to pomalidomide and dexamethasone, referred to as the pomalidomide arm, in patients with relapsed/refractory multiple myeloma.

The patient population enrolled had received 2 to 4 prior lines of therapy and had to be refractory to lenalidomide. The trial evaluated the same flat 40-milligram dose of melflufen with dexamethasone as the HORIZON trial. The OCEAN trial was conducted under a special protocol assessment, and the agreed-upon primary endpoint was progression-free survival superiority, assessed by an independent review committee. Key secondary endpoints included overall survival and overall response rate. Over the next few slides, I'll highlight the results from the OCEAN trial and the FDA identified issues.

This slide shows the baseline demographics on the OCEAN trial. As shown, baseline patient demographics and disease characteristics, including patients who had previous autologous transplant, and characteristics traditionally associated with poor prognosis, such as high-risk cytogenetics by FISH and ISS score III, were balanced between the two arms.

The first issue we will highlight today is

the potential detriment in overall survival in the melflufen arm compared to the pomalidomide arm, and the safety issues that indicate a potential for harm with melflufen. This slide shows the Kaplan-Meier curve and the median overall survival for the two arms on the OCEAN trial. In the table on the left, you can see there are more deaths in the overall population in the melflufen arm, 47.6 percent, compared to the pomalidomide arm, a rate of 43.4 percent. Additionally, the median overall survival was approximately 5 months shorter in the melflufen arm compared to the pomalidomide arm, raising significant concerns regarding the safety of melflufen.

This slide shows the updated overall survival results with a median follow-up duration of nearly 3 years. The median overall survival remains shorter in the melflufen arm, 20.2 months compared to 24 months in the pomalidomide arm, and the hazard ratio remains unfavorable at 1.14, indicating a 14 percent increased risk of death. The FDA's presentation will highlight the safety

issues that could have contributed to the potential survival detriment seen and indicate a safety risk with the use of melflufen.

The sponsor has made several contentions regarding the overall survival results. This includes that detriment in overall survival is not indicative of a specific toxicity signal; that overall survival is driven primarily by results in the transplant subgroup, specifically in patients with the time to progression within 36 months of transplant; and that for pomalidomide and immunomodulatory drugs, there is an overall survival effect modification based on age.

In the following slides, we will address the applicant's first contention that the potential detriment in overall survival is not indicative of a specific safety signal. In analyzing the deaths in the OCEAN trial, there is an increase in deaths in the melflufen arm compared to the pomalidomide arm in the safety population, similar to that observed in the overall population.

It is notable that the death beyond 60 days

is increased on the melflufen arm. Although the reason for the increase in death beyond 60 days is not clearly identified based on the narrative, there is concern that the increase in death beyond 60 days indicate that treatment with melflufen may impact the ability to receive and tolerate subsequent lines of therapy.

The safety results from the OCEAN trial demonstrate a high rate of grade 3 to 4 treatment-emergent adverse events, dose reductions, and dose interruptions. Even with early dose modification, grades 3 to 4 adverse events remained higher in the melflufen arm compared to the pomalidomide arm, indicating concerns of the overall safety of melflufen in the relapsed/refractory multiple myeloma patient population.

This slide shows the most common treatment-emergent adverse events. It is important to note that over 80 percent of patients had grade 3 to 4 thrombocytopenia in the melflufen arm compared to only 14 percent on the pomalidomide

arm. While the rates of grade 3 to 4 hemorrhage were relatively low, there were 3 fatal hemorrhagic events.

As mentioned previously, myelosuppression was the major safety concern for melflufen, identified in the single-arm trial, HORIZON. The lack of a comparator arm limited the assessment of the risk of myelosuppression on the overall benefit-risk. Given the potentially worse overall survival noted in the randomized phase 3 trial OCEAN population, it is possible that myelosuppression is leading to prolonged marrow toxicity, which could have a lasting negative impact on the patients.

I would like to remind you, again, of the overall survival results from the OCEAN trial, indicating a consistent result with a follow-up of 3 years. Overall survival is not only an indicator of efficacy but also provides for an evaluation of safety. Given the toxicity data from the OCEAN trial, the potential detriment in overall survival is indicative of a significant safety concern with

melflufen. We will review the limitations of the sponsor's post hoc analyses and reasons for continued concern in the upcoming slides.

The sponsor has conducted multiple exploratory analyses and has concluded the overall survival finding is primarily explained by those patients who had received prior autologous stem cell transplant, especially those patients with a time to progression of less than 36 months, however, the FDA does not agree with this conclusion.

First, I would like to briefly highlight a few caveats about subgroup analysis. The subgroups proposed by the sponsor were not prospectively included in the statistical analysis plan with control of type 1 error. Subgroup analyses are important. They can be used to confirm a consistent treatment effect across subgroups, thus providing greater assurance that the treatment effect observed applies to the entire patient population studied. However, results from one subgroup cannot be used to confirm a subset of

patients who benefit when the total patient population has shown a detrimental treatment effect.

As previously presented by Dr. Gormley, there are concerns with post hoc subgroup analyses. As another example, the FDA analyzed the OCEAN data to illustrate how post hoc subgroup analysis can lead to false conclusions. When subgroup analyses of overall survival are conducted by month of randomization, which is independent of the treatment effect, the resulted Kaplan-Meier plots are in opposite direction for patients randomized in March and July.

On the left shows comparison of overall survival curve for patients randomized in March, and on the right is for patients randomized in July. We cannot conclude that the overall survival effect is different for patients randomized in March and July, based on this post hoc subgroup analysis. This has no scientific basis but illustrates how false conclusions can be obtained by looking for differences in treatment effect in a

post hoc manner.

This apparent difference in treatment effect is a random artifact of the data. It is not clear that other observed differences the sponsor proposes may be due to random chance alone. Prospectively defined hypotheses should be evaluated in prospectively designed studies to support a conclusion. However, acknowledging the limitations of subgroup analysis, we reviewed the applicant's analysis of time to progression from previous transplant.

Before looking into the results of this subgroup further, I would like to point out the limitations of the definition. While the International Myeloma Working Group guidelines state that duration of remission after the first autologous stem cell transplant procedure is an important prognostic factor, this is in reference to the outcome for progression-free survival after a salvage transplantation. The IMWG guidelines also state the 3-year cutoff is arbitrary.

Acknowledging the limitations of the

definition, if we review the results of the subgroup of time to progression from previous transplant on the forest plot, we note that the confidence interval for patients without a previous transplant and patients with a time to progression greater than 36 months crosses 1, indicating a lack of difference between treatment groups. We cannot conclude a detriment if not occurring in these subgroups; while on the other hand, those patients with a time to progression less than 36 months from a previous transplant clearly fared worse with melflufen. Overall, the results from this subgroup are consistent with the results seen in the ITT population.

Here, I would like to point out that the sponsor had previously proposed a different analysis for the transplant subgroup, utilizing a different definition, time since transplant. The two definitions are shown on the slide. Time to progression, the current definition used by the sponsor, is defined as the time from the transplant date to progression date after the transplant.

This is irrespective of treatment initiation with melflufen following progression. The previous definition used by the sponsor is time since transplant. The time since transplant is evaluated from transplant to randomization on the OCEAN trial and considers patients who received melflufen at relapse.

To illustrate the limitations with post hoc analysis, FDA conducted an analysis based on the sponsor's previous definition, time since transplant. Utilizing the time since transplant definition, the previous definition proposed by the sponsor and the cutoff of 36 months, the new time frame proposed by the sponsor, the results show that regardless of the time frame, less than or greater than 36 months, the hazard ratios are greater than 1, indicating potential harm. The upper limit of the confidence interval of the hazard ratio for the no transplant group is also greater than 1, indicating that potential harm cannot be ruled out.

I would like to underscore that FDA does not

endorse any conclusions based on post hoc analyses. The FDA conducted this subgroup analysis to highlight the limitations of post hoc analyses and making conclusions, based on these analyses, by simply varying definitions for the cutoffs, different results are obtained.

To further illustrate this point, this slide depicts the two subgroup analyses side-by-side. As stated earlier, the sample size end results differ based on the definition of the variable. In the subgroup analysis of time since transplant, previously proposed by the sponsor on the right, the hazard ratios, regardless of the less than 36 months or greater than 36 months, are greater than 1, indicating potential detriment and harm; whereas in the analysis based on the current sponsor-proposed definition of time to progression on the left, the group with a time to progression greater than 36 months has a hazard ratio less than 1. This illustrates the concerns regarding exploratory post hoc analyses.

Additionally, even if we consider the

results of the post hoc subgroup analysis, the detriment in overall survival is not limited to the time to progression from previous transplant less than 36 months alone. In the next slide, I will review the results from subgroups identified by the sponsor for further exploratory analysis.

This slide shows the forest plot analysis for subgroup identified by the sponsor for further exploratory analysis. We want to highlight that the potential overall survival detriment seen in the ITT population was seen across multiple subgroups. Multiple subgroups showed a hazard ratio favoring the pomalidomide arm, and the majority of others include a confidence interval which crosses 1. Therefore, the overwhelming result is one that suggests a decreased overall survival with melflufen.

Although the sponsor had highlighted the subgroup of patients who have not had previous autologous transplant as one which to derive benefit from melflufen, we do not agree with this conclusion. It is important to note that these

subgroups were not powered prospectively for individual analysis. They were only identified as exploratory analyses to be conducted, and therefore can only be hypothesis generating. The sponsor also contends that for pomalidomide and immunomodulatory drugs, or iMiDs, there is an overall survival effect modification based on age, and the overall survival results from the OCEAN trial should be viewed in the context of this heterogeneity.

The sponsor has concluded that there is an overall survival effect modification of age based on within treatment comparison of age groups in the OCEAN trial. The FDA does not agree. The OCEAN trial was not designed to compare or evaluate the effect of pomalidomide treatment in the various age subgroup evaluated by the sponsor. The subgroup analysis within the single-treatment arm is not a valid approach to explore the modification of overall survival effect because it was not a randomized comparison and is unlikely to be balanced with respect to prognostic factors. The

estimates provided from such comparisons would be influenced by many factors for which the investigator did not control.

Additionally, analyses within treatment arms do not provide information on the treatment effect of the study drug. Even if this post hoc evaluation of age was valid, it does not rule out the potential detriment in overall survival observed in the ITT population and multiple subgroups in the OCEAN trial.

The FDA reviewed the sponsor's exploratory post hoc model that was used to derive age and transplant as relevant factors. Although FDA does not endorse post hoc model building, FDA evaluated different post hoc models to further interrogate the variability in overall survival in the OCEAN study data. FDA only conducted this in order to evaluate if additional factors could explain the variability in overall survival. The results of the FDA analyses suggest that multiple factors, other than those suggested by the sponsor, can explain the variability in overall survival,

however, the post hoc models are unstable and the results rely heavily on the model being used.

These exploratory analyses indicate that different model approaches yield different results. However, as all models under discussion -- the FDA's and the sponsor's were based on a post hoc data-driven approach -- the results may only be considered hypothesis generating and are not suitable for making conclusions.

The sponsor also conducted additional post hoc analyses to investigate the modification of overall survival effect by age in immunomodulatory drug trials, and concluded that age interaction is also noted in other immunomodulatory drug trials. However, once again, there are several limitations. The age cutoff used for the sponsor's analysis is arbitrary and post hoc. FDA conducted its own analysis of age interaction with treatment in immunomodulatory, drug trials. This analysis was based on trial data submitted to the agency that isolated the treatment effect of an immunomodulatory drug.

The FDA's exploratory analysis did not indicate that there was an interaction between age and immunomodulatory drug treatment. Even if this post hoc evaluation of overall survival effect modification based on age is valid, these are exploratory analyses and does not negate the detriment in overall survival noted in the ITT population.

In summary, in evaluating the overall survival effect modification, the findings of this exploratory analysis of heterogeneity and overall survival should be evaluated in a prospectively designed trial. The sponsor's claims based on exploratory post hoc analyses, do not address the finding of potential overall survival detriment in the ITT population. The available evidence from the OCEAN study does not provide evidence that melflufen is safe and effective.

In summary, patients treated with melflufen had a potential detriment in overall survival, indicating a potential for harm. There are safety concerns with an increase in the number of deaths

and toxicity on the melflufen arm, suggesting a potential for harm. The FDA did not agree with the sponsor's conclusion that the overall survival detriment is limited to those patients with a time to progression less than 36 months, as the detriment in overall survival was seen across multiple subgroups. Post hoc subgroup analyses, while hypothesis generating, should not be used as confirmatory evidence to conclude a benefit of a treatment effect or lack of harm.

The second major issue to highlight today is the failure to demonstrate a progression-free survival benefit. We do not agree with the sponsor's conclusion on this progression-free survival benefit from the OCEAN trial. The primary progression-free survival results from the OCEAN trial did not meet the prespecified statistical superiority, and the potential detriment in overall survival negates any observed progression-free survival improvement.

This slide shows the original progression-free survival results submitted to the

FDA following database block. The applicant's original primary analysis of progression-free survival results submitted on June 9, 2021 showed that the OCEAN trial failed the primary endpoint, with a p-value of 0.0644. While the median progression-free survival in the melflufen arm was 2 months longer than the pomalidomide arm, the results were not statistically significant.

On July 6, 2021, the applicant submitted revised progression-free survival results. The applicant noted that these revisions were due to discrepancies in 29 patients identified by an independent audit. The independent audit was initiated by the applicant following the database lock and the top-line data readout on May 25, 2021. This slide shows the original progression-free survival Kaplan-Meier curve on the left compared to the revised progression-free survival results on the right. The progression-free survival from this revised data demonstrated nominally significant superiority with a p-value of 0.0322.

FDA conducted their own analysis on the

revised progression-free survival results. As the original primary analysis of progression-free survival results were not significant, all reported p-values, except for the original primary analysis result, are considered nominal and not suitable for inferring statistical significance.

FDA's assessment of the revised 29 patients confirmed the nominally significant p-value, however, the FDA obtained a p-value that was different from the applicant's due to a difference in FDA adjudication of 4 patients. When using FDA censoring rules, which censors unconfirmed progressive disease, progression-free survival analysis resulted in a p-value of 0.0837, indicating that there was no difference between the treatment arms.

Regardless of the method used for progression-free survival analysis and the significance of the p-value, the difference in median progression-free survival between the arms remained approximately 2 months or less. Additionally, the variability of the results

indicate a lack of robust treatment effect of progression-free survival. Importantly, given the detriment in overall survival observed, any difference in progression-free survival, whether statistically significant, clinically significant, or not, would not support a determination of clinical benefit.

Finally, this table presents the overall response rate and duration of response from the OCEAN trial. While there was a 5.6 percent median difference in overall response rate favoring the melflufen arm, the 95 percent confidence interval crosses zero, and thus no meaningful difference is apparent. Additionally, there was no difference in duration of response.

In conclusion, the sponsor concluded the progression-free survival results are significant, however, FDA does not agree. Regardless of the p-value, there is only a 2-month difference in progression-free survival. As a reminder, there is no difference in overall response rate and duration of response. Importantly, a potential detriment in

overall survival is noted.

Overall survival is the ultimate clinical benefit endpoint. Any marginal improvement in progression-free survival is negated by the potential detriment in overall survival seen in the OCEAN trial. The results from the OCEAN trial indicate a lack of a confirmed benefit for melflufen and a potential for harm. In the next few slides, we will show that this lack of benefit and increase in toxicity is likely due to lack of a dose that has been optimized for a favorable benefit-risk profile.

Another major issue is the lack of an appropriate dose. The applicant proposed a 40 milligram melflufen dose is poorly tolerated, and there was limited dose exploration of lower doses in the clinical program of melflufen. There are significant safety concerns with high melphalan exposure, which are not resolved with the applicant's melflufen dosing proposal.

The 40-milligram dose was identified to be the maximum tolerated dose in the phase 1-2 dose

escalation study and was the only dose used in subsequent clinical studies. As shown in the table, the lower doses were not fully explored, as only 4 patients treated with 15 milligrams and 7 patients treated with 25 milligrams had safety and efficacy data.

Pharmacokinetic data in the dose escalation study was derived only from 12 patients, and 8 of these patients received the 40-milligram dose. Further, no pharmacokinetic data was collected in the pivotal phase 2 study. Consequently, no population, pharmacokinetic, or exposure-response analyses were conducted to aid in dose selection to support the proposed 40-milligram flat dose before the phase 3 OCEAN study.

A postmarketing requirement was issued for an exposure-response analysis to aid dose selection, but this analysis was limited because all of the exposure-response data from the OCEAN study was derived from patients treated with 40 milligrams. An optimal dose remains unestablished.

Exposure-response analyses indicate that there are rates of several safety events increased with higher exposure following melflufen administration. Higher exposure was associated with increased risks of grade 3-plus anemia, any grade 3-plus treatment-emergent adverse event, grade 3-plus leukopenia, and treatment-emergent adverse events leading to melflufen discontinuation, dose interruptions, and dose reduction. Furthermore, no relationship between melphalan exposure and overall survival or progression-free survival has been identified.

The extensive dose modifications in OCEAN suggest that the flat 40-milligram dose is poorly tolerated. This figure shows the percentage of patients who received melflufen dose per cycle. All patients initially started with 40 milligrams in cycle 1, however, by cycle 7, more than half of the remaining patients needed dose reductions of melflufen. With successive cycles, progressively more patients required one or more dose reductions. By cycle 12, the 20-milligram dose was the most

commonly administered dose. The large proportion of patients needing doses lower than 40 milligrams illustrates that the 40-milligram dose was poorly tolerated.

This slide depicts two issues with the melflufen 40-milligram dosing strategy, contributing to poor tolerability. As you can see in the figure, patients with lower body weight had higher exposures. A similar relationship between body surface area and exposure was observed. As previously shown in the exposure-response safety relationship, higher exposure is associated with increased risk of various safety events.

Because the body size metrics of body weight and body surface area were significantly associated with melphalan exposure, the flat dosing with melflufen exacerbates the variability of the exposure even though there is still high pharmacokinetic variability at all body sizes. Therefore, dosing based on body size would decrease some variability in exposure and may reduce the overall risk of safety events.

These figures depict another representation of the higher exposure at lower body weights, just described on the previous slide. The upper panel displays exposure following 40-milligram flat dosing in all patients, with exposure and patients weighing 60 kilograms or less in the pink icon. The lower panel shows the predicted exposure with the sponsor's proposed dosing.

The sponsor is proposing a reduced starting dose of 30 milligrams in patients who weigh 60 kilograms or less in order to match the exposure in patients weighing 60 to 90 kilograms, in green. As you can see, the exposure in patients 60 kilograms or less in the pink icon is reduced to more closely match exposure in patients weighing 60 to 90 kilograms. However, the 40-milligram dose was poorly tolerated in the overall population and at all body weights in OCEAN, not just patients weighing 60 kilograms or less, so the exposure matching proposal is not adequate because it matches in exposure associated with significant safety concerns.

This conclusion is further underscored by the observation that patients across all body weights required doses lower than 40 milligrams in the phase 3 study, as seen in the doses administered over time according to weight category.

The top-right figure shows poor tolerance of 40 milligrams in patients weighing 60 kilograms or less. Similarly, the bottom figure shows that 40 milligrams was also poorly tolerated in the average weight subgroup; so the sponsor's proposed exposure matching strategy in patients weighing 60 kilograms or less would not resolve the tolerability issues in those patients. Further, the sponsor is still proposing a 40-milligram starting dose in patients greater than 60 kilograms, so the FDA safety concerns with the overall population have not been addressed.

In review, the limited data from the phase 1 and 2 studies raised concerns regarding the optimal dosing of melflufen and prompted postmarketing requirements for optimal dosing. In the phase 3

OCEAN study, there were high rates of treatment-emergent adverse events leading to dose reductions, and dose interruptions, and other safety events, which signal that the 40-milligram dose is poorly tolerated for the general patient population.

Multiple safety events were associated with higher exposure, and higher exposure is not associated with better efficacy. The proposed 30-milligram dose for patients with less than 60 kilograms is inadequate because it matches the exposure of the 40 milligram, which is considered too toxic. The FDA analysis also indicates that dosing by body size or weight may reduce variability and may be more appropriate for melflufen. Additional exploration of the dose and body size based dosing for melflufen is warranted.

Over the previous slides, we have reviewed the major issues which suggest an unfavorable benefit-risk profile in light of the potential overall survival detriment, lack of progression-free survival benefit, and lack of an

appropriate dose. Next, we will highlight some additional uncertainties in the clinical benefit of melflufen that arise from interpreting the results to the currently indicated patient population and inadequate representations of the U.S. multiple myeloma population.

Interpreting the results of the OCEAN trial to the currently indicated patient population indicates that the potential for harm exists for the currently indicated population as well. A total number of 30 patients, or 6 percent of patients, from OCEAN are consistent with the current indication of having both 4 prior lines of treatment and having triple-class refractory disease.

This slide focuses on the overall survival forest plot results for the patients that fall under the currently indicated patient population. While we cannot make definitive conclusions from this subgroup analysis, it is concerning that the overall survival hazard ratio favors treatment with pomalidomide in patients who are triple-class

refractory, have had 4 prior lines, and those patients with both, consistent with results seen in the overall ITT population. This raises serious concerns about the safety of melflufen in the currently indicated population.

Adding to the uncertainty is the applicability of the study results to the U.S. patient population. The OCEAN study had a low representation of the typical U.S. multiple myeloma population. Only 15 percent of patients on the OCEAN trial were 75 years of age or older, compared to 32 percent of patients 75 years of age or older diagnosed with multiple myeloma in the U.S.

The OCEAN trial also enrolled a very low percentage of U.S. racial and ethnic minorities, and most patients were enrolled outside of the U.S. Finally, only 18 percent of patients had previous treatment with an anti-CD38 monoclonal antibody. In the U.S. today, most patients would have received an anti-CD38 monoclonal antibody in the first two treatment regimens.

Now I would like to summarize FDA's

conclusion on the overall benefit-risk assessment of melflufen. The available evidence suggests an unfavorable benefit-risk of melflufen in the currently indicated patient population. Specifically, the overall survival results from the randomized confirmatory trial, OCEAN, not only show a lack of efficacy but also indicate a potential safety concern. The progression-free survival results indicate lack of a confirmed clinical benefit. Additionally, the flat 40-milligram dose is poorly tolerated in the general patient population. Further studies are needed to identify an adequate dose.

FDA's analysis indicates body weight dosing may be needed. Given what is currently known, we would not have granted accelerated approval as we cannot conclude melflufen provides a meaningful benefit over available therapies. In today's treatment landscape for myeloma, where multiple therapies exist and the overall survival benefit for patients come from their ability to receive and tolerate a sequence of therapies, the risk of

melflufen appears to outweigh any potential benefit. Further studies are required to establish the benefit-risk of melphalan flufenamide.

We'd like for the committee to discuss the benefit-risk profile for melflufen for the currently indicated patient population, considering the results of the confirmatory OCEAN trial. The voting question to the advisory committee is, given the potential detriment in overall survival, failure to demonstrate a progression-free survival benefit, and lack of an appropriate dose, is the benefit-risk profile of melphalan flufenamide favorable for the currently indicated patient population?

This concludes my presentation. Thank you for your attention.

Clarifying Questions to Presenters

DR. GARCIA: Thank you, Dr. Schwarsin.

We will now take clarifying questions for the presenters, Oncopeptides A.B. and the FDA. Please use the raise-hand icon to indicate that you have a question, and remember to clear the icon

after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if impossible.

Finally, it would be helpful to acknowledge the end of your question with a thank you, and end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Perhaps I can go ahead and start. Clearly, to me -- and thank you, both the FDA and Oncopeptides for great presentations -- there's a big difference in what I have heard today. One is no PFS improvement, and the applicant states that there is a PFS improvement.

I want to get a bit more understanding from the applicant related to their reviewed PFS that was resubmitted to the FDA after the initial PFS submission, and specifically if the applicant can expand as to how they censor their patients, and

equally important, what exactly happened to those 29 patients, which appear to be in question, and the reason why your PFS appears to be different compared to the initial PFS report. Thank you.

DR. BAKKER: Absolutely. Klaas Bakker here for Oncopeptides.

The data cutoff of the study was the 3rd of February 2021, and there was data cleaning ongoing until the 7th of May. The final IRC meeting took place on the 19th of April. That was before the end of the data cleaning. That of course should not have happened because the IRC should have the final data after all the data has been cleaned. This is an operational oversight that should not have happened, however, the CRO noted the 29 patients where changes had been made during the data cleaning process, and actually then asked the IRC to not reanalyze these patients but to look at the final data for these patients.

The IRC has been blinded throughout the full process. The sponsor had no involvement with the response assessment, and the 29 patients were

provided by the IRC. So the sponsor can only assert that there was a statistically significant primary endpoint here with a superior PFS, and more importantly, the IRC also agreed with this assessment.

DR. GARCIA: Thank you.

Dr. Waldman, do you have a question or a comment?

DR. WALDMAN: Yes, I do.

DR. GORMLEY: Can the FDA respond to that comment, please?

DR. GARCIA: Sure. Go ahead.

DR. GORMLEY: Great. Hi. This is Nicole Gormley. I just want to clarify from our perspective, the FDA received the top-line results, which did not demonstrate statistical significance. We shared our concerns with the sponsor, and then sponsor provided additional information per as they described just previously, but submitted new information then stating that it met statistical significance.

I think there are several concerns that we

have with the progression-free survival, in addition to the reassessment, which is highly unusual -- and I'll just leave it at that -- but also concerns with the censoring rules that were used; and then also our own readjudication, we had a discrepancy with 4 patients.

Regardless, though, of the method used, or the timing, or the original analysis, or the reassessment, from the FDA perspective, this still represents a very, very small relative difference in PFS of only 2 months. So I just wanted to add those comments. Thank you.

DR. BAKKER: Can the sponsor give a reaction to that comment?

DR. GARCIA: Please go ahead. If you can be succinct and precise, that would be great. Thank you.

DR. BAKKER: Absolutely.

Regarding the censoring rules, the sponsor used the censoring rules as was stated in the prespecified statistical analysis plan, which meant that for a progressive disease event, the second

assessment was necessary unless there was a subsequent initiation of treatment because the patient progressed too fast, prohibiting a second confirmation, or when there was progression of extramedullary disease, which also precludes the secondary measurement.

This is according to IMW guidelines, and what you see here is the letter from the chair from the IRC stating these points very clearly from their perspective, and this is how it states in the prespecified statistical analysis plan. So from the sponsor's perspective, there can be no misunderstanding whether the primary endpoint was met or not.

DR. GARCIA: Thank you for that.

Dr. Waldman?

DR. WALDMAN: Yes. This is Scott Waldman, Thomas Jefferson University. I'm just going to perpetuate this discussion.

Listening to the discussion and reading all of the materials, there seems to be -- and again, I'm going to amplify what Dr. Garcia said. There

seems to be an incompatibility with the data interpretation from the sponsor and the data interpretation from the agency; that is progression-free survival, at least by the agency's standards, doesn't look like it was met by prespecified standards, number one; and number two, in terms of overall survival, post hoc analysis is not sufficient to establish the hypothesis.

So I guess where I'm going with this is I need to hear discussion about how we either bring these things to compatibility or are we entrenched in incompatibility? I'm sorry. It's confusing.

(Pause.)

DR. WALDMAN: I'll take any response.

DR. GORMLEY: This is Nicole Gormley. I wasn't sure. Was that a question specifically to the FDA or were you asking the sponsor?

DR. WALDMAN: I'm actually asking both, and I apologize for maybe a little bit of a nebulous question, but there's clearly incompatibility in your positions. So yes, I'm asking the FDA and I'm asking the sponsor to respond.

DR. GORMLEY: Okay. This is Nicole Gormley again, FDA, and I'll start, and then allow others to chime in, and then we can turn it over to the sponsor.

Please, just to be clear, the FDA's position, we don't agree that a PFS statistical significance was demonstrated, but please note, even if we did, we would have significant concerns and would not be able to -- this trial would not provide demonstration of safety and effectiveness because of the overall survival results.

So we've had multiple instances throughout oncology -- and, unfortunately, particularly multiple myeloma -- where we've seen discordance between progression-free survival and overall survival. Overall survival is the paramount endpoint that is needed for determination of clinical benefit. When we have a primary endpoint of progression-free survival, we still require data from overall survival to ensure that it is favorable and that there's not a potential for harm. Unlike some other endpoints, the overall

survival in particular is really both a safety and an efficacy endpoint in that it incorporates information about toxicity and allows us, really, a better understanding of the overall clinical benefit.

So we can have discussions about whether or not the PFS endpoint met statistical significance or not, but please note that that's not the most germane issue for us. The most germane issue is that the data suggest potential for worse overall survival.

DR. PAZDUR: This is Dr. Pazdur. Could I just jump in on this? May I?

DR. GARCIA: Sure. Go ahead, Dr. Pazdur.

DR. PAZDUR: I would just like to emphasize it is the sponsor's requirement to demonstrate safety and efficacy, and that efficacy should be demonstrated by substantial evidence, not by post hoc analyses. It is not the responsibility of the FDA to demonstrate that the drug doesn't work or is unsafe. It is incumbent upon the sponsor to provide substantial evidence here.

Here again, when you have people resubmitting data and changing analysis, this could bring up issues of study conduct and integrity of the study also, which needs to be addressed, so there are many factors here. But I just want to emphasize they have to demonstrate, with substantial evidence, efficacy. It is not our responsibility to disprove something. And this is a central question here, is have they demonstrated with substantial evidence the safety and efficacy of this drug? It's their responsibility.

DR. GARCIA: Thank you, Dr. Pazdur.

Perhaps just to wrap up Dr. Waldman's question, maybe the sponsor or the applicant can also have a few minutes to address Dr. Waldman's question.

DR. BAKKER: Absolutely. Thank you. Klaas Bakker here from the sponsor.

First, I would like to state about the multiple analyses that have been provided to the FDA. The transplant has always been, straight from the beginning, the only interaction that the

sponsor submitted to the FDA as the interaction that mattered for Pepaxto. The interaction was based on a biological rationale and overall endpoint that moved with it.

It's very important to state that there were no reanalyses regarding that interaction, however, what is very important -- and this comes back to IMiD interaction that the FDA says doesn't play a role -- what we see here is OCEAN on the left with an ITT/PFS hazard ratio of 0.79, an ITT overall survival hazard ratio of 1.40, and one sees the clear split by age.

Earlier this year, albeit a phase 2 study, we saw a well-known proteasome inhibitor against pomalidomide with the same trend. The request from the sponsor, where Dr. Gormley alluded to potential postponing of this ODAC, was not to postpone itself; it is because we know that DREAMM 3 is imminently reading out, and we are just very curious what the ITT overall survival hazard ratio will be from that study. And given that that analysis is coming imminently, we think that the

panel would have benefited from seeing also that data. That was the reason for the sponsor to request the FDA to at least wait until this important data became available.

Then one final comment, the FDA mentioned that their own exploratory analysis basically refuted the age IMiD interaction, but I would only like to mention that from the five studies that were mentioned, three studies were actually -- two out of three were crossover studies that cannot be any pomalidomide isolation, and one study compared to a high-dose death.

When it comes to the conduct of the study, because I hear that was also a question, there have been audits all the time during the study. There have been no findings -- and this is very important. Additionally, and I think this is important to conclude with -- the sponsor is willing to corroborate the findings in a new study. The sponsor is willing to look into a new study, excluding patients at risk because we only use subgroups to identify a patient at risk, not to

identify patients with benefit. And it is very important to state that we are willing to do a new prospect study, prospective study, in the recommended population.

With that, I would like to give it back to the chair.

DR. GARCIA: Thank you for that.

Let's move on to Dr. Freidlin. Do you have any questions or comments?

DR. FREIDLIN: Yes. Boris Freidlin. I have a question to the sponsor.

You presented analysis that argues for heterogeneity of treatment effect, and indeed the analysis showed that some subgroups have detriment in the overall survival; for example, in younger patients, in women, and in patients with more than 2 lines of therapy. And then it is proposed that by excluding patients who progressed less than 3 years after transplant, they indicate a population will avoid OS detriment.

How can we be sure that these rules reliably exclude population with potential harm? For

example, consider a hypothetical 64-year-old patient who relapsed 40 months after transparent. According to your slide 44, OS hazard ratio for this patient could be as high as 2, indicating potential harm. How do you know treatment is safe for a patient like this? Thank you.

DR. BAKKER: Thank you. Klaas Bakker here from the sponsor.

The slide that is currently up shows the subgroups after the exclusion of the group at risk; that is the patients who progressed less than 36 months after their transplant. What you basically see is that all the point estimates move to the left, excluding any real potential risk. There is still an age relation visible, but that is due to the pomalidomide interaction with age. If you would, however, look at medians, the median for Pepaxto in the patients less than 65 years of age is 35 months; for pomalidomide, it's 31.5.

So this gives the sponsor reassurance that with all the point estimates moving to the left, basically taking away all the other FDA identified

heterogeneous subgroups, gives us confidence that this population at risk, and excluding, is sufficient to conduct further studies with this drug.

DR. GORMLEY: This is Nicole Gormley at FDA. Could we leave that slide up? I'd like to respond to that comment, if that's ok.

DR. GARCIA: Please go ahead, Dr. Gormley.

DR. GORMLEY: Great.

As you notice here on the slide -- and I think, Dr. Freidlin, you bring up a great comment -- most of these confidence intervals cross 1, so there is not confidence that just limiting the population to what they've prespecified would not cause harm.

I'd just also like to point out from a regulatory perspective, we do not use subgroup analyses to carve out indications, and we would wholeheartedly endorse the sponsor's proposal to conduct a prospective randomized trial in the population that they deem would not experience harm, but that should be done before an indication

of granted. Further information is needed to have confidence that we would not be causing harm to patients. Thank you.

DR. GARCIA: Thank you.

Dr. Nowakowski?

DR. NOWAKOWSKI: Hi. Greg Nowakowski; a question to the sponsor.

With all the uncertainty regarding PFS and overall survival, which could indicate potential harm for melflufen, I'm trying to look at other time-dependent endpoints here. Your slide CO-31 shows the median duration of response is essentially identical in both arms.

How do you reconcile this median duration of response? That's number one question. Then related to it, do you have any other time-dependent endpoints like time to next therapy per arm?

DR. BAKKER: Yes. I will ask in the meantime to bring up the time to subsequent therapy. The time to subsequent therapy was marginally longer for the pomalidomide arm, so patients on Pepaxto were somewhat earlier able to

start their new treatment. With regards to the secondary endpoint, as shown here, we see a benefit of melflufen, or Pepaxto, over pomalidomide.

I'd just like to respond to Dr. Gormley, who I thank for the outreach to conduct a new clinical study and recognize this population. I would like to state that it never has been the sponsor's intent to carve out a subgroup of benefit, as the FDA suggests. We have used guidelines to identify the patient group at risk, and that is consistent with when you meet a primary endpoint of PFS, that you have the obligation to look at subgroups. And of course; of course there are subgroups where the confidence intervals go above 1. I think there is no single study in oncology where you have all the subgroups with the full confidence intervals below 1. So I just think that's an important point.

DR. GARCIA: Thank you.

Dr. Crawford?

DR. NOWAKOWSKI: Sorry. I just wanted to summarize the response because there were additional comments from the sponsor, so I just

want to make sure that I'm clear.

The median duration of response was no difference, as you showed, and then you mentioned that the time to next therapy was actually favoring the standard arm in the study, the pomalidomide arm.

Is that correct?

DR. BAKKER: Yes. Sorry for the confusion. So it was favorable for Pepaxto, time to subsequent therapy. I just want to be clear there. That was shorter than for pomalidomide.

DR. NOWAKOWSKI: Oh, sure. Okay.

Then in terms of the overall survival, which we provided discussion here, one of the potentials for harm has been delayed toxicity, which then results in the ability of patients to receive effective additional lines of therapy primarily due to cytopenia or other residual delayed toxicity.

Do you have any data about what treatments patients received after progression, and how many were able to receive the treatment? Maybe you were able to capture PFS-2, with those treatments,

subsequently?

DR. BAKKER: Yes, we do have those data, and I hope you can see the slide that I see in front of me. A similar percentage of patients were able to receive subsequent therapy; in fact, a somewhat higher percentage of patients on the Pepaxto arm. There are two main differences between both drugs here. What is very clear here is that more patients on the pomalidomide arm were able to receive daratumumab following progression as a next line of therapy, whereas for Pepaxto patients that progressed, a significant number of patients received pomalidomide.

Now, we know from a study by Dr. Richardson, the [indiscernible] trial, that the earlier daratumumab was used, the more favorable the outcomes are. Of course this is a hypothesis generating, but it is clear that potentially this is impacting the pomalidomide arm favorably because of the earlier you daratumumab.

DR. NOWAKOWSKI: Okay. And that's on PFS-2?

DR. BAKKER: Sorry. No, we did not capture

PFS-2 as a formal endpoint.

DR. NOWAKOWSKI: Okay. Thank you.

DR. GARCIA: Thank you.

Dr. Crawford?

DR. CRAWFORD: Thank you, Mr. Chair.

This is Stephanie Crawford. Certainly I appreciate the presentations both from the sponsor and the agency. We have heard that exploratory post hoc analyses are not used in regulatory decisions; notwithstanding, because so much in both sets of presentations was on post hoc analysis. I ask a clarifying question to the sponsor.

I invite the sponsor's response to issues raised by FDA regarding inflated type 1 error without adequate statistical adjustments to control for the multiple comparisons in the post hoc analyses performed.

DR. BAKKER: Thank you for the question.

If I can ask to pull up slide CO-5, please? Regardless of whether we prespecify multiplicity for studies, it's important that a study meets its primary endpoint. According to the statistical

analysis, when the primary endpoint is met -- and that wasn't, according to the statistical analysis plan -- we are obliged to look at subgroups regardless of multiplicity adjustment. But because of the risk of a random finding, as illustrated by the FDA, by the patients randomized in March versus July, the endpoint [indiscernible] should be substantial, should be supported by a biological rationale, precedent, and other supportive endpoints, and this is actually what holds true for the transplant group. So while not formally prespecified in the statistical analysis plan, I stated it was a prespecified subgroup.

DR. CRAWFORD: Thank you.

DR. GARCIA: Thank you.

DR. CRAWFORD: Just to clarify, were statistical adjustments made in the post hoc analyses; and if so, what were they?

DR. BAKKER: I will ask our statistician, Marcus Thuresson, to answer your question.

DR. THURESSON: Hi. This is Marcus Thuresson, the statistician at Oncopeptides.

Well, while we are not making any formal claim on the subgroups in terms of statistical significance, we believe that we had a statistical significance on the overall PFS results, and the evaluation of subgroups revealed that we cannot really say that there is homogeneity across subgroups.

So it's more, as we discussed before, a way to sort out a subgroup of risk rather than identifying a subgroup where we have efficacy. So there's no --

DR. CRAWFORD: Thank you.

DR. THURESSON: -- need for adjustment for multiplicity.

DR. CRAWFORD: Thank you for the response.

DR. GARCIA: Thank you --

DR. GORMLEY: This is Dr. Gormley at the FDA. Could we just comment again?

I just would like to underscore -- and perhaps we could pull up FDA slide 80. I think the committee understands what I've mentioned earlier, is that we do not grant indications based on

subgroup post hoc exploratory analyses. And while the sponsor's claiming that they're not carving out the population by adding a limitation of use, that's essentially what they're doing, and that's what I'm referring to.

If we could have FDA slide 80, just to underscore -- perhaps this is not the correct one. Just to underscore, the statistical analysis plan outlined transplant, yes or no, as a -- outlined prior transplant, yes or no, as an exploratory analysis. There was no type 1 error control -- thank you -- for this analysis.

So as you can see here, this is a little analysis plan from 2021. It was listed as an exploratory analysis, and it was only prior transplant; yes/no. There was no mention of time to progression or 36 months. So from our standpoint, this is a really concerning analysis, and one that we cannot use to confirm clinical benefit. So I'll pause there, and I don't know if any other colleagues wanted to answer from the FDA.

DR. BAKKER: I would like to --

DR. GWISE: This is Dr. Gwise, the director of Biometrics IX. Yes, I'd just like to add that these subgroups are standard to look for heterogeneity in the treatment effect; they're not for testing, or reducing the population, or selecting the population.

DR. BAKKER: Klaas Bakker for the sponsor here; if I may give a quick reaction.

We, of course, agree that the only prespecified subgroup was prior autologous stem cell transplant. There is such a clear biological rationale that it merits further investigation, such a finding. And I would like just to ask Dr. Richardson if he would be willing to comment on the 36-month window that was put into place.

DR. RICHARDSON: Thank you very much, Dr. Bakker. I think the timeline is actually clinically very important to understand because what we know is that, in fact, in the past when patients relapsed within one year of a transplant, the pathobiology of the disease is particularly poor. With the advent of maintenance -- and the

backbone of maintenance now, of course, is lenalidomide -- that extended to 2 and then 3 years.

So I think this 1, 2, and then 3-year parameter that's been built has a strong clinical rationale, and I certainly would support the pathobiological argument behind that timeline.

DR. GORMLEY: This is Dr. Nicole Gormley. I'd like to just advance the slide.

So as you see here in a subsequent analysis, again, after we had top-line data, adjustment to the SAP, an additional time point that the sponsor planned to look at -- less than 2-and-a-half years; 2-and-a-half to 5; less than 5; more than 5; no transplant -- and 36 months is perhaps inclusive of the second bullet. But from the FDA perspective, this really just underscores data dredging, if I could say that. So thanks so much.

DR. GARCIA: Thank you, Dr. Gormley.

We'll move to Dr. Sekeres.

DR. SEKERES: Thank you so much, Dr. Garcia.

Reflecting back on some of the concerns

about the differences in interpretation of progression-free survival, maybe I'm an outlier, but that actually doesn't bother me that much. I think when you're playing a little bit on one side of statistical significance, or a little bit on another side of statistical significance, you're talking about a progression-free survival that probably isn't that great. And as has been shown previously, actually here at ODAC, progression-free survival can sometimes be in the eyes of the beholder or the eyes of the time of assessment.

So that doesn't really bug me as much. I kind of anticipate there's going to be some debate about assessment of progression-free survival. What does bug me a bunch, however, is an approximate 4-month worsening of overall survival for patients who got the study treatment, and I was wondering if the sponsor could provide some information on the duration of various grade 3 or 4 thrombocytopenia and neutropenia for patients who received mel-dex.

DR. BAKKER: I'll ask the team if they have

a slide specifically looking at the time of the thrombocytopenias and neutropenias. There's one comment that the sponsor would like to make here, and that is if I can ask to pull up the slide that was previously shown by the FDA, and I believe it was their slide 44, if I was right; and in the meantime we will create this slide, of course.

Let's see if the slide is coming up. I'm coming to the duration of grade 3/4.

This is the slide that the FDA showed about the flat 40-milligram dose that is poorly tolerated. What this basically shows, this graph, is the sponsor could have also used it to show actually that one needs the 40-milligram dose, because after one cycle, 85 percent of patients are still needing the 40-milligram dose. There's no need for dose reductions early because gradually decreasing the use of 40 milligram, which is standard if one uses a cytotoxic to get a disease under control, then when the patient fares well, you can often go with a somewhat lower dose. So I think from a dosing perspective -- to comment just

on one of the other major disagreements that the FDA and the sponsor have -- the 40-milligram flat dose actually is the right dose if we look at this graph.

I would just like Dr. Richardson maybe to comment on that.

DR. RICHARDSON: Thank you, Dr. Bakker.

I think, Dr. Sekeres, the critical question about your thrombocytopenia duration I think is important to address, and it's coming. I think it's addressed also by the fact that this was primarily seen in the peri-transplant population in terms of tolerability issues.

But going back to this 40-milligram dose, clearly dose optimization and so on is an ongoing process, but we established in the phase 1/2 study a clear dose-response effect; and also at the same time tolerability parameters that we felt comfortable with in terms of exposure and recognizing the novel mechanism of a peptide drug conjugate here, and therefore the exposure that was required for efficacy.

I think as we think about the dose reduction strategies here, it's important to share that in myeloma, obviously, we routinely dose decrease or dose adjust for pretty much all of our therapies according to tolerance, so I think that's an important other point to share. But in terms of the impact of tolerability and toxicity on that 4-month survival difference, I think, Klaas, that is very important to address, and I think you can do that, can't you, from what you want to bring up next to help Dr. Sekeres understand that better.

DR. BAKKER: Absolutely, and I now I have a slide available where I can talk better to that, and we will come back with the timing also, specifically.

But what we do want to point out is by carving out the subgroup at risk, which is common practice, we also take away this concern because, of course, we understand the potential concern by putting a patient on another alkylator shortly after they have failed basically a high-dose alkylator therapy is not the right thing to do.

And basically what we see here is this time-dependent increase, actually, or decrease of adverse events when looking at the recommended patient population, and the number of grade 3/4 adverse events goes down when we are asked at 36-month threshold, especially the need for dose modifications, and also the discontinuations go down.

So it's not only from an efficacy perspective, but it's also from a safety perspective that applying the 36-month threshold and taking out the population at risk, we really feel that we basically take away the risk of longer-deprived bone marrow function. And I will come back, after we pause for the specific slide, to the duration of grade 4 thrombocytopenia, to answer that question specifically.

DR. GARCIA: Does that satisfy your question, Dr. Sekeres?

DR. GORMLEY: Could the FDA respond to that comment? Sorry.

DR. SEKERES: Yes. Go ahead, and then I'd

love to actually get an answer to the question I asked, as opposed to the slide that the sponsor wanted to present.

DR. GORMLEY: You go first, and then we'll share some data. Please go ahead.

DR. GARCIA: Can the sponsor -- Dr Sekeres, perhaps you can actually repeat your question so you can clarify what you're really asking, instead of the slide, as you indicated.

DR. SEKERES: Yes, I know, and it's been a while since I asked the question, so I'm happy to repeat it if they've forgotten.

All I'm asking is what was the duration of grade 3 or 4 neutropenia and thrombocytopenia in your population? We're trying to get a cause of death here for the excess death rate that was seen on mel-dex; so let's start with duration of grade 3 or 4 neutropenia or thrombocytopenia in the entire population.

DR. BAKKER: I'm just hearing that we have it in the TLF, so we'll try to get a slide together to show after the break, specifically answering

your question.

DR. SEKERES: Well, thanks. So I can move on since you don't have that slide.

Can you discuss the cause of death, particularly among the excess patients who died on mel-dex?

DR. BAKKER: Absolutely. The majority is progressive disease. That is the only identified cause of death. Also, all death narratives have been shared with the agency, and I think together with the agency, we conclude that there was no specific toxicity signal there.

I will just pull this one up. The deaths within 30-60 days after first dose, we see the primary causes of death indeed being progressive disease, and within 60 days also adverse event, 3 percent versus 1 percent.

Now you need to look at the slide that I have in front of me. I'm going to put up a slide, and try to answer your question succinctly. Here we see the fatal AEs by various groups. On the left, we have the HORIZON study that supports the

accelerated approval, and of course we see more adverse events there because of the late stage of the disease, but on the OCEAN study, we see that the number of patients with at least one fatal AE, that it doesn't seem to be that there is a difference there between Pepaxto and pomalidomide, with 12 versus 13 percent, and if we look at the type of fatal events, we also don't see a difference there. Specifically, if we look at infections and infestations, it's basically balanced between the drugs, so there's no real clear toxicity signal that we could identify in this study.

DR. SEKERES: Okay. Thank you.

DR. GARCIA: Thank you.

I know there are a couple questions from Dr. Nieva and Dr. Kraus, and I apologize, Dr. Nieva and Dr. Kraus. Perhaps if we have a little bit of time between the OPH and our discussion of the topic in question, we can actually have the two of you make your comments or questions before anybody else.

But in the interest of time, I think it's time for us to take a break, so we will now take a 10-minute break. Panel members, please remember that there should not be chatting or discussion of the meeting topic with anyone during the break. We'll resume at 4:45 p.m. Eastern Standard time. Thank you all for a robust discussion.

(Whereupon, at 4:35 p.m., a recess was taken.)

Open Public Hearing

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

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the

committee of any financial relationship that you may have with the 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 the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way

where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 begin by stating your name and any organization you are representing for the record?

DR. ZUCKERMAN: Yes. Thank you. I'm Dr. Diana Zuckerman, president of the National Center for Health Research. We scrutinize the safety and effectiveness of medical products, and we don't accept funding from companies that make those products. Our largest program is focused on cancer treatments and prevention. My expertise is based on postdoctoral training in epidemiology and public health, and previous positions at HHS, and as a faculty member and researcher at Harvard and Yale.

All of us want more treatment options for refractory cancers, but we also want patients to be able to have confidence that FDA approval means that a product is proven safe and effective. The

OCEAN study of 495 patients has important information that was not available when this drug received accelerated approval. And even if some patients taking the drug do well, it's only with a randomized-controlled trial that we can determine if Pepaxto is helpful or if the patients would do better without it.

Our center's analyses support the FDA findings that the data do not confirm the indication. In the randomized trial comparing Pepaxto to another treatment option, the median survival was 5.3 months shorter and the death rate was slightly higher.

The sponsor says that some patients do better, but we agree with FDA that, quote, "Results from subgroup analyses cannot be used to conclude benefit in a subset of patients when the overall patient population has shown a detrimental treatment effect." We also agree with the FDA that progression-free survival is not improved, and that an, quote, "anti-cancer therapy that prolongs PFS is not considered safe and effective if the therapy

results in a detrimental effect on overall survival," unquote.

Public trust in the FDA has been weakened in recent years, and FDA standards matter to all of us. Would you want your loved one to take this drug rather than a superior treatment option? Unfortunately, not all oncologists will be as knowledgeable about the data as those serving on this panel, and they won't be able to make the best decisions for themselves or their patients.

It concerns us that the sponsor continues to ignore FDA concerns, rely on shortcuts instead of better research, and that the company withdrew the drug in October but then rescinded the withdrawal. Was this just a delaying tactic? We agree with the FDA that the sponsor did not provide new data, and with Dr. Pazdur, that FDA approval relies on solid information about appropriate dosage, and that's lacking here.

Maybe Pepaxto would benefit some types of patients, and better research is needed to prove that. As FDA states, "The preponderance of

evidence from the prespecified analysis, and in all other subgroups, suggests an increased risk of death in patients and a potential for harm."

Thank you very much for the opportunity to speak today. I know that many patients feel that this drug could be helpful to them, but we have to look at the science to see if that's true. Thank you.

DR. GARCIA: Thank you.

Will speaker number 2 please begin by stating your name and any organization you are representing for the record?

MS. AHLSTROM: My name is Jenny Ahlstrom, and I'm a multiple myeloma patient and founder of HealthTree Foundation for Multiple Myeloma, formerly known as Myeloma Crowd. I have been in myeloma advocacy for over 10 years, and last year helped over a million patients and caregivers through our programs. We have a program sponsored by Oncopeptides and all other pharma companies in the myeloma space in the past, but not currently.

The key question you're asking today is if

there's an appropriate risk-benefit for melflufen's approval. As a myeloma patient, I weigh risks and benefits every day as I make treatment decisions, and continue to relapse over and over again. For example, do I take a risk on CRS or ICANS with a CAR-T? Will I have recurring infections on a bispecific antibody? Will my eyes on Blenrep be a big problem? Can I tolerate the GI issues on Selinexor? Will Revlimid maintenance or a transplant give me a secondary cancer?

We are adept at having risk-benefit conversations with our doctor because we have to be. So as a patient, am I willing to risk using melflufen to gain benefit? If any of the IMiDs grew less effective over time and I was an older patient, I would risk it. If I were a younger patient with lots of options, I may not risk it. If I had a long-lasting transplant years ago but I didn't want to do a full salvage transplant again, I would risk it. If I needed bridging therapy to another option, I would risk it. If I'm one of 96,000 living myeloma patients having never

received a transplant, I would risk it. If I were on my fifth line of therapy and relapsed after pomalidomide, I would risk it.

Please give me the option to assess risk and benefit with my doctor. The worst thing would be not to have the option at all. We know that we have wildly different types of myelomas. We cannot all be treated in the same way. We need different tools in the toolbox.

So how do we learn more quickly how to subset and personalize care? For Selinexor and Blenrep, your early approval helped clinics across the country learn how to modify doses and better manage side effects. Not every patient will use these therapies, but this is a great success for patients to have options, so thank you. Conversely, panobinostat was FDA approved but unused for the most part. Doctors and patients together assessed the risks and benefits, and said, "No thanks." We are smart like that.

For melflufen, important information was learned as part of the HORIZON and OCEAN studies,

but [indiscernible] took the learning and approved around it. Don't use it for patients who didn't respond to transplant; it won't work well. Perhaps don't use it right after transplant; the impact on marrow recovery may look too similar. The over-75 patients had clear benefit on the melflufen-dex arm, which is a plus for patients who typically can't have transplant.

We've come a very long way in treating myeloma, but we need to go further and faster because 42 percent of my friends are still dying of myeloma within 5 years. Subsetted [ph] more personalized care is where we are all headed. I want to have all options on the table when I talk to my doctor about what I'm going to do next.

There is utility for this drug, and I request that you approve it and allow patients with their doctors to assess the risk and benefit of its use for their individual situation. More choices equal better outcomes for patients. Thank you.

DR. GARCIA: Thank you.

Will speaker number 3 please begin by

stating your name and any organization you're representing for the record?

DR. LAUBACH: Hello. This is Dr. Jacob Laubach. I serve as the clinical director and the chief of the multiple myeloma division at the Dana-Farber Cancer Institute and have been a long-time member of our program. I have a large clinical practice focused in the care of patients with multiple myeloma and other plasma cell disorders. I would add that I participated in the development of melphalan flufenamide as an investigator agent primarily through participation in the phase 2 HORIZON trial. I do not have any financial conflicts of interest associated with this drug or others.

Following the FDA's accelerated approval of melphalan flufenamide in February 2021, and prior to the point that approval of the agent was withdrawn, my colleagues in the multiple myeloma program and I treated 12 patients with standard-of-care melphalan flufenamide; 8 of those 12 patients were from my practice. We have

gathered, with the help of our pharmacy team information related to these patients, clinical characteristics, treatment response, and reasons for treatment discontinuation from the electronic medical record, and I would like to share that with you now.

The median age of these patients was approximately 74 years of age, ranging from 52 to 81, and patients had been diagnosed with multiple myeloma, a median of 11 years prior to receiving the drug, with a range of 3 to 24 years. They had received a median of 5.5 lines of therapy, a range of 3 to 8. All patients had previously been treated with Revlimid, bortezomib, and daratumumab. Many of the patients, 75 percent, had been exposed to the carfilzomib; 92 percent to pomalidomide; and 50 percent to cyclophosphamide; 25 percent to elotuzumab; 5 out of the 12 patients had undergone autologous stem cell transplantation.

The median number of doses of melphalan flufenamide administered to these patients in the standard-of-care setting was 4. Response data was

available to us in 11 of 12 patients. The overall response rate was 55 percent using uniform criteria. A complete response was achieved in 3 patients, very good partial response in one, and a partial response in 2 patients. Patients discontinued treatment due to progression in 58 percent; market withdrawal in 25 percent; adverse effects in 8 percent; and death in 8 percent. Mucositis, alopecia, and secondary bone marrow cancers were not noted.

I would highlight the fact that treatment of patients who have what is considered penta-refractory disease is a very important area of unmet medical need in our field. . I would highlight the fact that alkylating agents have played a very important role in the management of multiple myeloma for over 5 decades.

I would also highlight the fact that in our experience in the standard-of-care setting at Dana-Farber, the median age of patients was greater than 70, and they had received 5 prior lines of therapy as a median. I would also point out that

less than half of these patients had undergone a prior stem cell transplantation with high-dose melphalan conditioning.

In selecting patients within my practice who I consider to be good candidates to receive melphalan flufenamide, I favor those who had not previously undergone autologous stem cell transplantation with high-dose melphalan conditioning and were not in a position to do so in the future because of age, frailty, or the patient's own preferences regarding use of high-dose melphalan in their care.

Thank you very much for the opportunity to share my insights gained from experience with the standard-of-care use of melphalan flufenamide for the treatment of relapsed myeloma.

DR. GARCIA: Thank you.

Will speaker number 4 please begin by stating your name and any organization you're representing for the record?

MR. JOHNSON: Hi. My name is Scott Johnson, and I have no connection, financial or

otherwise -- just treatments -- with any institution. I was diagnosed in April of 2012 with multiple myeloma and received a series of treatments since then, some in Hartford Hospital here in Connecticut, at Smilow Cancer Institute in New Haven, Connecticut, and at Dana-Farber in Boston.

My experience with it began in April of 2012 coming downstairs here at home, and a severe pain hit me in the back. I told my wife afterwards it was like an alligator biting me in the back. It was horrible pain. She helped me to the couch, and I eventually was feeling a lot of pain. I got to the hospital, and they felt that I had some kind of a slipped disc or something and that it was best to seek chiropractic help, and they gave me pain pills, which was much relief but still noticeable pain, and the chiropractic work didn't get me anywhere.

My physician gave me at that point more blood tests, and discovered that I had to come into the office. I went in, and he explained I had no

back problem that chiropractic work could help, but that I had a not very common cancer called multiple myeloma, but there were treatments, and you could expect to be around for two or three more years. I began those treatments, and within a year or so I got a stem cell transplant at Smilow Cancer Institute, and then different treatments for a number of years.

Finally, we ran out of FDA approved treatments, and my doctor got me in at Dana-Farber under the care of Dr. Richardson. The treatment I'm on now is one that Dr. Richardson has used for me, and the one prior to that was melflufen, a little over a year ago, and I was on that for a little over a year, and for me, melflufen worked pretty well. I didn't have the nausea that some of my other treatments caused, and I also didn't have as much tiredness. I did have bone pain, which even Tylenol would temper down a bit, and that only lasted for about a day after each infusion.

Over the course of using it for around a year or so, I'd say it is a pretty good treatment.

It wasn't like all of them, a cure -- they told me there's no cure for it -- but it was sort of a life preserver that got me downstream a little further and made it so that, like melflufen, which wasn't even available when I started -- another treatment was available, and that's what I'm on right now.

So for me, it was a positive treatment, and it worked. It got me through some time and provided me the next treatment, so I'd say it has worked pretty well. Thank you very much for this time to relate my story. Bye-bye.

DR. GARCIA: Thank you.

Will speaker number 5 begin by stating your name and any organization you are representing for the record?

MR. ELLARS: The name is Ronald Ellars, and I have no financial relationship to anyone or reference to this discussion. I was at 81 years old initially diagnosed in 2013 with myeloma. I'm very supportive of this treatment, and I want to just make a quick discussion. But I found out about this speaking engagement by accident, so here

we go.

My understanding, the best way to evaluate treatments and its effect on me is with bone marrow, so I'll just give you my last bone marrow evaluation, which was done in May. Sorry I'm cutting out here on this thing.

I had a 1 percent plasma cell [indiscernible], and less than 0.1 percent myeloma cells on the full symmetry. Yes. I've been on a treatment for just over a year, and it's done an awful lot for my health. As an example, I was using a 4-wheeler to get around because of back problems and was unable to stand very long without an aide prior to being on the treatment. After Dr. Blau put me on this treatment, I only use a cane if I'm going to try walking more than, let's say, 20 yards. The only real problem I have is my platelets tend to be low, so sometimes it's difficult to get the monthly treatment.

I have no problems with infections, nor any significant problems with fatigue. My treatment now includes immunoglobulin, which I understand

will help with the platelets, and Evusheld, which helps with the white blood cells, but I've only recently started their use. We'll see how it works with those. But however, due to my improved health and immune system, being on this treatment, I support it wholeheartedly, and it needs to be still an option for an 81 year old, as I'm running out of possibilities of different types of treatments that I can be exposed to.

In closing, I just want to add, thank you a lot for letting me speak. I'm having a little problem here with getting this out, but I hope you can continue to make this treatment available to especially older patients who have been through a multitude of different treatments. I need that option, and I don't feel that it should be taken away from me.

So with that, I conclude. I'm sorry for the delay. Thank you.

DR. GARCIA: Thank you.

Will speaker number 6 please begin by stating your name and any organization you're

representing for the record?

DR. PATEL: Hi. This is Dr. Taral Patel, working in Columbus, Ohio in private practice for almost 25 years. I have no relationship with sponsor, Oncopeptides. I had a patient -- I submitted the case -- who was a 64-year-old male, and has had all the possible treatments preapproved, including stem cell transplant. Even the stem cell transplant was unable to put this patient on complete remission. All of the treatments, including CD38 antibodies, lenalidomide, pomalidomide, all the treatments were given, and unfortunately his condition continued to deteriorate.

He was about to go hospice, and we discussed two treatment options, including CAR-T. Unfortunately, CAR-T was in short supply because of deaths, so we decided to start him on melphalan flufenamide, on a commercially available drug last year around May 2021, and the patient tolerated it fairly well, except mild thrombocytopenia and not mild neutropenia. And to avoid the complication,

looking at the package insert, I did start him on a secondary prophylactic with the white cell growth factor. He's a plumber. He works full time. His quality of life has improved. We did the bone marrow on May -- I think sometime in March, March 2022, and the bone marrow shows complete response.

So this is a patient who was unable to go in complete response with even stem cell transplant with the high-dose chemo and radiation. I just saw him again yesterday, and fortunately he's still in the complete response, and he's tolerating treatment fairly well.

I understand I saw some comment about the FDA and about the toxicity. As a physician, it's our job to talk to the patients about risk versus benefit, and patients most of the time make informed decisions. So I really appreciate that the FDA panel will relook at this. It's not for everybody but a subset of the population, so this can benefit patients like me, and I appreciate everybody's time. Thank you.

DR. GARCIA: Thank you.

Will speaker number 7 please begin by stating your name and any organization you're representing for the record?

(No response.)

DR. GARCIA: Speaker number 7?

(No response.)

DR. GARCIA: Maybe they're having some difficulties, so let's just move on to the next speaker.

Speaker number 8, please begin by stating your name and any organization you're representing for the record.

DR. BLAU: Yes. I am Dr. Sibel Blau. I'm a medical oncologist and also president and CEO of the national organization of Quality Cancer Care Alliance Network and Exigent Research. I have been working as an oncologist for more than 20 years, and I did training and worked at the Fred Hutchinson Cancer Research Center as a transplanter before going into independent oncology private practice.

In 2015, my own husband, Dr. Tony Blau, was diagnosed with multiple myeloma, underwent several transplants, and has been doing great. But we were fortunate enough to be in that situation, always waiting a possible day that this disease might return, looking at all the options that are available. So I have not only been treating multiple myeloma very intensively, but also I have been a caregiver and a worried wife of a multiple myeloma patient.

My husband was a professor at the University of Washington, and he retired in 2019 to develop also a cure, where it is a data sharing platform where patients can register, and after they agree to the terms of the privacy policy, the records are curated completely from all institutions and places the patients are treated. The information is put on a dashboard where the physicians, patients, and scientists can collaborate in the decision making.

We are fortunate to have many drugs available in multiple myeloma, but partly because of that, it has become very complex in how to treat

these patients. My patient is a 74-year-old man at the time of his diagnosis with multiple lines of therapy, the best response being a very good partial response at the time of diagnosis, with a very short duration, and more drug was added at that time. But after relapsing and going to several lines of therapy, melflufen was started in July 2021, and the data in this slide shows that the patient, if you look at the lines, the blue shows the shots that he's having, and yellow is the treatment.

The patient has been in complete response ever since he was placed on this drug. He responded so well to the treatment for the first time in many years, since his diagnosis, that when FDA's disapproval came, we had to apply for a single IND, and the patient has been on this drug on a compassionate basis going. This is now an older patient who has not had a transplant and had a great response to treatment. My hope is to be able to select my patients and continue treatment on the ones that can respond to treatment as well

and, of course, monitor the toxicities knowing the overall survival data, and hope that we can use the real-world data to treat these patients effectively. Thank you very much for this opportunity.

Questions to the Committee and Discussion

DR. GARCIA: Thank you.

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

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

I will now read our discussion question. The task is for us as a group to review and discuss the benefit-risk profile of melphalan flufenamide

for the currently indicated patient population, considering the results of the confirmatory OCEAN trial.

Are they any issues or questions about the wording of the question?

(No response.)

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

Dr. Kraus, I apologize again that we couldn't get you earlier, but now is your time. Please go ahead.

DR. KRAUS: Thank you, Dr. Garcia.

Yes. I wanted to bring a point up that's relevant to the benefit-risk, the discussion of survival decrement, as well as the interpretation of benefit. It's around trial design and the differences versus some trials that are designed differently here.

Often in oncology, we have, let's say, a new therapy on top of existing best therapy versus a placebo plus existing best therapy, and there

you're truly looking at the benefit or decrement of a new therapy. In this case, we have a comparison of this melphalan analog agent with dex versus pom-dex, and pom itself, if I'm recalling correctly through my memory in myeloma, has a very substantial progression and survival benefit over dexamethasone.

So the interpretation of the data, to me, should encompass that thinking, meaning when we talk about survival decrement, it may not actually be a decrement, if there is one; it may be less benefit than pom, or similar benefit than pom. You can look at PFS similarly. If indeed there was a benefit of PFS 2 months, it may be that's a benefit over quite an active therapy combination of this newer agent.

So I think that's important to keep in mind as we think about interpreting decrement data and benefit data, particularly in what I think people have aptly described, benefit to patients. Many, many different agents and drugs approved have been helping the survival of myeloma patients as the

number of agents have multiplied over the years. I think there's good information on that.

So I would just encourage -- and I won't ask the question of the sponsor or FDA, but I would encourage ODAC to consider that because I think that's an important element. I was going to ask it, and ask for both sponsor and FDA to comment but, to me, that is an important analysis element, given what the trial design is, that wasn't really brought out yet. And I just think you need to consider that as ODAC when you're thinking about these various elements. Thank you.

DR. GORMLEY: Hi. This is Nicole Gormley. I'd like to just respond to that comment, and then I'll ask Dr. Kanapuru to provide some other additional information.

You're absolutely right. This is a trial against an active comparator, and that trial design is used in oncology, and has been. The larger point, though, is that, again, we're looking at a trial that there's potential detriment in overall survival. It's not statistically significant.

This is an active comparator trial. But the onus is on the sponsor to prove, with the clinical trial data that they have, that the product is safe and effective.

So that's the issue that we're stuck with, is that with this trial design, we don't see an improvement in overall survival. We don't see a robust progression-free survival result, so all of these things are concerning.

I'll turn it over maybe to Dr. Kanapuru to mention about some of the other trial design aspects that you mentioned.

(No response.)

DR. GORMLEY: Dr. Kanapuru?

(No response.)

DR. GARCIA: Dr. Kanapuru, I think you're still in mute.

(No response.)

DR. GORMLEY: So perhaps she's having some technical --

DR. KANAPURU: Yes, I'm here. Can you hear me?

DR. GORMLEY: Yes.

DR. GARCIA: Yes. Please go ahead.

DR. KANAPURU: Thank you.

Thank you for that question. As Dr. Gormley just pointed out, this trial was designed to demonstrate superiority and also to show that there was at least no detriment in overall survival, but the trial designs of active comparators have been used in oncology and in multiple myeloma.

If I could just bring up FDA slide number 72 onto the screen. I would like to point out that we have had prior approvals where we had active comparators, and on the slide, that will just show up in a short while, you can see that there were two trials, one with the carfilzomib deaths versus the bortezomib deaths. Again, here these were actually two similar mechanism of action proteasome inhibitors, and in this trial there was a significant PFS improvement, as well as an overall survival benefit, so it showed superiority for PFS, as well as benefit in overall survival. Similarly, we had another trial called the fourth

[indiscernible] trial, but there was actually a doublet comparator compared to a standard-of-care triplet, and even in that trial, there was improvement in progression-free survival and overall survival. So these trial designs have been used, and the drugs have shown that they could demonstrate superiority as well as OS benefit.

What we have here is a trial that was designed to show superiority for PFS, and at least it's not an improvement. It was also designed to show an improvement in overall survival, but there's not a demonstration of superiority for PFS, and what we have here is a concerning potential detriment in overall survival. Thank you.

DR. GARCIA: Thank you.

I probably have a comment. I just want to open the group for good, provoking talks, perhaps. When I look at the data, I just want to make sure that -- again, everybody, I think that all of us would agree that -- I personally, just my own personal thoughts and comments, come to these meetings with an open mind, and I come after

reviewing the docket and the documents.

I'm not a multiple myeloma expert; I'm a drug developer in GU oncology. But when I see the data, after I review the docket, based upon the FDA presentation, based upon the applicant presentation, it's hard for me to understand how we use subset analysis to try to tease out true benefit for a treatment. That goes against everything that I have actually been taught for statistics for clinical trial design and for drug development.

I think, eloquently, many of you have actually reviewed why post hoc analysis are hypothesis generating and should not be actually used for us to make decisions as to who gets therapy. Forest plots are very, very imperfect, but even if you were to look at that, I'm also perplexed, because if you look at every single possibility for survival, there is a detrimental potential because every single hazard ratio crosses the confidence interval of 1.

So that is what I'm trying to wrestle here

with, is, yes, maybe there's a treatment that has some activity. Yes, there's no doubt that the natural history of multiple myeloma may allow some patients to have access to these agents, but every single point, data, that I see here, really leads me to believe, without confidence, even if the PFS is real, I cannot tell a patient I'm going to actually be able to put you in a therapy that may delay your progression-free survival, but it may have the chance of actually harming you and cause detrimental outcome by shortening your survival, and that's what I think many of us perhaps are struggling with.

So with that, maybe I'll ask Dr. Nieva to express his thoughts.

DR. NIEVA: Thank you, Dr. Garcia.

I think, really, the central question here is this PFS question because if we say that -- in consultation with the FDA, and with the FDA's understanding of what the planned statistical analysis was going to be -- this was a positive trial for PFS, well then, the company's done

everything they've asked them to do, and shown that, yes, we showed in the first trial that we had a response rate, and the second trial we showed a PFS benefit.

So the issues to me are, really, was the statistical analysis plan something that was brought to the FDA as a fait accompli and the FDA would view it as being wrong, or was this developed in consultation with the FDA? So that's a question that either the FDA or the sponsor can answer.

But I think the other thing that this data is clearly telling us is that this drug really shouldn't be used in people who are melphalan resistant, and the data for looking at subgroups I think can tell us safety signals that certain people shouldn't get a drug.

We know that the FDA has sort of said, and I think that the community accepts, that EGFR and ALK-mutated lung cancer patients, for example, shouldn't get checkpoint inhibitors; that even though they may have been included in some studies, they clearly don't show benefit. And I look at

this in a very analogous way, that we've identified a clinical subgroup that shouldn't get the drug, but aside from that clinical subgroup, everything actually looks very good.

So I'll see if anybody wants to talk about the statistics and whether there was actually collaboration in this statistical design, or whether or not the statistical design that was presented was not viewed by the FDA beforehand, and now they say, well, no, clearly it was wrong. Thank you.

DR. BAKKER: For the sponsor, I have the data that was asked just before the break as well, if I may show that, and then come back to the question that was just asked about the statistical analysis plan. So I'll put up the slide on the duration of thrombocytopenias and neutropenias. I'm waiting for it to now appear on the screen. Here we have it.

So the median time to resolution of grade 3 or 4 neutropenias was 8 days in both arms; for the thrombocytopenias it was 15 versus 9 days. I think

very important to mention, for those who are concerned with the MDS and long term, is that was only one patient in both treatment arms that developed MDS.

To the question about the statistical analysis plan, this study was developed under a SPA [ph], and with that comes the development of the statistical analysis plan together with the agency. So the SAP was initially submitted early in 2017, and there were modification agreements along the line until 2019, where no changes to the SAP were submitted. The final submission of the SAP was in February 2021, and there has been no further commonly agreed changes. So the censoring rules were based mutually under a SPA with the FDA. That's the sponsor's view.

DR. GARCIA: Thank you for that.

Let's just go ahead and ask Dr. Kwok for a comment.

DR. GORMLEY: Oh. Can the FDA respond, please? Actually, I think it was a question to both groups. Is it ok if we respond?

DR. GARCIA: Go ahead, Dr. Gormley, yes.

DR. GORMLEY: Yes. Nicole Gormley. There are several aspects here, and I'm going to allow some of my statistical colleagues to comment as well.

First, the SPA process is one that we engage in with sponsors in order to try to reach alignment on the major aspects of the protocol. It is not by any means a uniform endorsement of every aspect of the protocol or the statistical analysis plan.

I can have my statistical colleagues comment a little bit more about some of the specific issues, but the censoring rules that we shared are the typical censoring rules that we use in multiple myeloma, but even though we can discuss the SAP and other analyses planned, it did not include for the reassessment that occurred. That obviously was outside of the SAP.

Then also, I want to just comment as well that when we make any assessment for a product, there's a requirement that there's demonstration of safety and effectiveness. So we don't look in an

isolated fashion at just one endpoint; we look at the entire clinical picture of the data that's presented. So as stated previously, we would never rely on a positive PFS value if there was evidence of detriment of overall survival. And when we've used subgroups in the past, the ITT result has been positive. We have not and do not use subgroup analyses to find a population that has a favorable benefit when the overall is negative.

So I'll turn this over to our statistical colleagues.

(No response.)

DR. GORMLEY: Dr. Rodriguez, do you want to comment?

DR. RODRIGUEZ: Hello. Yes. This is Lisa Rodriguez, deputy director for Division of Biometrics IX. I agree with what Dr. Gormley just said. There are various PFS censoring rules that we looked into: FDA's analysis, censored unconfirmed PD, for example. I think what was stated earlier, though; however, regardless of how PFS was analyzed, the difference in the median PFS

between the arms still remained approximately 2 months or less, and still the overall finding in the ITT population for OS is a concern. So we don't think limiting an indication based on a subgroup is appropriate.

We also --

DR. GARCIA: Thank you.

DR. RODRIGUEZ: Sorry. I wanted to add, we also did previously communicate in censoring with the sponsor. Thank you.

DR. GARCIA: Thank you, Dr. Rodriguez.

Let's just get back to our group and try to actually address some of the comments that the committee members have.

Dr. Kwok?

DR. KWOK: Hi. My name is Mary Kwok. I'm from the University of Washington, Fred Hutchinson Cancer Center. I have a clarifying question first.

When we're just talking about the indicated patient population, now we're talking about patients that are greater than 36 months from transplant; is that correct?

DR. GORMLEY: This is Dr. Nicole Gormley. No, that's not the indicated patient population. That's the new indication or new population that the sponsor is proposing. But currently, the indicated patient population is those that have received the 4 prior lines and refractory to at least one proteasome inhibitor, one IMiD, and one CD38. It does not --

(Crosstalk.)

DR. KWOK: -- as the study was designed [indiscernible]. Thank you. That's helpful.

I treat patients with myeloma, and as I'm looking at these slides and hearing the presentations, I completely appreciate the viewpoints that were shared by the clinical members and then the public, because I agree that there's a huge need for a medicine like melflufen. But at the same time, I think, how am I going to face the patient in front of me and describe -- how do I explain this trial to a patient?

I think, Dr. Garcia, you mentioned that's where the struggle lies. Even if the patient may

potentially benefit from it, a conclusion from the study is that there's an increased risk, a detriment to overall survival. I think that is something that's very, very difficult to do with a treating physician.

I also think that the takeaway, for me at least, from the study is, really, probably that this would not be the desired treatment, at least in the first 2 to 4 lines of therapy; then I also think of pom-dex as a comparator. A lot of times when we treat patients, especially with early relapses, we're treating with triplets, so I don't know that it would be easy to make direct comparisons in actual clinical practice, especially for the first 2 to 4 lines of therapy.

This is just an open-ended question, but I just want to know how to think about melflufen, especially when it's given as a single agent, and perhaps, like what was suggested, that it finds its role in patients that are elderly, no transplant, relapsed and refractory. But I don't think that's the question that's being asked here. Thank you.

DR. GARCIA: Thank you

DR. BAKKER: Can I respond as the sponsor? Just one thing to clarify the sponsor's position is that we propose a limitation of use, so we very much agree that the findings from OCEAN should be applied to the current indicated population. So for the current label, we want to take the learnings from OCEAN into account, and I cannot emphasize this enough.

DR. RICHARDSON: If I may just add to that, I just want the efficacy in U.S. patients for HORIZON, please, Ted, to be put up. It's a very important slide.

Dr. Kwok raises an extremely good point. We see, obviously, the challenges of the heterogeneity in OCEAN, recognizing that we're dealing with a mechanism of action challenge between the two drug classes, and indeed one's a doublet -- both are doublets, rather. I think as we think about the current label, to me anyway, the current label points to the HORIZON population, and I think it's very important to share with the audience this

particular slide of efficacy in U.S. patients because HORIZON was a study in which we enrolled -- the majority were actually U.S. patients, and we saw clinical benefit as reflected by these numbers, reflecting response in PFS. And, obviously, when you break them up according to the pre- and post-transplant populations, you can see the benefit here. So I hope this data is helpful in making some sense of in what setting one would consider Pepaxto for patients.

DR. GARCIA: Yes, and I appreciate that. Thank you for bringing that.

I think it's important for us to really actually get to our discussion point within the committee rather than trying to clarify questions that really, to some extent, have been addressed and depicted in the prior presentations, but thank you for that.

Dr. Nowakowski?

DR. NOWAKOWSKI: Yes. Thank you. Greg Nowakowski. I just wanted to comment on the comment by Dr. Nieva.

For me, the PFS issue is not necessarily really an essential issue here because I think like with any other trial -- and others expressed their sentiment as well -- we have to look at the totality of evidence, and here the possible detriment and safety signal, or the detriment of overall survival, is very concerning, regardless if this PFS difference, which is pretty modest, is real or not, and how do we interpret that dose.

The other comment is just a short comment about the subset analysis. I appreciate all the effort which the sponsor really put into understanding different subsets and dissecting it in different ways, and even comparing with the IMiDs cohort. I also appreciate all the effort FDA took also to address those concerns and conduct a number of sensitivity analyses and subset analyses in those.

In the big picture when one takes the bird's-eye view on this, I was just thinking to myself what I would tell my residents or medical students about this study, and what I would say is

they're all hypothesis-generating. So they're very interesting hypotheses, scientific hypotheses, on which group may or may not benefit from the intervention, but it's not a definite proof, and I think that's what we are struggling here with.

DR. GARCIA: Thank you.

Dr. Sekeres?

DR. SEKERES: Thank you, Dr. Garcia. Mikkael Sekeres from Sylvester Cancer Center, University of Miami.

With accelerated approval, we have the opportunity to get drugs that work better than other drugs out there to desperate patient populations who have few other options, and that's predicated on a trial actually confirming the initial magnitude of benefit and safety, and ideally extending that to something that's more clinically meaningful like overall survival.

What we see here is a progression-free survival that, depending on how you interpret progression, toys around significance, but in the end is a median improvement of only 2 months, and

we have a worsening of overall survival by 4 months.

We look at the totality of these data. We look at progression-free survival, overall survival, and if it's available to us, we look at patient-reported outcomes -- it's not available here -- and the totality of data for me doesn't add up. And I keep circling back to what Dr. Kwok mentioned earlier, and that is, how the heck would I give informed consent to a patient to receive this drug and explain that progression-free survival, which itself is a difficult concept to explain to anyone, may be better by a couple of months, but that that person will live 4 months shorter than if he or she didn't get this drug? And that's where I get stuck with this application.

DR. GARCIA: Thank you, Dr. Sekeres.

Dr. Madan?

DR. MADAN: Hi. Ravi Madan, NCI.

We spent a lot of time talking about how we should censor and how the FDA did it versus the sponsor, but when you take a step back, you realize

that the PFS benefit changes just by shifting 4 or 5 patients, or less than that, and I think you have to wonder, is that really robust data? And then you default to the survival data and whether or not the outcomes are worse -- it's not better -- based on the data presented. So I think that really factors into this part of the discussion significantly for me. Thank you.

DR. GARCIA: Thank you.

Dr. Harrington?

DR. HARRINGTON: Thank you. My question has been answered by the previous two questioners. Thank you.

DR. GARCIA: Thank you.

Dr. Chen?

DR. A. CHEN: Hello. I was wondering if there's a precedent -- I couldn't think of one -- where someone is changing the label based on subgroup analysis, and also changing the dosing without prospective studies to support that; a question for the FDA.

DR. GORMLEY: This is Nicole Gormley. No,

this is an unprecedented scenario. Thank you.

DR. GARCIA: Thank you. Thank you all.

If I can summarize some of the points that the committee has discussed, it does appear that for some PFS issues, and discrepancies between the FDA PFS and the sponsor PFS, it did not appear to be of a significant concern, based upon how you censor and based upon how you measure PFS as described by Dr. Sekeres.

It also is clear that all of us, for the most part, feel that the subset analysis and the post hoc analysis is really hypothesis generating and should not be interpreted as a doc deciding who gets therapy and who does not, including perhaps what the applicant is trying to address right now, which is to try to actually encase their agent into a very specific patient population, based upon that subset analysis for which it doesn't appear that a statistical design was actually built within the study. Clearly, the biggest issue is survival and the challenges of seeing every single hazard ratio, however you dissect the data, that crosses 1, and

clearly appears to be with a potential detriment of around 4 months compared with pom-dex.

So I think that's the theme of our discussion right now, and with that, I think 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 proceed, and if there are no further questions -- and I'm sorry; I was misreading my section here, so I apologize. But if there are no further questions, maybe we can actually move on to the next question, Dr. Chen.

This is a voting question, and the question is, given the potential detriment in overall survival, failure to demonstrate a progression-free survival benefit, and lack of an appropriate dose, is the benefit-risk profile of melphalan flufenamide favorable in the currently indicated patient population?

DR. S. CHEN: Thank you, Dr. Garcia, and I will provide instruction for the voting. This is

She-Chia Chen, the DFO.

Question 2 is a voting question. Voting members will use the Adobe Connect platform to submit their votes for this meeting. After the chairperson has read the voting question into the record, and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you are a voting member, you'll be moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected.

Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote. You will have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, I will

announce that the vote is closed.

Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Next, the chairperson will go down the roster and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to.

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

(No response.)

DR. CRAWFORD: Yes. To the chair, Dr. Garcia, may I ask a question about when would be the appropriate time to discuss the wording of the question?

DR. GARCIA: Maybe right now since we're moving to the voting.

DR. CRAWFORD: Thank you. This is Stephanie Crawford. I do want to state in fairness to the sponsor there was a comment made by the sponsor earlier that the voting question can be considered leading, and it can be, the first two-and-a-half

lines. Perhaps it would be fairer to just start the voting question -- because some would say the first almost two-and-a-half lines would be a false premise to some, maybe it would be fairer for the voting question to just start with the verb "is," is the benefit-risk profile of melphalan flufenamide favorable for the currently indicated patient population, without the part that was, quote, "given." Thank you.

DR. GARCIA: Thank you.

Does anybody else have any question or comments concerning the wording of this question?

DR. KRAUS: [Indiscernible].

DR. GARCIA: I'm sorry. Who is speaking?

DR. KRAUS: Sorry. I had my hand up. I'm just agreeing with the comment the individual just said. There was obviously some disagreement about some of the data representation, so I'm agreeing with the prior comment -- Albert Kraus, industry representative -- in how to adjust the question a little bit.

DR. GARCIA: Maybe we can ask the FDA for

guidance as to how to retweak it if the committee --

(Crosstalk.)

DR. PAZDUR: That would be fine; is the benefit-risk --

DR. S. CHEN: Excuse me. The question -- sorry. I'm so sorry. This is She-Chia. The voting question is going to stay as is. The panelists will go ahead and vote when it starts, and then you can make comments once you finish the vote. Thank you.

DR. GARCIA: Alright. So I'll repeat and re-read the question.

Given the potential detriment in overall survival, failure to demonstrate a progression-free survival benefit, and lack of an appropriate dose, is the benefit-risk profile of melphalan flufenamide favorable for the currently indicated patient population?

Maybe, Dr. Chen, you can move us to -- if there are no questions or additional comments, we will now begin the voting on question number 2

DR. S. CHEN: Thank you, Dr. Garcia.

We will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. S. CHEN: The voting has closed and is now complete. Once the vote results are displayed, I will read the vote results into the record.

(Pause.)

DR. S. CHEN: The voting has closed and is now complete. The vote results are displayed. I will read the vote totals into the record, a total of 2 yeses, 14 noes, and zero abstentions.

The chairperson will go down the list, and each voting member will state their name and their vote into the record. You can also state a reason why you voted as you did, if you want to. Thank you.

DR. GARCIA: Thank you, Dr. Chen.

We will now go down the list and have everyone who voted to state their name and vote into the record. You may also provide

justification for your vote, if you wish to.

We will start with Dr. Chen.

DR. A. CHEN: I voted no. I think there's marginal PFS benefit, and then the setting of significant concerns about overall survival.

DR. GARCIA: Thank you.

Dr. Sung?

DR. SUNG: Anthony Sung, Duke University. I voted no. I do think it is possible that there is some benefit in specific subpopulations, but on the whole, I do not think that the benefit outweighs the risk.

DR. GARCIA: Thank you.

Dr. Freidlin?

DR. FREIDLIN: Boris Freidlin. I voted no. I believe that given the potential for a detriment, the data provided does not allow reliable justification of the population in whom the benefit-risk profile is favorable.

DR. GARCIA: Thank you.

Dr. Lieu?

DR. LIEU: This is Chris Lieu. I voted no.

We've discussed this. The post hoc analysis really should be used for hypothesis generation as opposed to labeling and indication for use. There's certainly a need for better drugs, we all feel that, but we shouldn't be using drugs that might actually be harming patients.

To me, the answer here is pretty simple. You have an analysis which may support the use in a specified patient population that could show a benefit, and a confirmatory study should be performed in this population, but the data do not support the use of this agent at this time.

DR. GARCIA: Thank you.

Dr. Harrington?

DR. HARRINGTON: David Harrington, Dana-Farber Cancer Institute. I voted no. In the indicated population, the results of the trial are fragile because of the marginal PFS benefit and the possibility of a safety signal for survival. I think the proposal by the sponsor on how to trim the population will only lead to confusion if it's not confirmed in a subsequent trial.

DR. GARCIA: Thank you.

Mr. Mitchell?

MR. MITCHELL: Yes. Thank you. I voted no, and I'd like to take a minute to explain why.

The vote was very difficult and personal. I'm a candidate for this drug. I'm a multiple myeloma patient diagnosed 12 years ago, and now with relapsed/refractory myeloma, who's presently receiving a proteasome inhibitor and immunomodulatory agent, a CD38-directed monoclonal antibody and dex. I've not had an autologous stem cell transplant, so even based on the sponsor's post hoc analysis and suggestion for how to use the drug, I'm a prime candidate.

My care is directed by oncologists at Dana-Farber, so the presence of doctors from Dana-Farber participating in this meeting weighs on me as well. Frankly, this could be a life-or-death decision for me and others like me, but after listening closely to both the sponsor and FDA presentations, I conclude that melflufen has demonstrated a lack of confirmed benefit, inferior

overall survival, and a potential for actual harm.

Post hoc analysis shouldn't be used to confirm a drug. If the history of ASCT and age are considered as hypotheses to explain and demonstrate effectiveness of this drug, then the sponsor should run a prospective randomized clinical trial and test those hypotheses; then I and other patients will be able to take the drug with confidence, based on substantial evidence that it's safe and effective. And thanks for letting me have that time to explain.

DR. GARCIA: Thank you, Mr. Mitchell.

Dr. Nowakowski?

DR. NOWAKOWSKI: Thank you. Greg Nowakowski, Mayo Clinic. I voted no due to reasons that others mentioned and we discussed. There was a questionable benefit in terms of the progression-free survival and potential detrimental impact on overall survival, raising safety concerns with this drug.

I will also point out that the presentation of the U.S. population in the trial was relatively

limited, and it was not representative of the U.S. population diversity as well, which is an additional factor which limits the applicability of this study to the U.S. population.

DR. GARCIA: Thank you.

Dr. DeFlice?

DR. DeFLICE: I appreciate what everyone has said, although I think there is a need for off-the-shelf treatment options for relapsed/refractory multiple myeloma and treatment of the extramedullary disease; therefore I voted yes.

DR. GARCIA: Thank you.

Jorge Garcia. I voted no. I remain concerned about the lack of PFS benefit based upon how I reviewed the statistics of this study, and certainly the biggest issue, again, are the concerns for detrimental outcome regarding overall survival in the entire patient population.

Dr. Nieva?

DR. NIEVA: Jorge Nieva. I voted yes. The OCEAN trial is a positive trial based on the PFS

using a prespecified analytic plan. I think it's problematic to have the sponsor submit an SAP to the FDA, have the FDA see it, and have the FDA analyze the data using an alternative methodology.

I think everything flows from the ITT analysis. When it's positive, you should look at subgroups, and when it's negative, you should not. It does appear that the OCEAN study confirms clinical response and benefit seen in HORIZON, and to say it does look to me like an exercise in moving the goal posts.

I do not think the numerical difference in OS is a safety signal, but it's a lack of efficacy signal. While it may not have been obvious at the time of study design that you shouldn't use melphalan in a melphalan-resistant patient population, it certainly seems obvious now, and the analysis provided shows that patients may benefit as long as they're not melphalan resistant. The sponsor, however, is making highly problematic recommendations in setting that time frame at 36-months post-transplant, and the clear concern on

the part of the FDA that this is retrospective is understandable. This minimum duration for avoiding melflufen is post hoc, but it didn't have to be. The cutoff dates could have been transplant, yes or no, or one of the prespecified numbers, and it's a shame that we were not provided those. Thank you.

DR. GARCIA: Thank you.

Dr. Kwok?

DR. KWOK: I also voted no, based on the inferior overall survival with melflufen. I also hope that melflufen has a place in future treatment of myeloma, but probably not in this patient population defined in OCEAN.

DR. GARCIA: Thank you.

DR. Sekeres?

DR. SEKERES: Mikkael Sekeres, and I voted no. Accelerated approval is designed to get drugs to patients who desperately need them quicker than they would get to those patients through the regular approval process, but a critical aspect of accelerated approval is that follow-up trials actually confirm the initial benefit that's seen.

Unfortunately, in this case, the follow-up trial flopped, and not only did it not show the magnitude of benefit that we saw initially, but it potentially showed an increased risk of death in patients with significant toxicity. And for that reason, I voted no.

DR. GARCIA: Thank you.

Dr. Kunz?

DR. KUNZ: Hi. Yes, this is Dr. Pamela Kunz, Yale Cancer Center. I also voted no for many of the reasons stated, but mostly given the results of the confirmatory trial that showed the marginal PFS benefit and potential detriment with overall survival. I'm also not supportive of using a subgroup analysis for the indication like others have stated, and also open to seeing a prospective trial done to look at the subgroup. Thank you.

DR. GARCIA: Thank you.

Dr. Madan?

DR. MADAN: If I may, I just want to say that I appreciate Mr. Mitchell's ability to be objective in these circumstances and eloquently

state his rationale.

This is Ravi Madan in the NCI. I voted no. Essentially, I don't think the trial supported robust activity here as it was designed to do. I do appreciate the sponsor's willingness, as I stated, to conduct a prospective study, based on the hypothesis-generating data from this trial. Thank you.

DR. GARCIA: Thank you.

Dr. Waldman?

DR. WALDMAN: This is Scott Waldman, Thomas Jefferson University. I voted no for the same reasons that everybody else did. I think the confirmatory trial was not confirmatory. I don't think it demonstrated clinical activity, or at least remarkable clinical activity, and I think there is a risk, a potential risk, for overall survival in the patient population. So for those reasons, I voted no.

DR. GARCIA: Thank you.

Dr. Crawford?

DR. CRAWFORD: This is Stephanie Crawford.

I voted no for the reasons stated by others. In consideration of the high bar of evidence needed for approval by FDA regarding safety and efficacy, I can only consider and evaluate the study results currently available and vetted, which is the reason for my vote.

That stated, however, I think all of us would agree that multiple effective modalities are greatly needed for relapsed or refractory multiple myeloma. Melphalan flufenamide may hold promise for some patients. I also note that the sponsor expressed willingness to corroborate findings in a new prospective trial in the recommended population. In my opinion, that would be of benefit, and I would hope that the results would be considered by the FDA at the appropriate time. Thank you.

DR. GARCIA: Thank you, Dr. Crawford.

If I can summarize the voting, obviously, the vast majority of the committee voted no. For our two colleagues who voted yes, it appears that was just the consideration, and the study met the

primary endpoint, and perhaps the lack of issues with survival related not to detrimental but rather to lack of efficacy of the agent.

For the vast majority of us who voted no, clearly it related to the marginal PFS benefit regardless of however one addresses that PFS and certainly the concerns about detrimental outcome survival, specifically with the hazard ratio in favor against, I should say, the combination of melflufen and steroids.

Certainly, I think that we all embrace the ability clinically to do post hoc analysis, as they may allow us to tease out patient populations who may derive benefit in future studies. And certainly I think you have heard, and the applicant has heard, loud and clear that we all embrace new treatments for multiple myeloma, and we're encouraging you to work with the FDA to see if you can actually identify the right patient population, for the right clinical trial, with the right statistical design, if you really believe this agent has promise in multiple myeloma.

With that, before we adjourn, are there any last comments from the FDA?

DR. GORMLEY: Yes. This is Nicole Gormley. I'd just like to say thank you for your discussions and considerations today.

Adjournment

DR. GARCIA: Well, thank you all for that robust and active discussion. We will now adjourn the meeting. Thank you again for all your participation. Have a great night.

(Whereupon, at 6:05 p.m., the afternoon session was adjourned.)