FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Virtual Meeting

Wednesday, October 4, 2023

9:30 a.m. to 3:35 p.m.

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(9:30 a.m.)

Call to Order

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

My name is Dr. Christopher Lieu, and I'll be chairing this meeting. I will now call the October 4, 2023 Oncologic Drugs Advisory Committee meeting to order. Dr. Joyce Frimpong is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

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

Dr. Conaway?

DR. CONAWAY: Mark Conaway, University of

Virginia School of Medicine, biostatistics.

DR. FRIMPONG: Dr. Gradishar?

(No response.)

DR. FRIMPONG: Dr. Gradishar?

(No response.)

DR. FRIMPONG: I'll come back to you, Dr. Gradishar.

DR. GRADISHAR: I'm here, Northwestern, Chicago.

DR. FRIMPONG: Thank you.

Dr. Lieu?

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

DR. FRIMPONG: Mr. Mitchell?

MR. MITCHELL: I'm David Mitchell, and I am the consumer representative to the ODAC.

DR. FRIMPONG: Dr. Nieva?

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

DR. FRIMPONG: Dr. Pappo?

DR. PAPPO: Alberto Pappo, pediatric oncologist at St. Jude Children's Research Hospital.

DR. FRIMPONG: Dr. Spratt?

DR. SPRATT: Hi. I'm Dr. Dan Spratt, chair of radiation oncology at Case Western Reserve and UH Seidman Cancer Center.

DR. FRIMPONG: Dr. Vasan?

DR. VASAN: Hi. Good morning. Neil Vasan. I'm a breast oncologist at Columbia University, Irving Medical Center.

DR. FRIMPONG: Now for our industry rep, Dr. Cheng?

DR. CHENG: Good morning, Jon Cheng. I'm a medical oncologist, and I'm the industry rep, and I'm at Bristol-Myers Squibb.

DR. FRIMPONG: Thank you.

Now, for our temporary voting members, Dr. Alexander?

DR. ALEXANDER: Hi. I'm a practicing internist and pharmacoepidemiologist. I'm a professor of medicine at Johns Hopkins and

professor of epidemiology there, and I am director of an FDA-funded Center of Excellence in regulatory science and innovation, and former chair of the Peripheral and Central Nervous System Advisory Committee.

DR. FRIMPONG: Dr. Asgharzadeh?

DR. ASGHARZADEH? Shahab Asgharzadeh. I'm a pediatric oncologist at Children's Hospital Los Angeles and University of Southern California.

DR. FRIMPONG: Dr. Cosenza?

DR. COSENZA: Good morning. I'm Mary Ellen Cosenza. I'm a regulatory toxicologist and I'm an independent consultant.

DR. FRIMPONG: Dr. Kim?

DR. KIM: Hi. Good morning. My name is AeRang Kim. I am a pediatric oncologist at Children's National in Washington, DC.

DR. FRIMPONG: Dr. McMillan?

DR. McMILLAN: Good morning. I'm Gigi McMillan. I'm the associate director for the Bioethics Institute at Loyal Marymount University in Los Angeles, and today I am the patient

representative.

DR. FRIMPONG: Dr. Parsons?

DR. PARSONS: Hi. I'm Will Parsons. I'm a pediatric oncologist at Texas Children's Hospital and Baylor College of Medicine in Houston, Texas.

DR. FRIMPONG: Dr. Shaw?

DR. SHAW: Good morning. I'm Pamela Shaw. I'm senior investigator of biostatistics at Kaiser Permanente Washington Health Research Institute.

DR. FRIMPONG: Dr Sturmer?

DR. STURMER: Good morning. Til Sturmer. I'm the chair of the Department of Epidemiology at the University of North Carolina at Chapel Hill.

DR. FRIMPONG: Dr. Twist?

DR. TWIST: Good morning. I'm Clare Twist. I'm a pediatric oncologist at the Roswell Park Comprehensive Cancer Center in Buffalo, New York.

DR. FRIMPONG: Dr. Unguru?

DR. UNGURU: Good morning. I'm Yoram Unguru. I am a pediatric hematologist/oncologist at the Children's Hospital at Sinai in Baltimore and a bioethicist at the Johns Hopkins Berman

Institute of Bioethics.

DR. FRIMPONG: Dr. Weiss?

DR. WEISS: Hi. I'm Brian Weiss. I'm a pediatric oncologist at Riley Children's Hospital, Indiana University School of Medicine.

DR. FRIMPONG: Doctor Widemann?

DR. WIDEMANN: Good morning. Brigitte Widemann. I'm a pediatric oncologist at the National Cancer Institute and the chair of the pediatric oncology branch there.

DR. FRIMPONG: Thank you.

And now for our FDA participants, Dr. Pazdur?

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

DR. FRIMPONG: Dr. Kluetz?

DR. KLUETZ: Good morning. I'm Paul Kluetz. I'm a medical oncologist, deputy director in the Oncology Center of Excellence and acting supervisory associate director in the Office of Oncologic Diseases.

DR. FRIMPONG: Dr. Donoghue?

DR. DONOGHUE: Good morning. My name is Martha Donoghue. I'm a pediatric oncologist. I am the associate director for pediatric oncology in the Oncology Center for Excellence.

DR. FRIMPONG: Dr. Drezner?

DR. DREZNER: Good morning. I'm Nicole Drezner, and I am a pediatric oncologist and the deputy director of the Division of Oncology 2 at the FDA.

DR. FRIMPONG: Dr. Bradford?

DR. BRADFORD: Good morning. I'm Diana Bradford. I'm a pediatric hematologist/oncologist and the cross-disciplinary team leader for the application, in the Division of Oncology 2.

DR. FRIMPONG: Dr. Duke?

DR. DUKE: Good morning. Elizabeth Duke. I'm a pediatric neuro-oncologist and clinical reviewer at the FDA.

DR. FRIMPONG: Dr. Sinha?

DR. SINHA: Good morning. This is Arup Sinha. I'm the primary statistics reviewer, Division of Biometrics V.

DR. FRIMPONG: And Dr. Wearne?

DR. WEARNE: Good morning. This is Emily Wearne. I'm a nonclinical reviewer at the FDA.

DR. FRIMPONG: Thank you.

And Doctor Liu, I'll hand it over back to you.

DR. LIEU: Thank you.

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

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

meeting.

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

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

Conflict of Interest Statement

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

The following information on the status of

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

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

financial conflicts of interests of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves a discussion of new drug application, NDA, 215500, for eflornithine tablets, submitted by USWM, LLC, doing business as US WorldMeds. The proposed indication used for this product is to reduce the risk of relapse in pediatric patients with high-risk neuroblastoma who have completed multiagent, multimodality therapy. This is a particular matters meeting during which specific matters related to USWM's NDA will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the standing voting members and temporary voting members, conflict of interest waivers have been issued in

accordance with 18 U.S.C. Section 208(b)(3) to Dr. Albert Pappo, a standing voting member. Dr. Pappo's waiver involves his employer's research of eflornithine, funded by Children's Oncology Group, which his employer receives between $0 and $1000 per year. The waiver states that Dr. Pappo is the chairperson of the Oncologic Drugs Advisory Committee; however, Dr. Pappo is not the chairperson and will not be chairing this meeting.

The waiver allows for this individual to participate fully in today's deliberations. FDA's reasons for issuing the waiver are described in the waiver documents, which are posted on FDA's website, on the advisory committee web page, which can be found at www.fda.gov, and searching on October 4, 2023 ODAC. Copies of the waiver may also be obtained by submitting a written request to the agency's Freedom of Information Division, 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all

standing committee members and temporary voting members to disclose any public statements they have made concerning the product at issue. With respect to the FDA's invited industry representative, we would like to disclose that Dr. Jonathan Cheng is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Cheng's role at this meeting is to represent industry in general and not any particular company. Dr. Cheng is employed by Bristol-Myers Squibb.

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

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

DR. LIEU: Thank you, Dr. Frimpong.

We will now proceed with FDA introductory remarks from Dr. Diana Bradford.

FDA Opening Remarks - Diana Bradford

DR. BRADFORD: Good morning. My name is Diana Bradford, and I'm a pediatric hematologist/oncologist in the Division of Oncology 2. I am the cross-disciplinary team leader for the application for eflornithine or DFMO. I will refer to US WorldMeds as the applicant and eflornithine as DFMO for the remainder of the presentation. The applicant is seeking approval for DFMO with the intended indication to reduce the risk of relapse in pediatric patients with high-risk neuroblastoma who have completed multiagent, multimodality therapy.

FDA is bringing this application to the Oncology Drug Advisory Committee to enable public discussion regarding the strengths and limitations of the evidence of effectiveness of DFMO in the proposed indication. The evidence submitted by the

applicant to support the efficacy of DFMO relies primarily upon event-free survival results from Study 3b, a multicenter, single-arm trial, evaluating DFMO in patients with high-risk neuroblastoma in remission following completion of immunotherapy.

In order to permit interpretation of the time-to-event endpoint, EFS, in a single-arm trial in this application, the applicant conducted a comparative analysis of a subset of patients from Study 3b with an external control database from Study ANBL0032. ANBL0032 was a randomized, open-label trial of isotretinoin versus isotretinoin plus immunotherapy in patients with newly diagnosed high-risk neuroblastoma, who had completed induction and consolidation therapy. Patients in the immunotherapy arm form the basis of the external control arm provided in the NDA.

This trial is an externally controlled trial in which, according to the FDA guidance referenced here, outcomes in participants receiving the test treatment, according to a protocol, are

compared to outcomes in a group of people external to the trial who had not received the same treatment. Also, as per the FDA guidance, with this type of design, control patients should be as similar as possible to the trial population, and importantly, according to the ICH guideline referenced below, tests of statistical significance carried out in such studies are less reliable than in randomized trials.

Time-to-event endpoints such as EFS and overall survival, or OS, should generally be evaluated in randomized studies, as these endpoints may be affected by factors other than drug treatment, in this case DFMO, such as the natural history of disease or patient selection. EFS and OS results from externally controlled trials can be uninterpretable, as differences between the study and control populations may impact these endpoints and designs for these trials can be very complex.

Randomized studies minimize the effect of these known and unknown differences; however, as I will discuss later in the presentation, FDA may

consider data from an externally controlled trial in certain circumstances, and the interpretability of the results of an externally controlled trial depends on many factors, including the comparability of the populations, endpoints assessed, timing of assessments, and quality of data. Notably, FDA has not previously relied upon a single externally controlled trial to support an approval in oncology, necessitating discussion at today's advisory committee meeting.

To provide context for this rare disease, I will first provide a brief background on high-risk neuroblastoma and the current treatment paradigm, followed by an overview of Studies 3b and ANBL0032. I will then provide an overview of the regulatory framework for approval and the use of external controls. Finally, I will provide the discussion topics and voting question.

Neuroblastoma is a rare pediatric disease, which occurs in approximately 700 to 800 patients per year in the U.S. It represents 8 to 10 percent of childhood cancers and a disproportionate

percentage of childhood cancer deaths. It is a disease primarily of young children with a median age of diagnosis of 17 months. Neuroblastoma is a heterogeneous disease. Fifty percent of patients are classified as high risk based on age, stage, MYCN status, and tumor histology.

Typical frontline multimodality therapy for high-risk neuroblastoma is outlined here. After 18 months of treatment with induction, consolidation, and immunotherapy, the goal is to achieve no evidence of disease or no active disease. Patients in remission receive no further pharmacologic disease-directed therapy; however, there is is a risk of relapse with 50 percent of patients either being refractory to treatment or experiencing relapse. After relapse, survival is poor, with a 5-year overall survival of less than 10 percent.

DFMO is an oral ornithine decarboxylase inhibitor. Inhibition of ODC blocks polyamine biosynthesis. This enzyme is particularly relevant in neuroblastoma because the ODC gene is found

upstream of MYCN and aberrations of MYCN are correlated with poor prognosis and this disease. During their review, the FDA nonclinical review team determined that the submitted pharmacology studies supported the cytostatic mechanism of action of DFMO as a single agent in neuroblastoma.

Results of nonclinical studies considered during the review will be presented in detail by my colleagues in a subsequent presentation. As you will hear, unique to this application, the nonclinical data supporting the mechanism of action and animal models relevant to the proposed indication are being considered in the context of potential confirmatory evidence.

I'll briefly review some key regulatory history to provide context for this application. The primary study supporting efficacy for this application, Study 3b, was originally conducted under a research IND and later transferred to the applicant for further development.

In November 2015, FDA held an end-of-phase-2 meeting with the investigator

sponsor, at which time early data from Study 3b was shared. FDA stated that a randomized-controlled trial would be required in order to scientifically assess the effect of DFMO as a maintenance therapy to prevent relapse in patients with high-risk neuroblastoma. However, in 2018, a preliminary breakthrough therapy designation discussion was held regarding the results of Study 3b compared to a historical control rate from Study ANBL0032.

FDA recommended that the sponsor provide patient-level data from the studies intended to support a potential breakthrough therapy designation request, and in 2020, FDA granted breakthrough therapy designation for the proposed indication, based on a propensity score matched external control analysis from Study ANBL0032, which forms the control arm in this application. Subsequently, the applicant and FDA held several meetings to discuss the statistical analysis plan for the external control comparison to support a future NDA.

The high unmet medical need for patients

with high-risk neuroblastoma, the specific external control data source, and results of the propensity score matched analysis impacted FDA's willingness to consider an external control design in this circumstance.

I will also point out here that the results of Study 3b, as well as the results for the study from the external control, were known prior to the development of the statistical analysis plan for the externally controlled trial; however, FDA provided detailed recommendations on the design of the statistical analysis plan, including patient selection for the control group.

At the pre-NDA meeting in 2021, FDA stated that the proposed comparison to ANBL0032 appeared acceptable but that determination of substantial evidence and effectiveness will be based on an overall assessment of the results of multiple independent analyses. The application was submitted in November 2022.

To provide the primary evidence of efficacy in this application, the sponsor conducted a

comparative analysis of a subset of patients from Study 3b, in blue, compared to patient-level data from Study ANBL0032, in orange. 270 control patients treated on ANBL0032 were matched to 90 patients treated with DFMO in a 3-to-1 ratio, based on a propensity score algorithm for comparison of efficacy with a primary endpoint of EFS. Patients were matched based on 11 key clinical covariants, which my colleague will review in a subsequent presentation.

The Kaplan-Meier plots and hazard ratios for the applicant's proposed primary analysis of EFS and OS are provided here. As noted in my discussion of regulatory history, FDA will not rely on results of a single analysis, given the retrospective nature of the comparison and complexity of the externally controlled trial. Rather, as you will see in the statistical presentation, a rigorous approach to sensitivity analyses was taken to evaluate potential sources of bias and characterize the treatment effect estimate.

In assessing evidence of effectiveness of DFMO for the proposed indication, FDA considered four key steps: first, whether the external control is appropriate for use; second, whether the single externally controlled trial is adequate and well controlled; and third, whether the results of the externally controlled trial and confirmatory evidence are sufficient to establish substantial evidence of effectiveness; step 4, an overall risk benefit assessment would only be performed if substantial evidence of effectiveness has been established and would incorporate an assessment of the safety of the drug. I will review these steps briefly to outline the FDA's regulatory framework.

To start with step 1, appropriateness of use of an external control, there are several characteristics that strengthen the level of evidence that can be provided by an external control to establish effectiveness. These include a high unmet medical need in a rare disease with a well-defined natural history; a high degree of similarity with regards to baseline disease

characteristics and concomitant treatments; and a large estimated treatment effect. Evidence of change in the established progression of disease, such as tumor shrinkage, may also provide confidence in a treatment effect.

With respect to this application, patients with high-risk neuroblastoma have an undeniable unmet medical need. Notably, outcomes for patients with high-risk neuroblastoma have improved with time, making contemporaneity an important consideration for the analysis of results. The other factors outlined on this slide, including similarity of the external control population to the treatment group, will be reviewed with respect to this application by my colleagues.

Note that a large treatment effect may aid in increasing acceptability of an externally controlled trial. Given the results of the propensity score matched analysis presented at the time of the breakthrough designation and the rarity and natural history of the disease, FDA considered that an external control could be reasonable in

this setting. My clinical and statistical colleagues will discuss their review, based on the data provided in the application, regarding whether the data and the external control are fit for purpose and whether the populations are appropriately comparable.

Moving on to step 2, whether the results of an externally controlled trial can be considered interpretable depends on upon many factors. FDA considered whether the study was an adequate and well-controlled trial. To receive FDA approval, a drug or biologic product must demonstrate substantial evidence of effectiveness through adequate and well-controlled studies. An adequate and well-controlled trial must be appropriately designed and conducted. Poor execution of any trial design, externally controlled or not, could render a trial not adequate and well controlled, and not capable of establishing substantial evidence of effectiveness.

Characteristics of an adequate and well-controlled trial are outlined here and include

a clear statement of objectives and methods of analysis; a design which permits a valid comparison with a control; adequate measures to minimize bias in both subject assignment to treatment group and measures to minimize bias on the part of subjects, observers, and analysts of the data. An adequate and well-controlled trial must have well-defined and reliable methods to assess response, and finally, adequate analysis of the results of the study to assess the effect of the drug.

Based on the FDA clinical and statistical review, the review team considered that the externally controlled trial appeared to be adequate and well controlled, and we will be seeking the committee's opinion on the strengths and limitations of the evidence of effectiveness provided by this trial.

I will next discuss step 3, establishing substantial evidence of effectiveness, and discuss the regulatory framework. Effectiveness can be supported by either two adequate and well-controlled trials or one adequate and

well-controlled trial with confirmatory evidence of effectiveness. In this case, we will be considering the latter. In this NDA, the applicant submitted one externally controlled trial with supportive evidence. Using a single trial with confirmatory evidence may be acceptable depending upon the persuasiveness of the single adequate and well-controlled trial; robustness of the confirmatory evidence; seriousness of the disease and unmet medical need; and whether it is ethical and practicable to conduct more than one adequate and well-controlled investigation.

As noted, the strength of a single adequate and well-controlled trial will affect the extent of confirmatory evidence required. Examples outlined in the 2023 guidance are provided here. First, an adequate and well-controlled investigation demonstrating effectiveness of a drug in a closely related indication may be used as confirmatory evidence. A single adequate and well-controlled trial may be supported by earlier phase clinical results or testing that provide compelling

mechanistic evidence in the setting of well understood disease pathophysiology.

The guidance states that generally clinical testing would be used to provide mechanistic support, but data from relevant animal models may be used, alone or in combination with clinical data, supporting the mechanism of action. While typically used to support progressing a drug candidate forward from preclinical to clinical development, rather than support a finding of substantial evidence, in some instances, sponsors may use data from an established animal model of disease as confirmatory evidence and effectiveness.

Whether it is appropriate to rely upon such evidence as confirmatory evidence depends upon many factors, and only models that have proved to be translational are likely to be considered as confirmatory evidence. In some cases, the trial may be supported by the well established natural history of the disease, which reinforces a very persuasive finding.

Scientific knowledge of the effectiveness

of drugs in the same pharmacological class obtained through an adequate and well-controlled trial could provide confirmatory evidence. Finally, in certain cases, confirmatory evidence may come from a real-world data source or from high-quality data obtained through expanded access use of the drug.

In the applicant and FDA presentations, you will hear the available nonclinical and clinical evidence that could serve as confirmatory evidence. Again, whether the available supportive evidence is sufficiently strong to be considered confirmatory evidence depends both on the strength and persuasiveness, and any uncertainties associated with the single adequate and well-controlled trial serving as primary evidence, and the strength of the supportive evidence itself.

Typically in applications in oncology, we are able to rely upon findings of efficacy and other indications, or upon antitumor activity in early clinical investigations like response rate. In this case, we do not have reliable data suggesting that treatment with DFMO as a single

agent results in objective responses. Objective responses may not be expected, based on data suggesting a cytostatic mechanism of action of DFMO as a single agent; however, this presents a challenge for this application.

FDA considered information provided by the applicant, as well as information from an independent literature search. The supportive data considered included nonclinical data and preliminary clinical data. Clinical data sources consisted of limited numbers of patients from two studies and an expanded access program. The strengths and limitations of the confirmatory evidence will be discussed further by FDA and the applicant in subsequent presentations. We ask that the committee consider the strengths and limitations of the available potential confirmatory evidence in their discussion.

Finally, returning to our four steps, if FDA determines that substantial evidence of effectiveness has been demonstrated by the single adequate and well-controlled trial and confirmatory

evidence, an overall risk-benefit assessment is made, which incorporates the safety profile of the product in the context of the disease under study. If substantial evidence of effectiveness has not been demonstrated, a drug cannot be approved, and the risk-benefit assessment could not be made in the absence of efficacy.

We greatly appreciate that you are here today to provide your perspectives on this application. As discussed, according to our regulatory framework, our ability to establish effectiveness is dependent upon the determination that the externally controlled trial is adequate and well controlled.

We ask that you discuss the following topics. First, discuss the strengths and limitations of the externally controlled trial results to support the use of the DFMO in pediatric patients with high-risk neuroblastoma. Second, discuss the strengths and limitations of the additional nonclinical and clinical data to support the use of DFMO in pediatric patients with

high-risk neuroblastoma. Finally, we will ask you to consider whether the applicant has provided sufficient evidence to conclude that DFMO improves event-free survival in patients with high-risk neuroblastoma. Thank you for your attention and participation in today's meeting.

DR. LIEU: Thank you, Dr. Bradford.

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

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

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

We will now proceed with the US WorldMeds' presentation.

Applicant Presentation - Kristen Gullo

MS. GULLO: Good morning. I'm vice president of Development and Regulatory Affairs for US WorldMeds. I would like to thank FDA and the panelists for your time today as we share the results of our clinical program, supporting the use eflornithine, also referred to as DFMO, as maintenance therapy for children with high-risk neuroblastoma.

Advancing therapeutic options is critical since the goal for treating these young patients is to achieve remission and prevent relapse. The impact of high-risk neuroblastoma and the medical

needs of these children is one I have felt directly, when in 2019, my 3-month old nephew, Finn, was diagnosed with high-risk neuroblastoma, and in that moment, my professional and personal lives collided in ways I never imagined. I turned to the scientific literature and research groups, including Beat Childhood Cancer, for education and hope.

I met BCC's founder, Pat Lacey, whose son Will was also diagnosed with high-risk neuroblastoma as an infant. She shared Will's 7-year treatment journey, including his participation in an early phase 1 investigation of DFMO. Pat shared that BCC was looking for a partner to shepherd the product through the FDA registration process, and after reviewing the data, we began a partnership with Beat Childhood Cancer with a goal to improve treatment outcomes for patients with this devastating disease.

Today, young children like Will and Finn undergo an intense, toxic standard-of-care regimen that still leaves them vulnerable to relapse and

death, a risk that is the highest in the first few years after achieving remission. About half of young children diagnosed with high-risk neuroblastoma die within 5 years of diagnosis. This high mortality rate is driven primarily by a high risk of relapse. Today, we are missing treatments that follow the existing standard of care to sustain remission. Avoiding relapse is key to survival. We will review data showing that DFMO maintenance extends remission and improves survival outcomes beyond published historical rates or propensity-matched populations, and DFMO safety data aligned with expected risks that are outweighed by its benefits.

Our program was influenced both by the rarity of high-risk neuroblastoma and by its high mortality. Study 3b was a single-arm study designed to add DFMO maintenance treatment following the current standard of care to improve survival outcomes. To demonstrate efficacy, we used a rigorous propensity-matched control from the landmark registration quality study, ANBL0032, or

just 0032 for short. 0032 aligns with guidelines on the use of externally controlled studies, enabling comparison of highly similar populations that have common characteristics and backbone therapy. This approach is consistent with recent emphasis on needed regulatory flexibility for rare diseases in general, and for pediatric cancer in particular.

The findings from our study are supported by multiple sources of confirmatory evidence, meeting the requirements for substantial evidence of effectiveness. The DFMO clinical program also demonstrates an acceptable safety profile in the context of its benefits. Given FDA's goals for today's discussion are focused on efficacy, I am sharing only a high level overview of safety data.

In our database of over 300 patients, grade 3 and 4 adverse events were generally consistent with known risks of DFMO. These risks include new or worsening hearing loss to grade 3, which indicates the need for intervention such as hearing aids. Other risks include hepatotoxicity

and myelosuppression. Serious events were generally associated with infections and included pyrexia, dehydration, vomiting, and pneumonia, and no adverse events resulted in death.

DFMO was generally well tolerated, with few patients requiring dose modification and even fewer requiring discontinuation. Hearing loss was more thoroughly evaluated due to the importance of hearing on early development. Only 2 percent of patients discontinued treatment due to hearing loss events, and importantly, dose management strategies had a 63 percent success rate in achieving improvement or resolution of hearing loss events. This supports FDA's overall conclusion that the risk of DFMO therapy can be monitored and managed with recommendations proposed for product labeling.

Turning to our regulatory history, DFMO received orphan designation in 2017, followed by breakthrough therapy designation in 2020. We leveraged the intensive FDA guidance offered for breakthrough programs to collaborate closely on the design of our pivotal externally controlled trial

by seeking and implementing advice from the review team throughout the program.

We reached agreement with FDA on all key aspects of our application, and prior to the submission of the NDA in 2022, FDA granted participation in the Real Time Oncology Review and Project Orbis. These programs are intended to accelerate development and registration of promising oncology therapies. Accordingly, the NDA was granted a priority review. Our proposed indication is to reduce the risk of relapse in pediatric patients with high-risk neuroblastoma completing multiagent, multimodality therapy.

Next, Dr. Sholler will provide an overview of high-risk neuroblastoma and the need for therapies to avoid relapse; Thomas Clinch will present the DFMO efficacy package that includes the pivotal externally controlled studies, as well as highlights of our confirmatory evidence; and Dr. Susan Cohn will provide her clinical perspective. We also have additional experts with us today. With the exception of Dr. Sholler and

Ferguson, all outside experts have been compensated for their time and travel to today's meeting.

Thank you. I'll now turn the lectern over to Dr. Sholler.

Applicant Presentation - Giselle Sholler

DR. SHOLLER: Thank you.

My name is Giselle Sholler, and I'm the chair of the Beat Childhood Cancer Research Consortium. I treated my first neuroblastoma patient in 2003 when outcomes were incredibly poor and have since dedicated my career to improving treatment for these children. Since 2010, I have been working on the preclinical and clinical research of DFMO for neuroblastoma.

Neuroblastoma is a rare pediatric cancer diagnosed in about 800 children per year in North America. While rare, it's the most common cancer in infants. Ninety percent of cases are diagnosed in children before 5 years of age. This solid tumor cancer most commonly starts in the adrenal glands, although it can originate in other nerve tissue. Patients are classified by their risk for

relapse and treatment is tailored based on whether they have low, intermediate, or high-risk disease.

High-risk patients face the poorest outlook in terms of survival. This is in contrast to low- and intermediate-risk patients, who are managed with monitoring or limited therapy, and have overall survival rates greater than 90 percent. High-risk neuroblastoma accounts for half of new diagnoses. These patients often present with widespread metastatic disease that is more aggressive and more difficult to treat. The overall survival rate for these patients is only 50 to 60 percent despite receiving the most intensive treatment.

The upfront standard of care for high-risk patients includes three phases of difficult and toxic treatment, consisting of induction, consolidation, and immunotherapy. Over approximately 18 months, patients endure multiple rounds of chemotherapy; surgery; stem-cell transplants; radiation; and inpatient antibody infusions.

The immunotherapy phase of standard of care was established by the Children's Oncology Group, or COG, through their study, 0032. 0032 included a randomized-controlled phase that evaluated the benefit of adding post-consolidation anti-GD2 immunotherapy. Patients were then followed for up to 10 years. The primary endpoint for the study was event-free survival and the secondary endpoint was overall survival. The findings showed that adding immunotherapy improves event-free survival, with fewer patients experiencing relapse from the start of immunotherapy.

The initial reporting from this study resulted in a single-arm expansion phase, with more than a thousand additional patients receiving post-consolidation immunotherapy. It also supported the FDA approval of the dinutuximab and the addition of immunotherapy to the upfront standard of care for high-risk patients. However, as we can see in this yellow box that shows outcomes from the end of immunotherapy, even with the latest improvements to upfront care, many

children are still at risk of relapse. From the end of immunotherapy, the event-free survival curve continues to decline, and only 70 percent of patients are still in remission at 2 years.

Avoiding relapse gives patients the best chance at surviving into adulthood but, unfortunately, 30 percent of patients remain at risk for relapse within 2 years after completing immunotherapy, and most relapsed patients will die within 5 years. That is why we investigated DFMO as a maintenance therapy to enable more kids to sustain remission and avoid relapse.

Let me explain how we conducted our clinical program for DFMO, beginning with why we selected DFMO for evaluation. Polyamines are required for cell growth and division and are frequently upregulated in neuroblastoma. DFMO directly binds and inhibits ornithine decarboxylase, known as ODC, which decreases polyamine synthesis. This reduction in polyamines drives a cytostatic response through several mechanisms. In vitro assays show that

DFMO-mediated inhibition of polyamine synthesis leads to a restoration of balance in the LIN28/Let-7 pathway, which regulates cancer stem-cell growth and metabolism.

DFMO also induces G1 cell cycle arrest to promote senescence at clinically relevant drug concentrations, and DFMO suppresses neurosphere formation in both MYCN-amplified and non-amplified cell lines, showing that the cytostatic effect of DFMO occurs regardless of MYCN status. Taken together, these mechanisms highlight how DFMO drives the cytostatic response in neuroblastoma and why DFMO makes an attractive therapeutic option for maintenance therapy.

In vitro preclinical data identified DFMO concentrations needed to inhibit ODC and neurosphere formation. Additionally, multiple published adult chemo prevention studies reported successful ODC inhibition, reduction of polyamines at the cellular level, and positive clinical outcomes using doses as low as 500 milligrams per day. This data guided our selection of the

starting dose for our first investigation in high-risk neuroblastoma patients.

The initial investigation was a phase 1 dose escalation study with the primary objective to evaluate safety. We studied doses ranging from 500 milligrams per meter squared to 1500 milligrams per meter squared twice daily in 18 patients with active relapsed or refractory high-risk neuroblastoma. DFMO was administered alone in cycle 1, and then in combination with oral etoposide chemotherapy for four additional cycles. No maximum tolerated dose was identified.

Secondarily, we observed polyamine reduction and evidence of tumor stabilization or response across the dose range. This included 12 of 18 patients with a disease stabilization or response after the initial cycle of DFMO alone. Seven patients continued treatment with DFMO alone after cycle 5 and then no further therapy. There are three long-term survivors, including patients treated at the highest and lowest doses. PK evaluations in this study also demonstrated plasma

concentrations consistent with our in vitro drug effects.

Together, these data guided our selection of the 750, plus or minus 250, milligrams per meter squared dose for Study 3b, which covered the majority of the dose range determined to be well tolerated and providing preliminary evidence of efficacy in this phase 1 study.

Now, turning to our Study 3b design, a total of 140 intention-to-treat patients were treated with DFMO who were prospectively divided into two groups. One group, labeled Stratum 1, included patients in initial remission after upfront therapy, while the other, labeled Stratum 2, included patients in remission following treatment for relapsed or refractory disease, a group known to have a worse prognosis. The results of Stratum 2 patients will be shown as part of our confirmatory data package later in the presentation.

Our primary evaluation was focused on Stratum 1 patients. The intention-to-treat

population for efficacy analysis is 105 patients. The majority of patients have either completed the study or remain in ongoing long-term follow-up. Study 3b was a single-arm study that added DFMO as a 2-year maintenance therapy following the standard-of-care event. Event-free survival was a primary endpoint and overall survival was the secondary endpoint. The goal was to keep as many patients in remission as possible, lowering the risk of relapse.

The study enrolled patients in remission following upfront treatment. The studied population had characteristics similar to the demographics reported for patients with high-risk neuroblastoma. The majority of patients were stage 4 with unfavorable histology and were older than 18 months of age at diagnosis.

Let me share the efficacy results. In our group of DFMO-treated patients in upfront remission, the 2-year event-free Kaplan-Meier curve estimate was 85 percent. The statistical plan assumed historical 2-year, event-free survival rate

of 70 percent from the end of the immunotherapy, estimated based on the published results of 0032. The lower confidence interval was well above that historical rate, as shown by the intersection of the dashed line. Thus, Study 3b met its prespecified primary endpoint.

The overall survival estimate was 95 percent at 4 years. The event-free survival and overall survival results were encouraging because they were the highest rates achieved in any interventional study for high-risk neuroblastoma patients to date. These positive results exceed our expectations and prompted discussions with FDA about possible pathways for registration of DFMO as maintenance therapy.

FDA's recommendation was to conduct a follow-on, randomized-controlled trial; however, as a viable alternative and within the existing regulatory framework, we presented a counter proposal for externally controlling Study 3b. These discussions initially took place in 2015 and 2016, when we were looking at the interim data from

the maintenance study.

By 2018, the full 2-year outcome data for all enrolled patients became available and further reinforced the promising event-free survival and overall survival compared to published rates. In this same year, the FDA published a draft guidance on the use of real-world evidence to support new product registration.

Because these results indicated the possibility to reduce the number of patients we see that relapse and die, and because of the availability of 0032 as a uniquely optimal external control, we solidified our decision to pursue registration with Study 3b in order to offer this benefit to patients sooner.

Let me introduce Thomas Clinch, the biometrics leader for DFMO program, who will take you through our use of 0032 as an external control to Study 3b. Thank you.

Applicant Presentation - Thomas Clinch

DR. CLINCH: Thank you.

My name is Thomas Clinch, senior director

of Biometrics and Clinical Development at US WorldMeds. We developed a systematic approach to demonstrate the efficacy of DFMO maintenance therapy using 0032 as an external control. We chose 0032 because the post-immunotherapy follow-up aligns with Study 3b. It serves as a benchmark for event-free and overall survival in patients with high-risk neuroblastoma receiving standard of care in the contemporary era to Study 3b.

Because patients in both studies receive the same upfront therapy, we can compare patients that went on to receive post-immunotherapy DFMO through Study 3b participation with those who did not. In fact, due to the timing of the studies, the majority of upfront remission patients in Study 3b had participated in 0032.

In addition, patients in both studies were followed from the end of immunotherapy with similar surveillance and long-term follow-up requirements to assess event-free survival and overall survival. This framework provides the best possible use of real-world data. In fact, 0032 provided an optimal

external control for Study 3b since the studies align on essential features recommended by expert guidance that permit a credible external comparison.

Because both studies exclusively enrolled high-risk neuroblastoma patients, the study populations have similar demographics and disease characteristics, and because their conduct was contemporaneous, patients received consistent upfront therapy and the studies employed consistent long-term follow-up, including outcome measures and frequency to evaluate survival outcomes using identical event definitions. And because 0032 is so uniquely fit for purpose to control Study 3b, FDA has been supportive of our approach.

As such, we collaborated with FDA to overcome challenges and optimize the robustness of the external control analyses. We addressed the lack of data granularity and the historical published estimates, which limited the ability to account for population similarities and differences. We addressed the lack of

randomization and incorporated ways to address potential sources of bias.

We obtained patient-level data from Study 0032, given that it was the original source of the published historical control for the upfront remission group. We then implemented propensity score matching to ensure similarity of patient characteristics, treatment patterns, and prognosis, providing the most robust way to compare the groups, and we designed the analysis plan with multiple sensitivity analyses to challenge assumptions about the population. Finally, we performed a blinded independent central review of imaging to confirm the reliability of EFS outcome reporting by Study 3b investigators.

I'll now take you through the statistical analysis plan. The first step was to establish selection criteria that would identify comparable patients. The overall goal of the selection rules was to find groups of patients that achieved the same remission status at the end of COG standard upfront therapy so that the only difference was

whether they received DFMO or not. This meant applying rules to the Study 3b population to find patients in remission following COG therapy before receiving DFMO, and within the 0032 database, we applied rules to identify patients with an end of immunotherapy disease status consistent with Study 3b eligibility criteria, thus giving us a group of patients that could have but did not receive DFMO.

Of the 140 patients in the Study 3b ITT population, 48 were removed because they had prior relapse, would not have met eligibility for 0032, or received a different upfront treatment than 0032. This left 92 patients who followed the 0032 defined standard of care.

The 0032 database includes 1,328 high-risk neuroblastoma patients who were treated with the COG standard of care. Of these, 476 were removed, most because they did not achieve end of upfront treatment remission status consistent with Study 3b enrolled patients. We also omitted those who did enroll in Study 3b and were treated with DFMO.

Notably, the patients removed from the control population had an event rate of 65 percent, which is twice that of published rates from the end of immunotherapy, so their exclusion did not benefit DFMO.

Selection rules resulted in similar populations. For example, most had stage 4 disease, a comparable proportion were MYCN amplified, and there was a comparable distribution of end of immunotherapy response. All these attributes are important prognostic indicators. With these selected groups of similar patients, we applied a propensity score matching approach as the primary analysis for evaluating efficacy.

PSM is recognized as an effective statistical tool to reduce potential biases when comparing data from different sources, such as between DFMO patients in Study 3b and no DFMO patients in 0032. PSM analyses are designed to balance baseline covariates, including factors that may influence patient prognosis. By matching individual patients based on propensity scores, PSM

enables us to further optimize the similarity of the groups being compared. Altogether, this results in reducing confounding differences in order to better isolate the treatment effect for the outcomes being evaluated.

We identified 11 key covariates common to both studies that predict for outcomes or have potential to introduce variability. Using them adds to the robustness of the propensity score matching analyses. Notably, every patient was required to match exactly on MYCN status because it is associated with different tumor biology.

This slide shows how we arrived at the two upfront remission populations based on propensity score matching. First, patients needed data reported on all 11 covariates in order to be included. That left 91 patients in the DFMO treated group and 516 external control patients who could be considered for propensity score matching.

Propensity scores were calculated for all covariate patients. One DFMO patient was excluded from matching due to having a propensity score that

was too unlike the no DFMO patient scores. In total, 90 DFMO patients were matched to the no DFMO patients that had the closest propensity score using a greedy nearest-neighbor algorithm. This process was repeated two additional times to arrive at a 1-to-3 ratio of DFMO to no DFMO.

Now, let me show you the effect of matching. This Love plot illustrates the effectiveness of propensity score matching and achieving balance across all covariates listed on the Y-axes. We specified a target standardized difference of plus or minus 0.1, indicated by the vertical dashed lines. In comparisons, many PSM analyses use the range of plus or minus 0.3.

The green dots represent the standardized difference for each covariate in the populations prior to matching. Covariates outside of the vertical dashed line indicate a larger difference between the DFMO and no DFMO populations. The goal was to move the standardized difference within the target range to enhance the comparability of the selected no DFM patients. The blue squares

represent the difference after matching and show all covariates are now extremely similar, with all blue squares between the vertical lines.

The same characteristics table presented before shows the high similarity across key demographics and disease characteristics for the matched populations, supporting the assessment that these balanced patient groups are expected to have comparable risk of relapse.

Let's look at the outcome comparison in these matched populations. The end of immunotherapy served as the common index date, and when the matched populations are compared for EFS outcomes, the results are positive. We achieved a hazard ratio of 0.48 and the p-value confirms statistical significance. This means that fewer patients will be forced to undergo retreatment and face the dire prognosis that accompanies recurrence.

We see continued and widening separation in these curves over time, adding confidence in the clinical benefit of DFMO maintenance. When the

propensity-matched groups are compared for overall survival, the results also favor DFMO. The hazard ratio is 0.32 and the p-value is, again, significant. This result supports the conclusion that a lower rate of relapse predicts for a lower risk of death.

Because the externally controlled analysis was not prospectively planned for Study 3b, it was important to modify it in a variety of ways to rule out the possibility that outcome differences could only be observed with the decisions made for the primary analysis. This plot includes some sensitivity analyses, which we concluded were most important, including changes in propensity model, patient selection, imputation, and others.

For example, we did a 1-to-1 ratio, which finds the single best matched control patient for each DFMO patient and analyses conservatively designed to favor the no DFMO group and analyses, where we find matches for only the DFMO patients that participated directly in 0032. You can see all analyses remain in favor of DFMO. This

remarkable consistency increases our confidence in the primary analysis, showing benefit to event-free survival. We applied the same sensitivity analyses to overall survival comparisons, and like the EFS results, all were consistent, favoring DFMO.

While propensity score matching is a powerful analytical tool to address potential bias, it cannot totally rule out other potential differences that could impact outcomes. Consequently, FDA guided evaluations to further characterize the patient populations and we still did not identify differences that appear to influence outcomes. We verified little opportunity for selection bias in the DFMO group and consistent results when limiting the control group to those free of such potential biases.

Propensity-matched analyses remained consistent when we incorporated additional baseline covariates such as histology. There was a similar geographic distribution of patients within the United States, and in evaluating the types of centers that participated in the two studies, we

found that patients in the no DFMO group who were treated at high volume centers of excellence trended towards better outcomes, but those centers did not contribute DFMO patients, so this difference could only benefit the control group.

We verified that nearly one-third of the DFMO patients had household poverty exposure, which is similar to reported rates for a group of 0032 patients, and given there were no clear differences influencing outcomes in the analysis populations, we also compared the DFMO and no DFMO groups without matching. Those are the groups of 92 and 852 patients meeting the analysis population selection rules before removing patients with missing covariate data.

Again, the results consistently favored DFMO for both EFS on the left and OS on the right. In fact, the survival outcomes are essentially the same as the propensity-matched population, which was expected, given outcomes were similar in control patients with and without missing covariate data.

Additionally, and at FDA's request, we conducted a blinded independent central review of imaging for patients in the DFMO group. The BICR reviewed all available imaging through long-term follow-up. Most patients had more than two years of images. The review followed a typical blinded methodology that used dual reads with ad hoc adjudication. A high concordance was observed between local and central review, indicating little to no bias in the local evaluator reporting of EFS, and when we looked at EFS using just the BICR determined outcomes, the results confirmed what was observed in the primary analysis.

Moving beyond the pivotal study, 3b and the matched comparisons, we also have supportive evidence of the DFMO efficacy in a confirmatory package. Confirmatory data is an important part of the regulatory framework for new product registration and a topic identified by FDA for discussion today. Our confirmatory efficacy package includes a variety of sources consistent with those identified in FDA's newly issued draft

guidance. All of this stems from nonclinical research confirming the cytostatic and anti-tumorigenic effects of DFMO and clinical evidence of expected pharmacodynamic effects at the recommended dose and supporting analyses and additional cohorts of DFMO maintained patients.

Efficacy is also supported by expanded access use and findings in patients with active disease. These data are included in our briefing document but will not be presented here. For the presentation today, I will focus on the highlighted elements. While each component is not intended to stand on its own, together the quantity and quality of the evidence support the findings from the pivotal comparisons.

Let's begin with the anti-tumor effect. We used an extreme limiting dilution analysis experiment in xenograft mice to evaluate DFMO's in vivo effect on reducing tumorgenic potential. Here, DFMO treatment decreased the frequency of tumor formation by over 60 percent when compared to controls. DFMO treatment also led to a reduction

of MYCN and LIN28 expression and a 6-fold increase in expression of pro-senescence markers.

Another lab demonstrated that DFMO had tumor suppressive effects in a well established neuroblastoma mouse model. In this transgenic model, neuroblastoma tumor spontaneously form, but the DFMO treatment resulted in a 65 percent reduction in tumor formation rates compared to control animals. DFMO also led to a reduction of polyamine levels in these animals. Taken together, both neuroblastoma in vivo models demonstrate that the DFMO is effective in suppressing tumorigenic events and has on-target pharmacodynamic activity.

Now turning to the clinical data, we observed a reduction in urinary polyamines that aligns with DFMO's mechanism of action. This reduction was observed in the phase 1 study of patients with active disease and in a preliminary analysis of 21 patients in Study 3b. We also observed increased Let-7 expression, which is a micro RNA tumor suppressor. There was a median 3-fold increase when comparing pre- and post-DFMO

plasma samples in a preliminary analysis of 33 patients. These patients participated in a separate ongoing study and received the same dose evaluated in Study 3b.

To further explore maintenance benefits, we also evaluated event-free survival in additional cohorts of DFMO-treated patients in remission. This included an exploratory evaluation in a group of 47 patients receiving DFMO treatment after completing European standard upfront treatment. The European strategy applies a three-phase approach similar to COG, and published outcomes for patients treated by this approach are similar to those from 0032.

Secondly, we evaluated outcomes in the group of Study 3b, Stratum 2 patients achieving remission after relapse or refractory treatment. This group received DFMO treatment and follow-up consistent with the upfront remission group, but due to significant differences in prognosis, the analysis was prospectively separated for this poor risk group.

Before we present survival outcomes in the additional patient cohorts, here again are the findings for the DFMO patients in our primary analysis. In patients treated with DFMO after European upfront standard of care, preliminary analyses indicates similar trends as those observed in our primary analysis, and in the group of Study 3b patients in remission after relapse or refractory therapy, we see expected lower EFS rates compared to upfront remission patients, but with results exceeding the prespecified historical control rate for this group.

There are limitations to each of the additional cohorts we've presented; however, there is consistency in outcomes. After completing 2 years of DFMO, patients remaining in follow-up are able to maintain remission with virtually no late relapses, supporting a durable benefit. This is unlike published outcomes in both the U.S. and Europe, consistent with the control group for the primary analysis, now shown in the upper-left figure, which demonstrates relapse events are

expected even beyond year 4 in patients that do not receive DFMO treatment.

To summarize, the pivotal externally controlled comparisons in Study 3b provide primary evidence of DFMO's efficacy in reducing the risk of relapse for high-risk neuroblastoma. The rigorous comparisons to 0032 patients show improvement in EFS that is both statistically significant and clinically meaningful. The hazard ratio of 0.48 supports that patients in the DFMO group had approximately half the risk of relapse compared to the patients in the no DFMO group, and the confirmatory data package adds further confidence to the conclusions. The preponderance of the evidence establishes substantial support for DFMO as an effective maintenance therapy in high-risk neuroblastoma.

I will now turn the presentation over to Dr. Susan Cohn, who will provide her clinical perspective of DFMO.

Applicant Presentation - Susan Cohn

DR. COHN: Good morning. I'm Dr. Susan

Cohn, and I'm a pediatric oncologist and professor in the Department of Pediatrics at the University of Chicago. I've devoted my professional career to caring for children with neuroblastoma and conducting research focused on developing more effective treatment strategies. I served as the first chair of the Children's Oncology Group Neuroblastoma Disease Committee and remain an active member. During my tenure as chair, we developed and conducted a number of seminal clinical trials for patients with newly diagnosed neuroblastoma.

Throughout my career, I've had a singular focus to identify new approaches that will improve the outcome of children with neuroblastoma and, in particular, patients with high-risk disease. This, of course, has also been the goal of those exploring DFMO as a possible maintenance therapy after patients complete their current treatment paradigms.

Over the past three decades, survival for high-risk patients has improved with increasingly

intensive multimodality therapy, including post-consolidation immunotherapy with anti-GD2 antibody; however, approximately 30 percent of patients who receive our current standard of care with immunotherapy continue to relapse. Thus, new therapies and new approaches are still needed to improve the outcome of high-risk patients.

Looking at data from the single-arm DFMO trial, I was originally concerned that the design prevented the ability to draw any conclusions regarding the efficacy of the drug. Despite its theoretical promise, based on improvements compared to historical published rate, evidence supporting its benefit was lacking. A comparator arm was needed to enable an objective evaluation.

The data we have seen today offer the ability to compare children who received DFMO following immunotherapy with an external comparator arm of well-matched patients who were not treated with this drug. The sponsor team has conducted a wide range of statistical analyses, and the results appear consistent and compelling, in favor of DFMO.

The data demonstrate activity of DFMO in patients with high-risk neuroblastoma. The addition of post-immunotherapy DFMO improves event-free survival and overall survival and have led me to conclude that DFMO can offer a benefit to high-risk neuroblastoma patients.

I also believe the risks have been adequately characterized and are outweighed by the potential benefits. The data enable those of us who treat patients with neuroblastoma to recommend the option of DFMO as we counsel families once they have achieved remission.

The design of this program and the strength of its evidence also demonstrate the importance of regulatory flexibility when there is clearly an unmet medical need and a breadth of data that provide compelling evidence to address it. I'd like to encourage you to support DFMO as a potentially important addition to high-risk neuroblastoma treatment paradigms. Thank you.

Applicant Presentation - Kristen Gullo

MS. GULLO: Thank you, Dr. Cohn.

Before we conclude, I would like to update you on Will and Finn's stories. Despite the odds, Will and two other patients in the earliest DFMO study beat high-risk neuroblastoma. Will is an adult today but is shown here in remission 3 years after completing participation in the phase 1 study of DFMO. As for my nephew, Finn made it through upfront treatment to achieve remission in 2020. He received DFMO maintenance through BCC's expanded access program for 2 years, including on his first day of preschool, shown here, and I'm happy to tell you we recently celebrated his 3-year remission anniversary.

Of course, individual patient journeys are not enough to make ultimate conclusions about a therapy's safety and efficacy, but they do inspire us to work toward evidence-based treatment options that give all patients the best possible chance of success, and our goal was to share that evidence for DFMO with you today. We aim to evolve the treatment landscape by making DFMO maintenance therapy available to children with high-risk

neuroblastoma and enable more kids to achieve long-term remission, resume their childhood, and live to become adults. Thank you, and we welcome your questions later in the meeting.

DR. LIEU: Thank you so much.

We will now proceed with FDA's presentation, starting with Dr. Elizabeth Duke.

FDA Presentation - Elizabeth Duke

DR. DUKE: Good morning. My name is Elizabeth Duke, pediatric neuro-oncologist and clinical reviewer at the FDA. Today my colleagues and I will be presenting FDA's review of the application for eflornithine, or DFMO, for the maintenance treatment of pediatric patients with high-risk neuroblastoma, submitted by US WorldMeds Pharmaceuticals, which I will hereby refer to as the applicant. This slide lists the members of the FDA multidisciplinary review team. Our presentation includes their collective input.

The applicant's proposed indication is to reduce the risk of relapse in pediatric patients with high-risk neuroblastoma who have completed

multiagent, multimodality therapy. The proposed dosing regimen is detailed here. DFMO oral tablets are to be taken twice daily for 2 years with body surface area based dosing.

Today, we will discuss the design of Study 3b and the use of an external control comparator as the primary evidence of efficacy in this application. We will review FDA's major efficacy considerations, including the comparability of study populations, the magnitude of effect observed in the externally controlled trial, and potential sources of bias. We will discuss additional nonclinical and clinical data to support the evaluation of effectiveness of DFMO for pediatric patients with high-risk neuroblastoma, followed by a brief summary of safety.

Dr. Bradford previously reviewed the disease background and standard upfront therapy for high-risk neuroblastoma. I will highlight that approximately 50 percent of patients relapse, and after relapse survival is poor, with a 5-year rate of less than 10 percent, and patients may benefit

from therapeutic strategies such as maintenance therapy to prevent relapse.

DFMO is an oral ornithine decarboxylase inhibitor. Inhibition of ODC blocks polyamine biosynthesis, thereby restoring the balance of the LIN28/Let-7 metabolic pathway involved in regulation of cancer stem cells and glycolytic metabolism. This enzyme is particularly relevant in neuroblastoma because the ODC gene is found upstream of MYCN and aberrations of MYCN are correlated with poor prognosis in this disease. Overexpression of ODC 1, the gene encoding ODC, and high expression of the oncogene LIN28B are also associated with poor outcomes in neuroblastoma.

As you will hear more later from Dr. Wearne, the FDA nonclinical review team determined that the available pharmacology data suggests that the primary mechanism of action in neuroblastoma is related to the LIN28 MYCN pathway, with suppression of tumor initiating cells rather than inhibition of established tumor growth, indicating that DFMO as a single agent in

neuroblastoma is cytostatic rather than cytotoxic, consistent with the proposed indication.

In most oncology applications, the evidentiary package is supported by dose-dependent tumor response data in early stage studies with or without additional clinical data showing early activity in other cancer indications. Given the suggested cytostatic mechanism of action of DFMO, response rate data are not expected in this clinical setting, and unique to this application, nonclinical data supporting the mechanism of action and animal models relevant to the proposed indication are being considered in the context of potential confirmatory evidence.

The source of the primary evidence of efficacy in this application is a single externally controlled trial. The applicant conducted a comparative analysis of a subset of patients from Study 3b with an external control arm composed of a subset of patients from the previously conducted clinical trial ANBL0032.

Study 3b was a multicenter, single-arm

study of DFMO monotherapy administered as extended maintenance for 2 years in patients with high-risk neuroblastoma who completed standard-of-care upfront therapy, including immunotherapy. The study enrolled approximately 100 patients in this disease setting from 2012 to 2016 and was designed with a primary endpoint of event-free survival, or EFS, at 2 years, with statistical assumptions based on trial results of ANBL0032, a large Children's Oncology Group sponsored multicenter randomized trial of standard upfront therapy plus immunotherapy versus standard therapy alone, which enrolled approximately 1400 patients with newly diagnosed high-risk neuroblastoma from 2001 to 2015.

As shown in the Kaplan-Meier curves on the right, in ANBL0032, EFS was higher for patients in the immunotherapy arm compared to standard therapy alone. These results published in 2010 resulted in the adoption of immunotherapy into the standard of care for newly diagnosed high-risk neuroblastoma and supported the approval of dinutuximab in the

U.S. in 2015. While 2-year EFS after immunotherapy was improved at approximately 70 percent, patients with high-risk neuroblastoma are at a high risk of relapse, and it was hypothesized that extended maintenance therapy with DFMO could help prevent relapse.

Thus, Study 3b was designed in 2012 as an open-label, multicenter study of DFMO monotherapy in patients who completed standard-of-care upfront therapy, including immunotherapy. The statistical assumptions for this study were based on the historical control rate derived from ANBL0032 trial results, and it was hypothesized that DFMO would increase the 2-year EFS rate from 70 percent to 80 percent. Study 3b results were published in 2018, and as shown on the left, EFS at 2 years was higher in the DFMO arm, at 85 percent, compared to the historical control rate of 70 percent.

The applicant conducted a comparative analysis of a subset of patients from Study 3b, in blue, compared to patient-level data from ANBL0032, in orange. To analyze comparable populations,

several selection rules were applied to both arms, and ultimately 270 external control patients, observed after immunotherapy on 0032, were matched to 90 patients treated with DFMO for an evaluation of efficacy with a primary endpoint of event-free survival. We will review additional details of the comparison shortly.

As discussed by Dr. Bradford, externally controlled trials differ in several important ways from randomized trials. As a result of non-random assignment, there may be differences in patient characteristics for concomitant treatments in the trial population compared to the external control population that lead to differences in outcomes that are unrelated to the investigational treatment.

As such, a randomized clinical trial would provide the strongest evidence to evaluate a maintenance treatment, and in 2015, FDA conveyed that a randomized trial would be needed to assess the effectiveness of DFMO; however, the applicant ultimately considered that the published results of

Study 3b made the practicability of initiating a new randomized trial in the same indication challenging due to concerns about equipoise, its effect on accrual and retention of patients, and the length of a new trial.

Despite the limitations of externally controlled trials, they can provide support for effectiveness in certain circumstances, and FDA considered that an externally controlled design could be appropriate in this unique circumstance; however, FDA has not previously relied upon a single externally controlled trial to support an approval in oncology. Given this context and in the setting of this unique clinical trial based on an external control, we're seeking additional feedback from the advisory committee.

In this application, some strengths of the proposed externally controlled trial, listed on the left, include the natural history established by prior clinical trials, the external controlled data source, which is clinical trial data verified by FDA inspections. Both arms received the same

upfront therapy with no subsequent anti-cancer therapy other than the investigational arm receiving DFMO, and the eligibility criteria tumor assessments and endpoints were similar between the two studies.

Some limitations, listed on the right, include that the data from both studies were published prior to the design of the externally controlled trial, which means that the results were known and prespecification of the ECT design was not feasible. While the design could not be prespecified, we note that FDA provided recommendations on the development of the statistical analysis plan to mitigate sponsor knowledge of Study 3b and 0032 results.

The trials were not fully contemporaneous, as ANBL0032 started enrolling a decade prior to Study 3b. Inherent in an external controlled design, there is less certainty in the treatment effect estimate and retrospective analysis may not include all covariates, which could be potential confounders and lead to bias.

Now, I will turn to FDA's major efficacy considerations for the externally controlled trial. Given the complexity of this application, we consulted four experts outside of FDA during the review process. The independent experts noted there were strengths and limitations of the data submitted. There were concerns expressed by some experts on reasons patients elected to enroll in an additional clinical trial, as well as the uncertainty in the magnitude of effect, alongside notation by other experts that the estimates appeared consistent and stable in demonstrating an effect.

Areas of residual uncertainty included the evaluation of specific variables contributing to the comparability of populations, such as contemporaneity and social determinants of health, and the measurement of the magnitude of treatment effect observed in the externally controlled trial. As you'll hear, FDA explored these areas of uncertainty with sensitivity analyses when possible, and key aspects of their specific

feedback are incorporated throughout the presentation.

Studies ANBL0032 and 3b were originally designed with similar eligibility criteria, as detailed in the first row of this table. All patients were required to be in remission at the end of immunotherapy, which completed within the preceding 1-to-4 months. No other anti-cancer agents were permitted during Study 3b, and the applicant submitted data to show that most patients observed on 0032 received no additional anti-cancer therapies until the time of relapse.

Data regarding post-relapse therapies are limited. Tumor assessments were required per protocol at baseline and regularly for 2 years after completion of immunotherapy, and then per institutional standard. Imaging after 2 years was available for at least 95 percent of patients at 3 years, 88 percent at 4 years, and 83 percent at 5 years. Independent central review of imaging was only available for patients on the DFMO arm. The primary endpoint for the externally controlled

trial was event-free survival, defined as the period from the last day of immunotherapy to the first occurrence of relapse, progressive disease, secondary malignancy, or death from any cause. Overall survival was a secondary endpoint defined as the last day of immunotherapy until death from any cause.

The flowcharts shown here provide additional details regarding the selection of patients in the investigational arm in blue and the external control arm in orange. Of the 105 patients treated on Study 3b who were in remission at the end of immunotherapy, 87 had been treated on ANBL0032 immediately prior to enrollment; 18 received similar upfront therapy off study. Of 1440 patients who enrolled on ANBL0032, 1328 received immunotherapy. Subsequently, 1241 patients were observed with serial imaging and did not receive DFMO in Study 3b.

The applicant proposed to use clinically important baseline covariates to build a propensity score model for the comparison of Study 3b patients

to the external control group. Propensity score and exact matching were used to ensure balance across 11 key clinical covariates. Of 852 patients who met the selection rules for inclusion in the analysis, 336 patients were removed due to missing covariate data, leaving 516 patients with data for all 11 clinical covariates.

To evaluate the potential for selection bias due to this exclusion, FDA evaluated the 516 patients who met the selection rules versus the 336 excluded due to missing data, and there were no apparent meaningful differences. Ultimately, patients were matched using a 1-to-3 ratio within the groups of 91 patients treated with DFMO and 516 control patients who were not missing any key covariate data. This resulted in a primary analysis comparing 90 patients treated with DFMO to 270 patients observed without further treatment after immunotherapy.

The 11 clinical covariates used in the propensity score model are listed here. The applicant used an exact match for MYCN status, as

it was considered the most important predictor of relapse and survival outcomes. These data reflect expected demographic characteristics for high-risk neuroblastoma with a slightly higher predominance of males and median age of diagnosis of 3 years. Patients were required to be in remission at the end of immunotherapy. While all patients were recorded to have at least a partial response, for approximately 10 percent of patients in the control arm, imaging data to confirm baseline and eligibility were not available.

The index date for the primary analysis was defined as the end of immunotherapy. There was some variability in the duration of immunotherapy due to the use of an end-of-study visit date rather than drug administration date for this definition. This study visit could have been delayed for a variety of reasons, and we considered this in our statistical evaluation.

This plot shows the standardized mean differences for the 11 matched clinical characteristics. As shown in red, patients in

Study 3b and 0032, with no missing data for the matched variables, had relatively similar demographic and disease baseline characteristics. After matching, patients were more similar, as shown in blue.

Listed here are other demographic and disease characteristics which were not incorporated into the matching algorithm. While all Study 3b sites were in the United States, ANBL0032 was an international trial with sites also in Canada, Australia, and New Zealand, 1 percent of patients in the DFMO enrolled on 0032 outside the U.S. compared to 14 percent of patients in the matched external control arm.

Almost all patients on both arms received the expected 6 cycles of immunotherapy. Tumor histology was generally balanced between arms, but 10 percent of patients had missing data. Regarding tumor cytogenetics and primary tumor location, it's unclear whether the arms are balanced, given the amount of missing data.

These additional non-matched

characteristics were considered by FDA. The potential impact of missing clinical data, evolution of supportive care over time, and lack of data regarding social determinants of health, such as socioeconomic status, were concerning to the clinical experts whom we consulted during the review period. Regarding contemporaneity of treatment, patients in the external control arm completed immunotherapy up to 7 years prior to patients on the investigational arm. We'll discuss methods for assessment of several of these non-matched characteristics later in the presentation.

This slide outlines FDA's overall considerations for the comparability of the externally controlled trial populations. Strengths include the similar protocol specified eligibility and tumor assessment criteria and the matching of relevant clinical characteristics. After the same upfront therapy, patients on both arms should not have received any anti-cancer therapy, other than DFMO for the investigational arm, until the time of

relapse.

FDA conducted multiple analyses related to the selected index date, the end of immunotherapy, and concluded these time points were similar in both arms and all study sites for Study 3b were also 0032 sites. Limitations include the non-matched variables previously discussed, as well as the unmeasurable variables and potential differences in patients whose families elected to go on to Study 3b for maintenance treatment, as oppose to observe, after an intensive 18 months of upfront therapy. This concern was emphasized by the clinical experts consulted during review of this application.

Approximately 40 percent of patients in the external control arm completed immunotherapy prior to the end of immunotherapy for the first patient in the investigational arm. Imaging was protocol specified only for 2 years and these data were available for less than 80 percent of patients after 5 years. ANBL0032 enrolled at 197 sites primarily in the U.S., but 14 percent of the

patients in the matched external control arm were treated in Canada, Australia, or New Zealand.

In the next section of the presentation, we will review FDA's analyses, which address these identified limitations. I will now introduce my statistical colleague, Dr. Arup Sinha, who will discuss the primary efficacy analyses and statistical characterization of the treatment effect of DFMO, based on the externally controlled trial.

FDA Presentation - Arup Sinha

DR. SINHA: Good morning. My name is Arup Sinha. I'm the primary statistics reviewer for this marketing application. I'll present the FDA's consideration for characterizing the treatment effect of DFMO in the intended patient population.

As previously mentioned, FDA recommended that the applicant conduct a randomized trial to determine the treatment effect of DFMO in this clinical setting. While FDA recommended a randomized clinical trial and continues to strongly recommend randomized clinical trials in the

maintenance setting or with cytostatic treatments, FDA felt use of an external control could be reasonable in this unique circumstance, given the availability of the specific external control, as well as the feasibility concerns, given the publication of results of trial Study 3b; therefore, FDA requested feasibility assessments of ANBL0032 data as an external control data source.

This initial assessment indicated reasonable relevance and comparability of the two studies to support the development of the statistical analysis plan. Some efficacy results of ANBL0032 and Study 3b were known at the time of statistical analysis plan development; however, FDA was blinded to patient-level data when making recommendations regarding the development of the statistical analysis plan.

The proposed primary analysis method was a propensity score matched analysis to estimate the treatment effect of DFMO on EFS and OS. While FDA agreed that this approach is reasonable, FDA noted that a thorough characterization of a treatment

effect will require several sensitivity and supportive analyses.

In her last slides, my colleague, Dr. Duke, described the major limitations identified in this externally controlled trial. In the statistical review, we categorized these limitations and then considered sensitivity analyses to address these potential threats to study validity. In the following slides, I'll describe these three groups of sensitivity analyses, including sensitivity analysis group 1, which addresses bias that may arise from trial design and data limitations; sensitivity analysis group 2, which addresses the potential for unmeasured confounding; and sensitivity analysis group 3, which addresses bias attributable to the chosen statistical methods.

The applicant's proposed primary analysis, hazard ratio of 0.48 for EFS and 0.32 for OS were observed. The Kaplan-Meier plots of EFS show early separation, which was maintained over the complete follow-up time; however, we know that there are potential threats to the validity of these results

introduced by study design and data limitations of this externally controlled trial.

The first group of sensitivity analyses examined the consistency of the observed results of the primary analysis when accounting for potential bias arising from non-contemporaneous populations, variability in disease assessment, and differential geographic regions. FDA will not present any p-values for the primary or sensitivity analyses, as we did not rely on any tests of statistical significance in this externally controlled trial. Specifically, we do not consider inferential tests to be reliable in this setting.

Two concerns related to index date in this externally controlled trial are the time period of patient-level index date and the potential for immortal time bias, which may occur if patients in the control arm have events in the immortal time period. This is the period between index date and the potential time of DFMO treatment initiation.

The two purple rows added to the table provide the results of the sensitivity analysis

that addressed these issues related to index date. The analysis in the first purple row considers only those patients in the control arm that have index dates in the same time period as the DFMO-treated population. The analysis in the second purple row excludes any control patients with events in the immortal time period to mitigate the impact of immortal time bias.

The blue rows added to the table address the concern related to imaging assessments across trials. Given that imaging was sporadic and not protocol specified at later times of follow-up, the first blue row limits the analysis to the first 5 years of follow-up during which the rates of regular imaging assessments are high and similar across arms. The second blue row provides an analysis of a blinded independent central review, or BICR, of EFS in the DFMO arm compared to the investigator-assessed EFS in the control arm.

BICR of EFS was not available for the control arm population; however, given that the BICR assessment had high concordance with the

investigator assessment in the DFMO arm and BICR disease assessment is generally more conservative than investigator assessment, this comparative approach for a sensitivity analysis was considered appropriate.

And finally, the teal row added to the table presents analysis to mitigate the impact of geographic location. This analysis includes external control patients from U.S. sites only. Overall, the results of these various sensitivity analyses are consistent with the results of the applicant's proposed primary analysis, but highlighting that there is uncertainty in the exact magnitude of treatment effect, as the point estimates of the hazard ratios do vary in each set of analysis.

The sensitivity analysis presented in the previous slides assess the potential impact of each of the study design or data limitations independently; however, in the most conservative scenario, many of these study design or data issues may occur and impact the estimation of treatment

effect concurrently. Understanding this potential for concurrent sources of bias, FDA performed several sensitivity analyses that combined approaches to address various threats to study validity.

Presented here is the most conservative sensitivity analysis FDA conducted, which addresses each of the limitations presented on the prior slides simultaneously. In this case, a 1:1 matching was most appropriate to ensure high fidelity of the corresponding covariate balance across arms due to the reduced sample size. Overall, the results from this conservative sensitivity analysis are consistent with those observed in the primary analysis.

The magnitude of the treatment effect from this analysis will be interpreted with caution, given the reduced sample size used in this analysis, as reflected by the wider confidence interval. This is particularly true for OS due to low event rate.

In a non-randomized trial, confounding may

exist by factors that are measured, as well as by variables that are not available or not collected. In the second group of sensitivity analyses, FDA considered the potential impact of these unmeasured confounding variables. These analyses address two of the limitations in the interpretation of the results of this externally controlled trial described earlier, namely the potential selection bias of patients who enrolled on the trial versus those who did not, as well as the influence of any unmeasured confounding variables.

The goal of the sensitivity analysis in group 2 was to understand how different the results might be if we had collected the unmeasured confounding variables and could adjust for them in our analysis. Before I describe the results of this group of sensitivity analysis, I'll walk you through an example that demonstrates the scientific approach of identifying and accounting for an unmeasured variable.

Children with high-risk neuroblastoma who have poor social determinants of health are likely

to have inferior outcomes; however, data on socioeconomic factors was not available in the database for these externally controlled trials, and therefore estimation of treatment effect did not account for this factor. Current literature suggests that children with neuroblastoma living in household poverty -- that is, those with public insurance -- have poor EFS outcomes, with a hazard ratio of 1.9, when compared to those children who are not living in household poverty. Given the negative effect of household poverty on the EFS outcome, one could ask, what if there were a greater proportion of patients on the control arm living in household poverty, and therefore the observed treatment effect may be attributable to the difference in prevalence?

Using statistical methods, FDA's sensitivity analysis tested this hypothesis. The analysis assumes that the DFMO arm has a prevalence of household poverty of 35 percent, specified per the earlier reference literature that identified the association with EFS; then this rate was

doubled such that the prevalence was 70 percent in the external control arm. Using the difference in prevalence and knowledge of the association with the outcome, FDA's analysis indicates that the hazard ratio accounting for household poverty with this assumption is 0.59.

The FDA review team has repeated this exercise several times for identified potential confounding variables from the literature and from consultation with external experts. FDA considered only those variables that had an association with the outcome established in current literature to ensure a scientifically sound approach. These analyses are included in this table, including variables that adjust for social determinants of health, primary tumor location, and cytogenetics.

The last column of this table provides the EFS and OS hazard ratios that adjust for the estimated relationship between the potential confounder and outcome, as well as the FDA assumptions regarding the differential prevalence. The results are generally consistent with the

primary analysis.

The FDA's conclusion from these analyses are that the observed treatment effect of the primary analysis is unlikely to be fully attributable to confounding by unmeasured variables or selection bias; however, these analyses to understand the potential effects of confounding were based on available literature, which may itself have limitations.

The last group of sensitivity analysis focused on use of alternative statistical approaches to assess the robustness of the estimated treatment effects. For non-randomized studies, statistical methods are used to ensure that the treatment effect is not subject to bias or confounding by differences in patient characteristics across comparative groups. However, the results of an externally controlled trial may be sensitive to the chosen statistical methods, so it is important to try alternative methods to evaluate the robustness of the observed results.

FDA recommended and considered several alternative statistical approaches to the applicant's proposed primary analysis of propensity score matching. In particular, FDA considered propensity score weighting methods. Weighting methods offer an advantage over matching by utilizing all patients with complete covariate information in the analysis as opposed to matching, which may exclude patients who do not have a match.

When considering weighting approaches as an alternative statistical approach, the EFS and OS results are consistent with those from the primary analysis of matching. Further, FDA used weighting approaches for analysis from sensitivity analysis group 1 -- that is, those analysis addressing known or measured limitations in the study design -- or data for this externally controlled trial. The results of those analyses presented in the briefing document were also consistent with the findings of the primary analysis.

In summary, FDA has not previously relied upon a single externally controlled trial as the

primary source of evidence in oncology; however, this externally controlled trial has specific strengths due to the design and provenance of the external controlled data. The analysis plan for this externally controlled trial was developed to minimize potential sources of bias by design, but there may be some remaining sources of bias. To address this issue, multiple sensitivity and supportive analyses were performed, including those suggested by statistical and pharmacoepidemiologic external experts. The estimation of treatment effect from these analyses generally appears to be robust with the potential sources of bias.

While the sensitivity analysis results suggest the observed treatment effect in this externally controlled trial is unlikely to be fully attributable to the potential sources of bias, there is uncertainty in exact magnitude of treatment effect.

I'll now introduce my colleague, Dr. Emily Wearne, to begin the discussion of the data submitted in this application, in addition to the

single externally controlled trial. Thank you.

FDA Presentation - Emily Wearne

DR. WEARNE: Thank you, Dr. Sinha.

Good morning. I'm Emily Wearne, a pharmacologist and nonclinical reviewer at the FDA. As discussed previously by Dr. Bradford, under certain circumstances, FDA can conclude that one adequate and well-controlled clinical investigation plus confirmatory evidence is sufficient to establish effectiveness. There are no other relevant approved indications for this drug or other drugs in class, and due to the cytostatic mechanism of DFMO as a single agent, there are not expected to be observed responses in patients with measurable disease. With this in mind, the FDA nonclinical team performed a rigorous evaluation of the nonclinical evidence. We will briefly review additional data submitted by the applicant and identified in an independent literature-based assessment in addition to the externally controlled trial.

The 2023 Confirmatory Evidence Guidance

states that under certain circumstances, strong mechanistic evidence of the drug's treatment effect in a particular disease may be appropriate to use as confirmatory evidence when the pathophysiology of the disease and the drug's mechanism of action are well understood, and the drug directly targets the major drivers of disease pathophysiology. Such mechanistic evidence would generally be obtained from clinical testing using a relevant and well-understood pharmacodynamic endpoint; however, the guidance states it could also be collected from other sources, such as in vitro testing.

In addition, data from an established animal model of disease could be used as confirmatory evidence of effectiveness. The use of such data depends on several factors, including similarity of pathophysiology and manifestations of the disease in the animal model and humans and the relatedness of animal efficacy to the desired benefit in humans.

Based on this guidance, we evaluated the potential for nonclinical mechanistic data to

contribute to the confirmatory evidence needed to establish substantial evidence of effectiveness for this application. To facilitate our review and in recognition of DFMO's limited utility as an anti-cancer agent over several decades of clinical investigation, we also conducted an independent scientific literature-based assessment, evaluating the effects of DFMO in neuroblastoma.

Notably, the published literature identified in our assessment was generally consistent with the studies and literature provided by the applicant, with both supporting that DFMO is cytostatic in neuroblastoma.

In vitro data in neuroblastoma cells has shown that DFMO inhibits the synthesis of polyamines, which act as oncometabolites in neuroblastoma, and induces cell cycle arrest. DFMO restored the balance of the LIN28/Let-7 metabolic pathway by decreasing expression of the oncogenic drivers MYCN and LIN28B and increasing expression of the tumor suppressor Let-7 in MYCN-amplified neuroblastoma cells.

DFMO also induced in vitro cellular senescence at clinically relevant concentrations and suppressed neurosphere formation in MYCN-amplified neuroblastoma cells. Similar results were seen with MYCN non-amplified cells, indicating a cytostatic effect irrespective of MYCN amplification status. In contrast, DFMO is not cytotoxic as a single agent and did not affect in vitro cell viability or apoptosis.

The applicant also submitted in vivo data showing that initiation of 2 percent DFMO when there were no tumors present, yet prevented or delayed the formation of MYCN-amplified neuroblastoma and improved event-free survival in a tumor prevention model in nude mice using extreme limiting dilution analysis, or ELDA, which appears to relevantly model the applicant's proposed clinical indication.

As part of our independent scientific literature search, we identified two publications from separate research groups evaluating the effects of DFMO on tumor prevention in TH-MYCN

transgenic mice. These mice overexpress human MYCN in neural crest cells and represent a well-established animal model of spontaneous neuroblastoma that shares biochemical and histologic features, as well as orthologous genomic alterations with human MYCN-amplified neuroblastoma.

Hogarty, et al. demonstrated that giving mice 1 percent DFMO in their drinking water from birth onward increased tumor-free survival in homozygous mice and prevented tumor formation in about 84 percent of treated hemizygous mice. DFMO-treated tumors exhibited decreased polyamine levels, thereby indicating on-target pharmacodynamic activity.

As seen in the figure on the bottom right, similar findings were shown in a publication from Rounbehler, et al., a separate research group. Specifically, Rounbehler, et al. concluded that giving mice 1 percent DFMO in their drinking water, beginning at 3 weeks of age, delayed the onset and incidence of neuroblastoma formation in TH-MYCN

transgenic mice and improved survival. In conclusion, these data support that DFMO can prevent or delay tumor formation and increase survival in a well-established transgenic mouse model of neuroblastoma.

We acknowledge that most marketing packages have nonclinical data supporting activity. This application is no different; however, unlike other applications, we are considering if it is appropriate to use nonclinical data as confirmatory evidence for establishing substantial evidence of effectiveness.

The nonclinical data supporting this application is particularly robust for several reasons. We highlight in vitro mechanistic data supporting that DFMO targets drivers of neuroblastoma pathophysiology and tumor-initiating cells. DFMO induces in vitro cellular senescence irrespective of MYCN amplification status, consistent with clinical data from Study 3b, suggesting that the observed treatment effect is not limited to patients with MYCN amplification.

In addition, there is confirmatory evidence from two well-established relevant animal models of neuroblastoma, exhibiting that DFMO prevents or delays tumor formation in mice who have no initial evidence of disease. Importantly, the ELDA and TH-MYCN transgenic mouse models evaluate clinically relevant endpoints, including event-free survival, which is the primary endpoint in clinical Study 3b and provide pharmacodynamic evidence of on-target DFMO activity.

A limitation is that doses used in these mouse studies are approximately 2-to-9-fold higher than the recommended human dose; however, mice were given 1 to 2 percent DFMO in the drinking water, so the estimated mouse doses are based on typical average water consumption, and thus may vary amongst individual animals. Overall, the nonclinical data submitted by the applicant supports a cytostatic mechanism of action and is further strengthened by supportive data in the published literature.

I will now turn the presentation back to

Dr. Duke.

FDA Presentation - Elizabeth Duke

DR. DUKE: Thank you, Dr. Wearne.

While single adequate and well-controlled trials are often the primary source of efficacy in oncology, either randomized or single-arm trials with tumor based endpoints, the confirmatory evidence is typically clinical rather than nonclinical alone. I will review the limited supportive clinical data in this application.

An early dose escalation study of DFMO was conducted between 2010 and 2012 in which pediatric patients with relapsed or refractory neuroblastoma received DFMO monotherapy for one cycle, followed by DFMO plus oral etoposide. Of 18 evaluable pediatric patients, three had either bone marrow positivity or PET avid disease at study entry, which improved after one cycle of DFMO alone; however, the contribution of DFMO is challenging to interpret, given these patients had received multiple prior therapies and administration of combination therapy after the first cycle.

An expanded access program for DFMO was initiated in 2015. Of 69 patients with neuroblastoma treated as of January 2023, 27 had high-risk disease in remission. For patients in remission after upfront therapy only, similar to the proposed indication, 8 of 13 remained in remission at 2 years. While some additional patients with active disease received DFMO, these expanded access data are challenging to interpret, given patient heterogeneity and the lack of prespecified response criteria.

Study 3b included a second stratum which enrolled 35 patients with high-risk neuroblastoma in remission. Previous cancer treatment details varied, as patients could have relapsed at any point during their initial treatment course and specific drugs previously administered were not recorded. EFS at 2 years was significantly higher, at 46 percent for patients treated with DFMO compared to a prespecified historical control rate of 10 percent. The historical control rate was based on a publication from 2008 and the analysis

in this publication was based on patients enrolled on studies at a single institution between 1991 and 2002.

The clinical data available for consideration as confirmatory evidence is limited due to small populations and variable prior therapies. Patients in the expanded access program had variable demographic and disease characteristics, and response criteria were not defined. The relapsed refractory stratum of Study 3b was compared to a historical control rate estimated from single institution data dating from the 1990s.

The anticipated EFS rate in a contemporary population is unclear, but based on the outcomes reported in published literature in more recent studies, it is likely that the proposed historical control rate of EFS of 2 years of 10 percent is lower than what is currently observed.

In addition, FDA has previously stated that interpretation of time-to-event endpoints in single-arm studies are uninterpretable. In this

case, while there's some early evidence of reduction of tumor recurrence compared to historic controls, there remains uncertainty in the results of these non-randomized, unmatched comparisons.

Additional clinical studies across other tumor types over years of investigation have largely not been submitted to the FDA to support marketing applications. One prior NDA was submitted for familial adenomatous polyposis and was not approved, with the reference SEC filing noting a small trend toward improvement in disease-free survival that failed to reach statistical significance. One trial in adult patients with high-grade glioma has supported breakthrough therapy designation in this indication. To date, there are no approved oncology indications for DFMO.

There are several ongoing trials with DFMO in patients with neuroblastoma from which data is not yet available, including those outlined here. Study 14 is a study nearly identical to Study 3b open at 41 U.S. sites. This study does support the

safety evaluation in this application. The applicant stated that efficacy data were not included with the NDA because it was designed with a 4-year EFS comparison and the planned interim analysis was approximately 2 years away at the time of NDA submission.

Two additional randomized studies are ongoing in the newly diagnosed and relapsed refractory setting, respectively. Study 12 is an open-label, randomized trial in the first-line setting of immunotherapy alone versus immunotherapy plus DFMO; however, all patients go on to receive DFMO in the maintenance setting, which may dilute an observed effect, given the short period of randomized therapy.

Children's Oncology Group Study ANBL1821 is an open-label, randomized trial in the relapsed/ refractory setting of dinutuximab with irinotecan and temozolomide with or without DFMO, with a primary endpoint of overall response rate. In this study, patients received 6 cycles of DFMO instead of 24.

Prior to summarizing the overall strengths and limitations of the application, I will briefly review the safety profile. Proposed warnings for DFMO include myelosuppression, hepatotoxicity, and hearing loss. In the pooled safety population of 360 patients, the most common adverse events are listed here. Grade 3 or 4 events occurred in 42 percent of patients and discontinuations in 7 percent. There were no deaths attributable to adverse events. Since these studies were investigator initiated and not initially intended to support a marketing application, adverse event collection was limited.

Grade 3 or 4 events of neutropenia, anemia, and thrombocytopenia occurred in 1 to 4 percent of patients. There was one treatment-emergent adverse event of bone marrow failure which resolved. While there were no events of liver failure or drug-induced liver injury, grade 3 or 4 events of increased liver function tests occurred in 2 to 7 percent of patients.

Hearing loss was an adverse event of

special interest due to the known risk with eflornithine in non-oncology populations and chemo prevention trials. Studies 3b and 14 included an audiogram prior to initiation of therapy at 6-month intervals and as clinically indicated. Most patients had an abnormal audiogram at baseline likely due to platinum-based therapy received during upfront treatment. Upon review of individual audiogram data, 13 percent of patients had new or worsening hearing loss. Most of those events were a worsening from baseline to grade 3 or 4.

Dose modifications due to hearing loss were required in 7 percent and DFMO was discontinued in approximately 1 percent. Of 47 patients with hearing loss worsened from baseline, it only resolved in four of those patients. While it is challenging to isolate the independent effect of DFMO from the ongoing toxicity of platinum therapy in this population, this risk was of particular concern to the clinical experts consulted during review of this application.

In closing, we appreciate the input of the advisory committee for this challenging application. We recognize that high-risk neuroblastoma is a rare and life-threatening disease with a high unmet need and we acknowledge the need for regulatory flexibility in disease settings such as this one. With regard to the application at hand, there are strengths and limitations as previously described and summarized here.

This application is unique in that we have not previously relied upon a single externally controlled trial as the primary source of evidence in oncology. The external control data is of high quality due to its provenance and the relatively large set of individual patient-level trial data, and the results of sensitivity analyses are generally consistent with the applicant's primary analysis. However, residual uncertainties remain, given the lack of a randomized design to interpret the effect on a time-to-event endpoint and the uncertainty in the magnitude of the treatment

effect.

Regarding confirmatory evidence to support the single trial, the available nonclinical data are robust and supportive of a cytostatic mechanism of action; however, nonclinical data is rarely used as the primary source of confirmatory evidence. There are some clinical data from small studies and an expanded access program, but there are limitations to their interpretability; therefore, we would greatly appreciate your consideration of the following discussion topics.

One, discuss the strengths and limitations of the externally controlled trial results to support the use of DFMO in pediatric patients with high-risk neuroblastoma, and two, discuss the strengths and limitations of the additional nonclinical and clinical data to support the use of DFMO in pediatric patients with high-risk neuroblastoma. The voting question is, has the applicant provided sufficient evidence to conclude that DFMO improves event-free survival in patients with high-risk neuroblastoma?

Finally, FDA recognizes the time and effort necessary to conduct cancer clinical trials. We would like to particularly thank the children and their families, as well as the investigators and research staff who participated in the research studies discussed today. Thank you for your attention, and we look forward to the discussion.

Clarifying Questions

DR. LIEU: Thank you, Dr. Duke.

We will now take clarifying questions for US WorldMeds and the FDA. Please use the raise-hand icon to indicate that you have a question and remember to lower your hand by clicking the raise-hand icon again 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 possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with,

"That is all for my questions," so we can move on to the next panel member.

So we're going to start the clarifying questions, and we're going to start with Dr. Alberto Pappo.

DR. PAPPO: Thank you for the opportunity; excellent presentations. I have questions actually for Dr. Sholler, Clinch, and Sinha. Am I allowed to ask so many questions?

DR. LIEU: Yes.

DR. PAPPO: For Dr. Sholler, one of the questions I have is there appears to be wide variability in the IC50, at least in the cell lines that you studied, with DFMO. I was just wondering how the dosing of 1500 to 1500 per meter squared was reached and what is the preclinical relevant doses that were used to come up with this dosing? And why is the dose in ANBL1821 6 times higher than what you're using in this clinical trial?

MS. GULLO: I'd like to start by addressing your question, but I'll also ask Dr. Sholler and also my colleague, Dr. Lee Schmidt, to join me to

to provide additional support to the response.

The dosing is informed by a collection of in vitro findings, as well as prior adult oncology studies that did report pharmacodynamic effects, as well as positive clinical outcomes actually at lower doses than we have used. Just to pull back up a slide that we showed earlier, initially the dosing was led by the in vitro findings, as well as these prior adult studies that established pharmacodynamic effects at lower doses than what we moved into a phase 1 study; then the phase 1 study established some preliminary evidence of efficacy, although the study was primarily designed for safety that led to the selection of the dose we moved into 3b. We've also considered the in vitro findings, as well as the pharmacokinetic data that we have in the application, to confirm that we are at a dose where we expect to achieve the on-target activity.

If I could have the slide where we show our PK data, please? Here we are showing our pharmacokinetic data collected in patients treated

at the recommended dose, where you can see the concentrations that were effective in achieving in vitro effects on neurosphere formation, as well as ODC inhibition. The shaded region represents the concentrations observed in 95 percent of our treated patients. These data support the selection of the dose. Beyond that, we also measured for pharmacodynamic effects in our treated patients. We have identified trends for decreased polyamines, as well as increased Let-7 expression at the recommended dose, confirming on-target activity with the dose we are providing to patients.

At this point, I would like to ask Dr. Schmidt to address your question about the preclinical models highlighted by both us and FDA, as well as then ask Dr. Sholler to discuss your question about the dose selected for 1821.

DR. SCHMIDT: I'm Dr. Lee Schmidt, senior manager of pharmacology and toxicology at US WorldMeds. In the neurosphere assay formation experiments, those were treated with near physiological dosing, and then we actually did see

a suppression in neurosphere formation at exposures that would be under what we see clinically. There are, of course, doses higher in that experiment, but this was also just on cellular neurosphere formation. It does not really go much beyond there.

DR. SHOLLER: Hi. Giselle Sholler. To address the question regarding the IC50s, it's true that IC50s really are to measure a cytotoxic effect, so the IC50s seen in vitro in the laboratory are at a higher level, and in our study, we are really looking for a cytostatic effect, not the cytotoxic effect in our PKs in the phase 1 study. At the doses that we are treating patients, we do see about a hundred micromolar PK level, and then translating that into the lab in the in vitro models, both in the neurosphere assays and the suppression of LIN28, we see that we're able to achieve that with the 100 micromolar level; and that was why that dose was chosen because in our phase 2 study, we're looking for a cytostatic effect. I believe in the COG clinical trial,

overall response rate is the primary endpoint, and therefore my assumption for that is they're looking for a cytotoxic effect, which would be at a higher dose level than what we're aiming for.

DR. PAPPO: Thank you. You answered the questions about pharmacodynamic monitoring, so you also answered that for me. The other two are just some clarifying questions for Dr. Clinch.

Can you just state again the subset of patients that have had a PR, or very good PR or CR, and the effect that this had on them? It was unclear to me. You showed a slide that some of them were excluded or something. What I wanted to ask, basically, was the effect; was this drug different for patients that were in CR versus VGPR or PR?

MS. GULLO: I can address your question. We have performed subgroup analyses looking at multiple demographic and disease characteristic attributes, which did not identify a lack of effect in any subgroup we've evaluated. With regard to the -- sorry. I'll show you again here the matched

population demographic, so we can have that here in view. In the matched populations, the proportion of patients achieving a PR or higher than a PR were similar, both at the pre-ASCT evaluation, as well as the end of immunotherapy response evaluation.

We actually took this a step further because this is an important question, and we applied a conservative sensitivity analysis, where we actually excluded patients with anything less than a complete response at the end of immunotherapy from the eligible matching population and the control group, and the results of that analysis were shown in our presentation, which I've pulled up again here.

We would specifically note the analysis that is described about halfway down this figure, which is titled, "Remove no DFMO patients with a VGPR or PR at the end of immunotherapy," thus giving the certainty that these patients had a complete response and would have been considered to be in remission, while maintaining patients that had less than a CR response in the DFMO group,

consistent with the eligibility criteria for 3b, and the results of that analysis are consistent. We can actually show you that figure here.

DR. PAPPO: That clarifies my question. Thank you very much.

I had a question for Dr. Sinha regarding the unmeasured confounding variables. When you looked at thoracic versus non-thoracic, if I understand correctly, that was taken into consideration for the final analysis that also showed a decrease in the hazard ratio for patients that received DFMO. Is that a correct assumption?

DR. SINHA: Sorry. This is Arup Sinha for FDA. Can you please pull up the slide for thoracic versus non-thoracic?

DR. PAPPO: I just want to [indiscernible] -- that I understood.

DR. SINHA: Right. For the tumor location --

DR. DREZNER: Sorry. That's, I think, backup slide 31.

DR. SINHA: Right. I can start answering.

For the primary tumor location, adrenal versus non-adrenal, the EFS hazard ratio was 1.1. Yes, that was from the paper reference there, and the non-thoracic versus thoracic, the non-thoracic did poorer than the thoracic. It's the same; adrenal did poorer than non-adrenal, then we adjusted that for the hazard ratio, estimation of the hazard ratio.

Does that answer your question?

DR. PAPPO: Yes, but patients that have non-adrenals tend to have less aggressive biological features and a better outcome, so that would be an important variable to analyze. Thank you very much. Yes.

DR. DREZNER: Sorry. Can we just go to main deck 31? Thank you.

DR. LIEU: Dr. Pappo, does that conclude your questions?

DR. PAPPO: Yes. Thank you very much. Thank you.

DR. LIEU: Thank you, Dr. Pappo.

Dr. Alexander?

DR. ALEXANDER: Yes. You guys have looked at these data very, very carefully, so thank you. This is a really helpful and cogent analysis. I do think there are an awful lot of companies that would like to do an open-label, single-arm study because they believe their evidence to date, such as from phase 2 trials, prevents equipoise or feasibility. I'm just saying, that's a little bit water over the dam but I think needs to be said.

With that being said, I think, FDA, you've really carefully examined these data, and I actually have, surprisingly, few questions regarding additional analyses, one or two, though, brief ones. One is whether you looked at the concurrent effects of multiple potential confounders, including performance status?

You reported doing sensitivity analyses that looked at the most conservative case for the group 1 analyses, but did you do something similar, where you looked at the potential combined effects of all of these various potential unmeasured confounders?

DR. DREZNER: Can I ask Dr. Sinha to take that question, please?

DR. SINHA: Sure. Hi. This is Arup Sinha from FDA. It's difficult to combine multiple sources of confounding and put it in the model, given the availability. But at the same time, we also thought about how likely it is that a patient will have these multiple sources of confounding at the same time, given the variables we have already adjusted in our propensity score model. So from that perspective, we did not account for multiple sources of confounding together.

DR. ALEXANDER: Thank you. That's helpful.

Are the animal models translational? I mean, it seems to me this is a critical matter. If you can stomach using the external control and the variety of ways that those data have been looked at, an awful lot, I think -- given the shortcomings of the clinical studies that would be used as confirmatory evidence -- the FDA, you yourselves have identified, in one case, serious shortcomings that substantially limit the utility of studies

such as 002, or 006, or Stratum 2, of serving as confirmatory evidence. It seems to me the animal studies are really, really important, and yet, we know that in more than 90 percent of cases, drugs studied and that appear safe and effective in animals aren't so in humans.

You spoke to this a little bit, but can you tell us again, are you guys confident that these models are translational?

DR. WEARNE: Hi. This is Emily Wearne from the FDA. In terms of the translatability, the treatment in the mouse tumor prevention studies was initiated when the mice had no evidence of disease, which we believe is an appropriate nonclinical model for patients with neuroblastoma who are in remission. One limitation of this is the absence of previous tumors in mice, unlike patients with neuroblastoma in remission.

Like you said, there are inherent uncertainties regarding translation to clinical studies, but we do consider the credibility of the nonclinical data to be strong. They provided data

supporting a cytostatic mechanism of action in neuroblastoma, and this was further supported by published data. However, whether the data is sufficiently strong to be considered confirmatory evidence should be considered in the context of the application and the primary evidence of effectiveness.

DR. ALEXANDER: Okay. It sounds like you want us to help you figure that out.

Then the last question is about the historic trial failures. I was surprised. It seemed like I got to page, I guess, 54 of 64, or 52 of 64, before there was a very short paragraph about historic trial failures of DFMO. If you're really serious about taking a totality of evidence approach, it seems to me that looking at, and summarizing for us, and helping us to understand historic trial failures of this product are important. I don't know. I did a quick search last night, and I found at least a half dozen, if not more, clinical trials -- they appeared to be well controlled; you'd have to tell me -- that

didn't pan out.

So do you have good reason to believe that neuroblastoma is -- so what is that evidence? Can you share with us a summary, a synthesis, of where DFMO has been studied in blinded randomized trials and what that evidence shows, and then how should we interpret that? How should we use that or contextualize that in the case of neuroblastoma? That's my final question, and that also is for the FDA.

DR. DREZNER: Can we ask US WorldMeds if they'd like to take that first? And if need be, FDA will chime in.

DR. ALEXANDER: I mean, my question is really for FDA; it's not for the sponsor. But I suppose if WorldMeds has a summary of all of the historic trials where DFMO has been studied that's been fine, I'm interested in that, but also from the FDA, why you think that this setting is different, and why those trial failures and other cancers -- whether GBM or colon cancer, or you tell me where else it's been studied -- why that

evidence isn't relevant or how we should interpret that.

DR. LIEU: Does the sponsor have a response before the FDA weighs in?

MS. GULLO: Yes. I'm happy to address that question. When we considered this issue, we first really focused on the studies where DFMO was used in a maintenance setting for chemo preventative similar indications, and in those studies, we found that although those programs have not yet resulted in registration of the product, there was consistent positive trends in the outcomes. Specifically, these three studies here, which also helped guide early dose selection for our phase 1 program, did show consistent pharmacodynamic effects and positive clinical outcomes.

I would note that the familial, FAP, indication is still under development today because that program was not considered a total failure. It was insufficient registration at the time, but work is ongoing. I would also note that specific to neuroblastoma, DFMO has been considered a likely

viable agent for this disease, not only by Beat Childhood Cancer but by all the major research groups who are continuing to study DFMO, specifically in this indication because of the well-established pathophysiology of the disease. So we don't necessarily conclude that DFMO has been proven to be unsuccessful in other oncology indications; it just has yet not risen to the threshold of supporting a registration.

DR. LIEU: Thank you.

And the FDA?

DR. DREZNER: Yes. I'll take that. Thank you for the question. I think that the reason why we had provided just a high level of the information on DFMO in other tumor indications is because our team has not reviewed those studies in detail, so we hesitated to provide more than a high-level awareness that DFMO has been studied in other tumor indications without providing other details. I think we acknowledge that there have been a lot of other trials, and we also acknowledge and agree with the sponsor's point about the two

indications, or the several indications, that they pointed out.

We consider, in general, in oncology applications, there are often other studies of the drug and other indications, but since these data have not been submitted for our review, I don't think we can say much about them. I think it's fair that the lack of positive studies across other diseases in which DFMO has been studied is a weakness, but we haven't reviewed them in depth.

DR. LIEU: Thank you.

Does that complete your questions, Dr. Alexander?

DR. ALEXANDER: Yes, it does. Thank you.

DR. LIEU: Thank you.

Dr. Vasan?

DR. VASAN: Hi. Neil Vasan, Columbia University. I have a question for both the FDA and the applicant regarding the cytostatic mechanism that has been cited in many slides, and for the FDA, this question really has to do with the invoking of this mechanism in the regulatory

decision.

Obviously, we have many cytostatic drugs that improve overall survival and are approved drugs. Does the FDA believe that the cytostatic mechanism supports the applicant since it is concordant with prior preclinical data; or given the external control framework, which obviously has different regulatory considerations, does the FDA believe that the cytostatic mechanism for DFMO and not a cytotoxic mechanism undermine the applicant's claims for efficacy as a maintenance treatment?

DR. DREZNER: Dr. Wearne, did you want to start with that, and then I can continue?

DR. WEARNE: Sure. This is Emily Wearne, FDA. We do believe that the cytostatic mechanism of the drug does support the maintenance treatment for this indication. So in terms of the nonclinical data, the drug is cytostatic, it's not cytotoxic, so we expect it to be involved with stable cell proliferation, and cellular senescence, and cell cycle arrest. We don't expect the drug to be killing tumor cells or shrinking tumors. So

from our nonclinical perspective, we do think that the cytostatic mechanism of action is supportive for that.

DR. DREZNER: And from the clinical perspective, we feel that this is consistent with the proposed indication because the patients are in remission at the start of therapy with either no evidence of disease or no active disease. Obviously, this makes it difficult to assess the response rate, which is one of the challenges with this application.

DR. VASAN: Great. Thank you for that. I guess just an observation that given this external control framework, imagining in the future if there are other applicants who are seeking similar approvals, that perhaps more granularity about overall response rate or surrogate biomarkers with cytostatic mechanisms may be helpful in the future.

My question for the applicant is, in terms of the mechanism of DFMO, it's been published many decades ago that differentiation is also a notable on-target mechanism, and that was not mentioned in

any of the cytostatic pathways that were discussed by Dr. Sholler. So I'm wondering if that has been investigated in neuroblastoma, either on the trial, in your clinical trials, or in preclinical data. So the question is, is DFMO inducing differentiation as a mechanism of efficacy that is still cytostatic?

MS. GULLO: I'm going to ask my colleague, Dr. Lee Schmidt, to address that.

DR. SCHMIDT: We've never directly at does it induce differentiation. We do have data that it drives a pretty powerful senescence phenotype. Depending on how you define senescence, that can be considered differentiation or irreversible cell lock. But to answer your question directly, we've not looked at a differentiated phenotype.

DR. VASAN: Thank you.

DR. LIEU: Thank you so much.

Dr. Sturmer?

DR. STURMER: Thank you. Camera is not working. I'll just talk then.

I understand that most patients in 3b came

from the trial used as a comparator, but I have not seen or heard sufficient information on how these patients were selected; who was approached by whom; who was not approached; how many refused; and what were the reasons for refusal to enroll in 3b. Note that all these are important to evaluate the potential for both unmeasured and residual confounding.

Now, I have not seen any crude data in the FDA document. The sponsor, however, lists in table 12 and figure 17 crude data, and this has also been presented by the sponsor today. This data provide some important clues on strong selection into 3b, for example, for Black and Asian patients and patients with partial response who are less likely to be enrolled in 3b. So I would just like to hear more about how patients were approached and enrolled in 3b to assess the potential for confounding, and this is both for the sponsor and the FDA.

MS. GULLO: Yes. I interpret your question to be around the topic of selection bias, which is

important to understand to interpret outcomes. First, Study 3b was a multicenter study, and given the rarity of high-risk neuroblastoma, there was good distribution of patients enrolled across 20 sites, with each of those sites really only seeing a small number of high-risk neuroblastoma patients in that time frame, so the opportunity for selection bias by the investigator was quite low.

As far as the practices during the enrollment time period, patients that would have been completing immunotherapy at those sites would have been offered the opportunity to enroll on DFMO. When we reviewed the data evaluating patients in the no DFMO group that completed immunotherapy, in the same time frame when that site had Study 3b open, we found that only 24 patients had the opportunity to enroll but did not enroll. And importantly, when we look at the outcomes in that group of 24 patients, the event rate is very similar to the overall no DFMO group.

So although we can't account for every possible reason that a patient did not enroll, they

do not appear to have an underlying difference that drives their outcomes relative to the overall control group.

DR. STURMER: Where do the differences, then, come from that you just showed in the slide in the figure? And that is on figure 17, page 70, in your document?

MS. GULLO: Could we have that figure?

DR. STURMER: I mean, it's obviously that you enrolled patients who are healthier and likely have a better prognosis than those who were not enrolled.

MS. GULLO: Which figure are we looking for?

DR. STURMER: The figure with the standardized differences.

MS. GULLO: I'm sorry. Yes. The figure being referenced is the Love plot showing the standardized differences in the pre-matched populations and the the post-matching populations.

DR. STURMER: Yes, and that's exactly what I'm talking about.

MS. GULLO: Yes, but the important thing here is that we did use these covariates in the propensity score model because of the potential for imbalance. Overall, we would actually conclude that the populations even prior to matching are quite similar, with all, even the green circles shown here, falling between the plus or minus 0.3, which is a typical standardized target even in propensity score matching analysis. But we used a very conservative target range of plus or minus 0.1, and the matched populations are highly similar, which gives us even further confidence in the outcomes.

DR. STURMER: I'm not questioning that you can match the categories of the data that we are looking at here, but having way more patients enrolled in 3b that have complete remission, for example, and having much less Black and Asian patients enrolled in 3b, I think -- again, I'm not an expert in childhood cancer nor neuroblastoma, but this figure essentially shows to me that there is strong selection into 3b and you controlled for

the measured covariates here. But we need to think about, and the clinicians need to chime in, what does this figure show you with respect to potential for prognostic differences and residual confounding in a category like partial remission, for example, which is clearly not a dichotomy.

MS. GULLO: If I could address that further, we approached this question in a number of ways, largely through sensitivity analyses, both those that FDA asked us to conduct, as well as others that we took upon ourselves. One of the most prognostic indicators was not even established until after our statistical analysis plan was developed, and it was reported from an analysis of the 0032, our control population, and identified the most prognostic indicator for long-term outcomes, the pre-ASCT evaluation. And that is an area where, prior to the matching, we did have more imbalance, but we did a modified analysis where we required an exact match on pre-ASCT, and those outcomes were very similar to the primary analysis.

So when we think about the confounders that

might indicate a more enriched population and really focus on those, or eliminate those as considerations that might have influenced outcome, we consistently find, not only in this analysis but across quite literally hundreds of sensitivity analyses, that we continue to arrive at the same answer to the question, which is that there is a consistent benefit in the DFMO group with the hazard ratio almost always landing between 0.4 and 0.6.

DR. STURMER: Thank you.

DR. DREZNER: Would it be possible for us to respond to that as well? If we could go to FDA backup slide 21, followed by 22, and Dr. Duke.

DR. DUKE: Hi. Elizabeth Duke, FDA. I just wanted to make the point that FDA considered this as a potential source of bias, this question of whether patients who enrolled on Study 3b were different from those who did not; they were on 0032, and then were they different in those two populations. I don't think we can say whether they were healthier or not healthier. We didn't have

performance status or other clinical data at the end of the immunotherapy visit for patients on the control arm to really answer that question.

We also considered a few other things. The immunotherapy regimen had been standard of care since 2010, so for patients enrolling on 0032, that was more of a standard of care, whereas DFMO perhaps was considered more investigational. Secondly, after 18 months of intensive upfront treatment on 0032, some patients may have preferred to continue on observation on a clinical trial rather than start a new treatment with more frequent assessments, hospital visits, and families' financial employment situations could have impacted that decision. Certainly, the impact of social determinants of health have been cited by experts as a concern.

So we did in this analysis shown here conduct sensitivity analyses of EFS and OS using patients in both arms who received immunotherapy at common clinical sites to try and get at this question. I can also turn to Dr. Sinha to add, as

needed.

DR. SINHA: Hi. This is Arup Sinha from FDA statistics. Just to follow up with Dr. Duke's thoughts, we have conducted sensitivity analyses of EFS and OS using patients in both arms who received immunotherapy at common clinical sites, and to note, restricting patients to the same site of immunotherapy received resulted in a smaller group of control patients, and accordingly, the matching ratio was reduced to 1 to 1, and this also impacted the quality of the available presentation of patients for matching.

Finally, we also thought about the unmeasured confounders, which is our sensitivity analysis on unmeasured confounding as presented in the main presentation slide, and were intended to evaluate the impact of potential unmeasured confounders. So that's the analysis we have done to address your question.

DR. STURMER: Thank you.

My follow-up on that would be following also Dr. Alexander's view to not look at one

measured confounder or residual confounder at the time. I think figure 17 in the sponsor document would be a good starting point for addressing multiple confounders at the same time, and I think there are methods out there, including those presented by Solomon and Schneeweiss several years ago.

I have another question, if I may. Forty percent --

DR. LIEU: We have a lot of questions, I think, coming through --

DR. STURMER: Fair enough.

(Crosstalk.)

DR. LIEU: -- so if you could [inaudible] and come back to it --

DR. STURMER: Yes.

DR. LIEU: -- and give others a chance.

Thank you, Dr. Sturmer. I appreciate it.

Dr. Shaw?

DR. SHAW: Yes. Thank you. Pamela Shaw at Kaiser Permanente Washington Health Research Institute. This question I'd like to direct

towards Dr. Sinha, the presenting statistician for FDA. I think maybe slide 18 might just be for the FDA presentation and would be a helpful visual aid.

This relates to the sensitivity analyses that were considered to address the non-matched clinical characteristics. I think on slide 18 for FDA, one of the things I believe you considered were treatment-related characteristics in your sensitivity analyses, these factors that weren't considered in the matching to create the 270 external versus the 90 DFMO patients. The one that I was really kind of interested in and wondered how you handled was the end of immunotherapy bone marrow response.

What I couldn't understand -- so what I think is the issue here is that for the external control, that bone marrow confirmed response, that's missing data for about 25 percent of the external controls. We don't have that information, but we had that information for all 90 of the DFMO. So my clarifying question is, really, did you consider a sensitivity analysis that would match

participants based on known bone marrow response at the end of the upfront immunotherapy? I'm particularly interested whether or not there was confirmed no residual disease, and if that wasn't, then do you think that would be a reasonable informative thing to do?

DR. DREZNER: Thank you for your question. I would like to go to FDA backup slide number 9, and Dr. Duke.

DR. DUKE: Hi. Elizabeth Duke, FDA. Yes, we analyzed this issue, and what it basically is, is that the ANBL0032 case report form had this bone marrow as an optional field. So at the end of immunotherapy, patients either had CR, VGPR, or PR, all reported -- all patients had that recorded -- however this missing was in addition to that. That is 25 percent. We looked at that for all of the broader controlled populations also, and it's around a similar percentage. So it's basically missing in that we can't a hundred percent confirm that for the CR, VGPR, and PR responses overall that were recorded, whether this

is consistent with that.

I will note that that 25 percent, all those patients had either a CR or a VGPR. There were no PRs in that, and per the 1993 response criteria per INRC, the bone marrow evaluation is not part of that determination, but it's an important thing to note. Thanks.

DR. SHAW: Okay. I think unless there's someone else, the sponsor or FDA, who had comments on that issue, that does answer my questions. Thank you.

DR. LIEU: Thank you.

Dr. Widemann?

DR. WIDEMANN: Thank you. Brigitte Widemann, NCI. My question is for the applicant. Looking at confirmatory data, clinical data, it looks like study number 14 that is ongoing could, actually, very nicely provide confirmatory data. With that in mind, what was the reason to select the 4-year event-free survival compared to historical control when the study population is the same and the primary emphasis of Study 3b was a

2-year event-free survival?

MS. GULLO: Well, first with the question about Study 14, that is an ongoing study and remains enrolling today, and is expected to continue enrollment through 2026. So at this time, those data are not mature and would require extensive review, and no interim analysis is planned. As far as the 4-year endpoint, that was selected because we saw even further widening separation when we looked at the Study 3b results, and generally speaking, the longer out we can confirm the difference in outcomes, the more meaningful.

DR. WIDEMANN: Thank you.

DR. LIEU: Thank you, Dr. Widemann.

Dr. Nieva?

DR. NIEVA: Yes. Thank you. My question is both for the applicant, as well as for FDA. This question here centers very much on whether or not it was feasible to conduct a randomized-controlled trial. I note that it appears that the dinutuximab study, which was used

in the control arm, was in fact a randomized-controlled trial in this disease population. So I'm curious to know what kind of formal feasibility analysis on the ability to conduct a randomized-controlled trial was done by the agency or by the company.

Was this just opinion or was there a specific analysis performed? Thank you. That concludes my question.

MS. GULLO: I can address the question first. I'd like to ask Dr. Sholler and Dr. Cohn to also help me provide their perspective. The feasibility of a randomized-controlled trial was not originally part of the decision making. It was really more around the the strength of the results that were observed, providing theoretical benefit to patients, and the availability of the 0032 database that led us down this externally controlled path.

But I'm going to ask Dr. Sholler to explain the rationale bringing us to the table today, and then I'll ask Dr. Cohn to give her perspective just

to build on this idea, because we do know that randomized-controlled trials are challenging in this patient population because of its rarity to begin with, but as we sit here today and think about what it would mean to conduct a randomized-controlled trial, that has additional considerations.

Dr. Sholler?

DR. SHOLLER: There were three factors that really drove our decision to pursue submission today. The first was that in our Study 3b, we saw significantly better outcomes compared to published survival rates. In our clinics across the country, we were seeing fewer patients relapsing and dying than we had previously seen, and that coincided with the new FDA guidance that allows real-world evidence to be used for rare diseases and enabled this team to outline a regulatory path to use this external control as a viable alternative, especially considering that the majority of patients came directly from the COG 0032 data, and access to this data was provided as a

fit-for-purpose external control.

So through extensive collaboration and discussion with the FDA, we were able to design the prospective statistical analysis plan using propensity score matching to allow us to follow the FDA guidance, which results in the rigorous analysis shown today. So it was truly the congruence of these factors, the better outcomes, the new FDA framework for regulatory approval in rare diseases, and the availability of the patient-level data that led us to pursue the regulatory path to bring this beneficial therapy to patients today.

Dr. Cohn?

DR. COHN: Susan Cohn, University of Chicago. As pediatric oncologists, we're well aware of how challenging randomized clinical trials can be. We have very small cohorts of patients, and many times these randomized trials take years; and, indeed, the 0032 study that was just referred to actually took over 10 years to complete because of the rarity of the disease, as well as concerns

from both physicians and parents about the randomized question. I believe to conduct a randomized clinical trial currently with the data that was presented today would be very, very challenging and difficult to pursue.

DR. DREZNER: And if possible, from the FDA side, I'd like to ask Dr. Donoghue to provide a response.

DR. DONOGHUE: Sure. Martha Donoghue, Oncology Center of Excellence, and thank you for the question. To answer you directly, we didn't conduct a formal feasibility analysis as to whether or not a randomized trial would or would not be feasible. As previously mentioned, and as we advised previously, our strong preference is for the conduct of randomized trials to establish effectiveness of new products in the maintenance setting for patients with high-risk neuroblastoma.

As you mentioned, we know this is possible because it has been done before, which was the case for 0032, leading to the approval of dinutuximab in this setting; however, in this unique case, once we

became aware of the results of Study 3b, we considered it appropriate to review this application, which of course relies on an externally controlled trial, which we don't consider real-world evidence per se, to establish the primary evidence of effectiveness for a few reasons. And the primary reason was due to the uniquely strong data source for the external controlled trial, namely the high-quality patient-level data from Study ANBL0032 and the fact that most of the patients in Study 3b had also enrolled in the same trial.

This particular source of data mitigated many of the factors that can preclude a determination that the data are fit for purpose as an external control. In this unique case, but to a lesser extent, but also important, we considered the already published results in Study 3b, which appeared to show a large treatment effect in a population that has a high unmet medical need.

I'd like to emphasize again that, generally, there is a high bar for considering

external control data -- resources fit for purpose, and that the use of a randomized design would have been a less risky approach from a drug development perspective, and could also potentially generate the necessary data more quickly.

DR. LIEU: Thank you, everybody.

DR. KLUETZ: This is Paul Kluetz from the FDA as well. Just to add on to Martha, it's been pointed out a couple of times that there is concern that this might be challenging to have randomized-controlled trials in the future. Again, we're pointing out that we recommended a randomized trial at the beginning, and now we have what we have. We have an externally controlled trial that's high quality, but it's placed us in a degree of higher uncertainty. But we have to review what's set before us, and I think the team's done a good job doing that.

But to answer the concerns, whatever decisions made in this very unique circumstance, with not real-world data but actually patient-level clinical trial data making up the external control,

really, an externally controlled study with confirmatory evidence would only be appropriate to review in rare circumstances with a very high-quality comparable patient-level data in an external control.

So I think what we're faced with now, which is some uncertainty in this application, it's not something that we need to be faced with in the future. So I just echo Dr. Donoghue's point that, really, randomized-controlled trials, particularly in the maintenance setting or in a cytostatic type of mechanism of action, is very important to conduct. Thank you.

DR. LIEU: Thank you, Dr. Kluetz.

I know that we're running up into our lunch. I think we're going to continue our clarifying questions for another 10 minutes, but then we will have time after the open public hearing to come back to the questions. But we'll continue for a few more minutes, so Dr. Cosenza, your question, please.

DR. COSENZA: Hi. I'm a toxicology

consultant. I just have a clarifying question for Emily Wearne on the section of the guidance that we're trying to use here to justify the nonclinical data. So the guidance states that only models that have proved to be translational can be used in this mechanism as supportive data. I see a lot of evidence, and I've gone back to the literature, that the model is translatable in terms of mechanisms, but are there any drugs or other treatments that have been shown to work in the model of neuroblastoma, transgenic animals?

DR. WEARNE: Hi. This is Emily Wearne from FDA. The definition of translational that they provide in the 2023 guidance is that prior drugs with the same intended clinical effect have been shown to have this effect observed in the animal model with similar exposure response. So that would not necessarily apply in this case. We have not seen other drugs using these same models, if that answers your question.

DR. COSENZA: Yes. Thank you.

DR. ALEXANDER: I had asked previously if

this was a translational model, and maybe I didn't frame my question well enough, but am I hearing that the FDA's position is that this is not a translational animal model as per FDA guidance?

DR. WEARNE: So based on the FDA guidance, which I'll point out just came out in September of 2023, that is the definition that is in the formal guidance, but obviously this guidance was not available prior to that date. And, in general, if you take a general definition of translatability, then we would consider it to be translatable.

DR. ALEXANDER: I want to take the FDA's definition, the FDA's current definition. So according to that definition, it sounds like it's not. Is that what you said a few minutes ago?

DR. WEARNE: So that is the definition that is in the guidance. I can give you some examples of other rare diseases where nonclinical data has been used as confirmatory evidence, if that will be helpful.

DR. DREZNER: Can we go to backup slide 106?

(Pause.)

DR. DREZNER: Thanks.

Dr. Wearne, did you want to mention the other diseases?

DR. WEARNE: Sure. There are some recent examples of rare disease indications that are outside of oncology that used one adequate and well-controlled investigation, along with confirmatory mechanistic evidence, to establish substantial evidence of effectiveness, and two examples from rare diseases that used animal models as part of the confirmatory evidence include the approval of Nulibry in 2021 to reduce the risk of mortality in patients with molybdenum cofactor deficiency type A and the approval of Nexviazyme for the treatment of patients 1 and older with late onset Pompe disease. There may be examples in oncology that we have not identified, but we recognize the limitations of our searches.

DR. DREZNER: Right. This is a relatively new area for us as well, and I just want to note that this is a newly released draft guidance and,

as such, is not binding.

DR. COSENZA: This is Mary Ellen Cosenza again. That's why I asked the question because it seems like this section is a little restrictive. The earlier section on mechanisms might give another way to address this on the mechanisms of pharmacodynamic evidence, where there is also some recognition of nonclinical data correlating with inhibition of oncogene development -- dependent pathways, rather, excuse me. So that could be another part of the guidance.

DR. DREZNER: Agreed, and this guidance is still open for comment, for public commentary, and generally guidances are not able to be completely comprehensive with each application taken individually.

DR. COSENZA: Thanks.

DR. LIEU: Dr. Cosenza, does that conclude your question?

DR. COSENZA: Oh, yes. I was not trying to muddy up the works; I was just trying to get clarification on how we were going to try to help

find a pathway.

DR. LIEU: Yes.

Well, I think we have time for one more question.

Dr. Conaway?

DR. CONAWAY: Yes. I had a question about the timeline. This is a question for either the sponsor or the FDA. Study 3b showed about 90 participants who did well on DFMO, and that could be under the null hypothesis just by chance or under the alternative that DFMO is effective. So under either hypothesis, wouldn't the results of the ECT look the same?

So my question specifically is, how does knowing the strong positive results of Study 3b prior to embarking on the ECT affect our interpretation of the ECT?

MS. GULLO: The strength of our conclusions about Study 3b really relate to the wide variety of analyses that have been conducted both by us and independently by FDA. The analysis was not prespecified as we noted and also FDA noted in

their presentation, which is why it was really important to design the plan for the analysis with so many variations, which have all been done; and then with additional data even received after the analysis plan was finalized, even further work was done to try to understand any potential differences. So our conclusions are based on the strength of the evidence across a very rigorous set of analyses, all demonstrating very consistent findings rather than emphasizing anyone particular analysis.

I noted that FDA in their presentation also reminded us that they were blinded to the data while they were providing input across three separate interactions, two formal meetings and one informal meeting, just to align on the methodology for the externally controlled analysis, and then even after those results were generated, continued to ask for further data and further assessment in order to support the conclusions.

DR. DREZNER: If we are able to take that as well, I'd like to ask Dr. Donna Rivera, followed

by Dr. Pallavi Mishra-Kalyani. Thank you.

DR. RIVERA: Thank you, Dr. Drezner.

Donna Rivera, associate director for pharmacoepidemiology, Oncology Center of Excellence. In regard to this question, the FDA acknowledges that the lack of prespecification is a limitation of this study. As described in the 2023 draft guidance on the Considerations for the Design and Conduct of externally controlled trials, ideally, the protocol for an ECT, including selection of the external control arm and the analytical approach, should be finalized prior to conducting the ECT.

This was not done in this case; however, FDA, who did not have access to patient-level data from Study 3b, provided feedback on the selection of the external control population and development of its statistical analysis plan, which is typical in discussions regarding trials intended to support a marketing application. The FDA recognizes that although prespecification is ideal, it may not be feasible in all circumstances. Thank you.

DR. MISHRA-KALYANI: Hello. This is Pallavi Mishra-Kalyani, deputy director of the Division of Biometrics V at FDA. I will add to my colleague's response to say that certainly it's true that there was some knowledge of the results, but I would take a different approach, I think, than your comment earlier, mentioning that either hypothesis would be equally valid. I think the approach is to evaluate in this externally controlled trial with a blinded approach, certainly blinded to outcome data approach, a patient-level outcome data approach, to developing the SAP, and then additional data is required due to the uncertainty of the results of the externally controlled trial, which I think is the major question that we're asking here at the advisory committee, in that the results of a single externally controlled trial may not carry the same level of weight as a single randomized-controlled trial, or a single trial that demonstrates, for example, a strong response rate in a single arm.

So while you are correct that there is

additional uncertainty, I think that uncertainty within the result is really about whether or not the results in and of themselves are sufficient to demonstrate an effect, rather than whether or not we can trust the inference that we made from that trial itself.

DR. CONAWAY: Thank you.

DR. LIEU: Thank you, everybody. And like I said before, after our open public hearing, we should have the opportunity to come back to our clarifying questions, so Dr. Spratt, Kim, and Pappo, please hold your questions, and we should be able to get back to them after the open public hearing.

We will now break for lunch. We will reconvene at 1:10 p.m. Eastern Time. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to reconvene at around 1 p.m. to ensure you are connected before we reconvene at 1:10 p.m.

Thank you, everybody. We'll see you in a bit.

(Whereupon, at 12:40 a.m., a lunch recess was taken, and meeting resumed at 1:10 p.m.)

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

(1:10 p.m.)

DR. LIEU: Well, welcome back, everybody. I hope everybody enjoyed their lunch. We will now proceed with the charge to the committee from Dr. Nicole Drezner.

Charge to the Committee - Nicole Drezner

DR. DREZNER: Good afternoon. My name is Nicole Drezner. I'm a pediatric oncologist and the deputy director of the Division of Oncology 2. Given the complex and unique nature of this application, I will provide a brief reminder of its key issue, establishment of substantial evidence of effectiveness by a single externally controlled trial and confirmatory evidence.

In 1962, as part of the Food, Drug, and Cosmetic Act, Congress determined that a drug's effectiveness must be established by substantial evidence. As a reminder, substantial evidence consists of adequate and well-controlled investigations by experts qualified by scientific training and experience to evaluate the

effectiveness of the drug involved on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have. In 1997, the Food and Drug Modernization Act further established that substantial evidence could be demonstrated by one adequate and well-controlled clinical investigation plus confirmatory evidence.

In the preceding presentations, you heard about the strengths and limitations of the evidentiary package supporting DFMO for the treatment of high-risk neuroblastoma, comprised of a single externally controlled trial and confirmatory evidence that is largely based on nonclinical data, in which our scientific judgment is that animal models recapitulate the disease under study. These factors summarized on the slide result in varying degrees of uncertainty, both when considered individually and in their overall balance. This presents a unique challenge in assessing whether the statutory requirement for the provision of substantial evidence of effectiveness

has been met.

FDA can exert regulatory flexibility where appropriate and rely on study designs that produce less certainty if a better design is not feasible. Inherent in less certain study designs is a greater risk of false positive conclusions compared to randomized superiority trials, and therefore less certainty about a drug's effectiveness. Higher uncertainty may be acceptable when the unmet need is high and the risk of a false positive conclusion must be balanced against the risk of rejecting or delaying the marketing of an effective therapy.

There are likely major feasibility challenges preventing the conduct of a randomized trial of DFMO for this specific indication now, primarily due to difficulty accruing, given the published results of Study 3b. Conduct of a randomized trial may have been feasible prior to enrollment of a large single-arm trial, and we feel this was a missed opportunity. Nonetheless, we are asked to review the evidence at hand.

Although FDA may rely on less certain study

designs if stronger designs are infeasible, establishment of substantial evidence of effectiveness is still required for FDA to render an approval decision, and this ODAC has been assembled to weigh the strengths and limitations of the evidence presented.

In summary, the elements of this application, including the single externally controlled trial and the confirmatory nonclinical and limited clinical evidence, represents a higher level of uncertainty than observed in most other marketing applications for oncology drugs. The level of uncertainty and degree of regulatory flexibility that are appropriate should be considered in the context of the strength of the scientific evidence, the risks of the drug, and the unmet medical need in this pediatric patient population with a life-threatening disease.

I echo my colleagues in our appreciation for your attention and willingness to provide your perspectives on this application, as well as in our gratitude for all the children and their families

who participate in clinical trials.

I will now read the discussion questions. First, discuss the strengths and limitations of the externally controlled trial results to support the use of DFMO in pediatric patients with high-risk neuroblastoma. Second, discuss the strengths and limitations of the additional nonclinical and clinical data to support the use of DFMO in pediatric patients with high-risk neuroblastoma. The voting question is, has the applicant provided sufficient evidence to conclude that DFMO improves event-free survival in patients with high-risk neuroblastoma?

Thank you for your attention, and we look forward to the discussion.

Open Public Hearing

DR. LIEU: Thank you so much, Dr. Drezner.

We will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at

the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the applicant. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your participation in the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have 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 only speak when recognized by the chairperson.

I'll also mention that there are a significant number of open public hearing speakers, which speaks to truly the importance of this topic and the engagement of our community. Given this and just to keep the meeting on track, at the five-minute mark, I may ask the speakers to conclude their comments; and if you could follow this, that would be wonderful and keeping our meeting on track. Thank you so much for your cooperation.

Speaker number 1, please unmute and turn on your webcam. Will speaker number 1 begin and introduce yourself? Please state your name and any

organization you're representing for the record. You have five minutes.

MS. BLOCK: Good afternoon. My name is Melissa Block. I have no conflict of interest with any of the sponsors or its competitors and I'm not being compensated for my testimony today. Thank you for giving me the opportunity to speak. I have one slide you can display during my time.

In late 2009, my 20-month year old daughter, Clare, was diagnosed with stage 4 high-risk neuroblastoma. Unbeknownst to us, she was a very sick little girl, and at 17 pounds, her tiny body was being ravaged by disease. We entered a new and scary world with a defined treatment plan, and our life for at least the next year was planned out with cycles of chemotherapies that we couldn't pronounce, anticipations of surgeries, and lots of unknowns and fear.

I remember her doctor telling us that neuroblastoma could become resistant to chemotherapies, so the plan was to throw everything but the kitchen sink at it in quick intervals to

shrink the main tumor site and eliminate the sites that it spread to. Her initial 2-week cycle showed some improvement, so we soldiered on with eight more cycles, coming into the hospital every 14 days or so to stay for a week inpatient. We isolated ourselves from friends and extended family to protect her fragile health, and we were lonely and scared. We watched her suffer from chemo side effects that would make grown men crumble.

We had an infant son we also cared for and jobs that needed our attention, all of which were upended time and again when she had to go inpatient at unanticipated times because she was neutropenic or when her chemo schedule was delayed, all due to the medications we were giving her.

She had two major surgeries, radiation, a round of high-dose chemo, followed by a stem-cell rescue, additional rounds of chemo and antibody therapy, none of which came without a variety of complications and setbacks that complicated our lives and put hers at further risk.

A year and a half post diagnosis, she

finally achieved radiographic remission and we celebrated that; however, her catecholamines didn't normalize, and that told us that there was still cancer hiding in her body, so back to chemotherapy she went. For another year, she underwent daily doses of chemo only to relapse, but we were lucky. Her relapse was minimal and was managed for the surgical procedure, and we continued with her maintenance chemo, and 6 months later her catecholamines finally normalized.

Well, at that remission phase, we were eager to return to a life that did not include spending a portion of every month in the hospital, bimonthly clinic visits, isolation, and harsh medications; however, after 2-and-a-half years of treatment, her marrow was tired. During what was supposed to be a time to return to life, she was in and out of the hospital with pneumonia, severe sinus infections, and a variety of other illnesses that she was unable to fight off. We had wrecked her body and her immune system, and she needed to heal. However, while we were in remission, no one

was resting easy because as we all know, neuroblastoma plays by its own rules. We needed a long-term post treatment plan to keep her in remission, and there were few options.

We were faced with a couple of choices. We could stay on the chemo regimen that she'd been leaning on for more than a year and a half and hoped that the cancer didn't become resistant, and continue with the negative effects of chemotherapy and all of the long-term effects that come with that; stop everything and see what happens; or enroll in a promising clinical trial for DFMO.

The choice for us was easy, and for a few reasons. It was a low toxicity option that we were no longer going to have to put chemo into her body. She was allowed to have her port removed. We could go to clinic once every 30 days instead of every 14. She could receive vaccinations again. Her immune system would recover and she would regain strength. For the first time in her short life, she would finally know what it felt like to be a healthy kid.

For my husband and I, it was like someone throwing us a life raft in the waters we were floating in and pulling us back to shore. We had new hope and a belief that we would see her grow up. DFMO gave her a chance at a long and healthy life at a time when long-term treatment options were few and not ideal. I would choose it again without hesitation.

And I just want to say that I remember at the beginning her doctor sharing with us that the hope was that we would get her to a point where we would worry more about her getting her driver's license than the cancer returning, and I am pleased to say that she's 15 and getting her license in about 6 months, and she's healthy and happy. So thank you for allowing me to speak. I end my time.

DR. LIEU: Thank you so much.

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

MS. BARTOSZ: Hello. My name is Sarah Bartosz. I appreciate the opportunity to address DFMO, and I am not being compensated for being here today. As the executive director of the Beat Childhood Cancer Foundation, I represent hundreds of families, including the 150 plus who submitted letters to the docket, as well as tens of thousands of benefactors who have collaborated at every stage to bring this drug to every child, everywhere. One of the main efforts of the foundation is to support the funding of clinical trials through the Beat Childhood Cancer Research Consortium. This includes the DFMO trials.

I think it is also important you know who I am. While I am a 28-year nonprofit professional, personally, I have experienced cancer on every front, as a daughter, a bereaved mother, a wife, now widow, and a survivor. Today, October 4th, I celebrate the birthday of my twins, Annie and Jack. Twenty-two years ago, these beautiful souls made me a mother, the only title I ever wanted. Unfortunately, I am only able to celebrate with one

child today, as high-risk neuroblastoma took my son Jack in 2012, just a few weeks shy of his 11th birthday. Jack bravely fought this horrible disease for 7 years with multiple relapses.

I believe everyone in this meeting recognizes the realities and tremendous needs that exist for children battling high-risk neuroblastoma. Standard-of-care therapies are difficult beyond measure, and upon completion, in spite what these kids go through fighting both the disease and the therapies themselves, the stories of relapse and poor outcomes being told in the parent communities and heard by the Beat Childhood Cancer Foundation far outweigh the stories of surviving and thriving.

There are currently no approved options parents can seek to offer hope and help in preventing relapse. Patients and families are simply left to watch and wait; that is, until data about DFMO's effectiveness went from anecdotal suggestion to demonstrated fact. The foundation receives calls, emails, and inquiries every week

from parents across the world who want access to DFMO. They know about it. They ask for it by name.

I heard questions this morning regarding the value of conducting a randomized clinical trial to confirm the results seen thus far, and while I am not a scientist, I am an advocate who speaks with hundreds of patients and family members. Parents are keenly and astutely aware of DFMO's trial results to date, and I can say with confidence they would be unwilling to enter a randomized clinical trial, and it is unethical to ask parents to do so. The parents we hear from and who involve their communities in fighting for their kids' lives are often burdened with having to raise money for travel and for an opportunity for their child to take DFMO. All they seek is an option, a chance at hope for their child.

The foundation has done everything in our collective power to bring DFMO to as many patients as possible. The evidence you have reviewed today is compelling. Now, all parents who seek to give

their child DFMO should have the access they are asking for. Moreover, the approval of DFMO has every opportunity to result in improved outcomes for patients, while not adding to the burden of long-term side effect or risk profiles.

Parents of children with high-risk neuroblastoma know what it's like to give highly toxic therapies to their kids, a decision no parent takes lightly, but the parents who have been given the option of DFMO say it was likely the easiest decision in their child's cancer journey, an opportunity at quality of life and quantity of years.

As an advocate, I am encouraged by the effectiveness and safety data regarding DFMO to fill a tremendous unmet need for high-risk neuroblastoma patients. I am joined by hundreds of families and thousands of supporters urging this committee to say yes. As a parent, I am simply left to wonder what might have been had DFMO been available to Jack.

Today is not an easy day, as Annie and

Jack's 22nd birthday now signifies that Jack will forever be gone longer than he was alive. If he were to have been given the chance to receive DFMO, perhaps I would be celebrating 100 percent of a birthday today, not just the remaining 50 percent. Every child everywhere deserves a fair chance at beating the odds. As the war against childhood cancer rages on, I am asking you to give other kids and families called to this battle a fighting chance with more options, a chance some of us were not given. Thank you so much for the time today.

DR. LIEU: Thank you so much.

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

MR. LACEY: Hello. My name is Patrick Lacey, and I have not been compensated for my time or participation in this meeting; however, I would say that I am biased, as I'm not only founder of the Beat Childhood Cancer Foundation, which helped

to fund the work discussed here, but I'm also an advocate of pediatric cancer patients, and most importantly, I am father to Will, who you heard about earlier today.

After 18 months of treatment failed to get his cancer to respond, Dana-Farber told us Will had exhausted all known curative therapies. He had just turned 2, and like so many parents before us, we had to make a decision. Do we want to force him to ingest wildly toxic and unproven drugs in the quest to keep him alive, or do we want to watch him die with the help of the pain team? So we traveled to all the NB experts, considered all the different potential therapies, and then we put him through an additional 3-and-a-half years of experimental treatments, phase 1 trials, and off-label combinations, and the brutality of it all was the only life he ever knew.

Sadly, his cancer never responded to therapy and the toll on his body was continuing to grow. It was an endless cycle of new therapies and side effects as we tried to balance his disease

status and quality of life while also trying to keep him strong enough to qualify for whatever may come next. And after 5 years of treatment, thankfully the thing that came along next for Will and changed the trajectory of his life was DFMO.

Will enrolled on this phase 1 study as part of the first cohort of patients, and given the low dose of this first cohort and that it was given as a single agent, I was, frankly, terrified that when we brought him into scan, that the disease would have progressed. Instead, to my utter amazement, the scan showed that his tumor had responded. After five long and brutal years, finally something had worked. He then took low-dose oral etoposide for a few cycles to complete the study before continuing on with DFMO alone for over two more years, before finally going off therapy for the first time after a nearly 8-year journey.

That was over 10-and-a-half years ago, and remarkably he was not alone. There are three long-term survivors from that study, including two patients from the first cohort at that lowest dose,

all of whom were told they were incurable; all of whom had done no other therapy since then, yet continued to be survivors; all of whom tried and failed every other option.

Today, my son is a freshman in college, but unfortunately continues to learn that life out on the long tail of survival is not for the faint of heart. The price he continues to pay for those 5 years of therapy before DFMO is impossibly high: a cerebral hemorrhage; an odontogenic cyst; metastatic thyroid cancer; and the list goes on and on and on. The visible and invisible burden that my son is forced to carry for his chance of survival is impossible to quantify.

But what if DFMO had been available to him earlier, before those years of toxicity? How much lighter would that burden be if DFMO could have prevented all the damage we did to him? Well, we certainly can't change the past for him, but the fact is that today you have it in your power to change the future for every child with neuroblastoma. You can keep kids in remission to

prevent their bodies from being ravaged by the current relapse therapies that far too often than not fail to save these kids and instead make them endure a harrowing and painful journey before ultimately being taken from their families.

For years, the rare disease community has been searching, and the FDA discussing, how to use regulatory flexibility in order to create treatment options to address the unmet needs of the rare disease patient population. Now obviously, no two solutions will look the same, but the ability for a flexible regulatory framework that meets the FDA stringent guidelines for safety and efficacy is achievable. The time is now, the unmet need is here, and the data presented this morning shows the patient benefit.

This is a very well-tolerated oral drug that is being given to infants, toddlers, and children, with an established safety profile and a long history. This is a drug that decreases a child's chance of relapse by greater than 50 percent. If not now, then when? If not this,

then what? On behalf of every child, every family, and every oncologist that can benefit from your decision here today, I urge you to deliver this landscape altering therapy to these kids who so desperately need our help, and you have the ability to alter the trajectory of their lives by preventing relapse. My son is the exception to the rule because he lived. Approving this drug will make him the exception to the rule, not because he lived, but because he's had to endure so much just for his chance at survival. Thank you.

DR. LIEU: Thank you so much.

Speaker number 4, please unmute and turn on your webcam. Will speaker number 4 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have five minutes.

DR. MITCHELL: I am Deanna Mitchell, and I'm a pediatric oncologist at Helen DeVos Children's Hospital in Grand Rapids, Michigan. I am not being paid for my testimony and I have no financial relationship with US WorldMeds. I was a

principal investigator for the NMTRC 003B at our institution and for other clinical trials in neuroblastoma that utilize DFMO. I've been in practice for 30 years and I have a strong interest in caring for neuroblastoma patients.

Our hospital sees approximately 120 new oncology diagnoses per year, including 5-to-10 high-risk neuroblastomas each year. I've cared for many patients with neuroblastoma who have relapsed and succumbed. In the past decade, we have had trials available through Beat Childhood Cancer for high-risk neuroblastoma that added DFMO as maintenance. The impact on survival at my own institution has been compelling. My clinical team and I have seen far fewer relapses with DFMO than without. Our clinical experience has matched the published data, with improved event-free survival with DFMO maintenance. DFMO has been well tolerated by patients. Families have been motivated and compliant with twice-daily treatment. The majority of high-risk neuroblastoma patients have hearing loss by the end of their standard

therapy.

While taking DFMO, a few patients have demonstrated a slight worsening in their audiograms. When DFMO is decreased or held, their hearing has returned to baseline levels. To put benefit versus risk into context for you, as a pediatric oncologist with three decades of experience, I am now reluctant to treat a high-risk neuroblastoma patient without DFMO maintenance. My hope is for DFMO to be approved for the treatment of high-risk neuroblastoma. I hope to eventually see less toxic induction and consolidation treatments.

I would like to share one of my patients stories with you. I believe he benefited from DFMO. By happenstance, my neighbor was diagnosed with stage 4 neuroblastoma when he was 2, presenting with bone marrow and bone metastasis. I was the pediatric oncologist on the inpatient service when his MRI demonstrated orbital tumor. His MIBG and CT scans showed no response after the first two cycles of induction. He proceeded

through 6 cycles of induction therapy and stem-cell transplant. Following transplant, he still had detectable neuroblastoma in his bone marrow.

As an oncologist, I watched with concern. These were the kids with neuroblastoma that I did not see stay in remission. As his neighbor, I watched him drive by on his Big Wheel from my laundry room window. He completed immunotherapy with dinutuximab, GM-CSF, IL-2, and isotretinoin. He then enrolled on the DFMO trial and was treated for 2 years of maintenance. He tolerated that therapy very well. He is now 14 and in the 8th grade, and I watch him run by in his cross-country jersey. He asked me what he must study to become a pediatric oncologist. He received a number of agents; however, I think that DFMO played a major contribution, and it's a privilege to watch him grow up.

I believe the data available with DFMO maintenance is the highest published event-free free survival we've seen to date in high-risk neuroblastoma. I appreciate the FDA reviewing this

data with care and critical evaluation. My hope is to see approval for this important medication in the treatment of high-risk neuroblastoma. Thank you.

DR. LIEU: Thank you so much.

Speaker number 5, please unmute and turn on your webcam. Will speaker number 5 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have five minutes.

DR. KRAVEKA: Good afternoon. I'm Doc Jackie Kraveka. First for pediatrics, I'm a pediatric oncologist at the Medical University of South Carolina, Shawn Jenkins Children's Hospital. I lead our solid tumor program and my clinical focus is on the treatment of children with neuroblastoma. I serve as a COG and BCC PI at my institution, and as such, I've been responsible for the conduct of over 80 clinical trials in pediatric oncology.

I've been involved in the design and conduct of DFMO trials as a member of the

respective clinical trial committees and my site's PI. My testimony today is [indiscernible] experience and represents my personal clinical perspective. I'm not being compensated, and I do not have a financial interest in the outcome of this trial.

My interest in neuroblastoma was formed as an intern in 1994 at Miami Children's Hospital. I took care of an 18 year old with neuroblastoma who was admitted for stem-cell rescue. I followed him through my three years of residency, from a stem-cell transplant to relapse, and his unfortunate death. He inspired me to become a pediatric oncologist and focus on neuroblastoma. As a pediatric resident, even as a fellow and young attending, I witnessed the majority of my patients with high-risk neuroblastoma relapse.

As you know, the treatment for children with high-risk neuroblastoma is one of the most intense and [indiscernible]. The acute and long-term side effects our patients experience are substantial, and while the addition of anti-GD2

immunotherapy has improved outcome, still, too many children relapse and die, and there are a few effective treatments for relapsed disease. The prevention of relapse is a critical and unmet need for children with neuroblastoma. I've treated 35 children with neuroblastoma with DFMO after maintenance immunotherapy, and I've only had 3 children relapse. This is a much better outcome than what I was used to in the past.

You have heard and reviewed the data presented today. From my perspective and as someone who cared for these patients, the data are very encouraging and compelling. Prevention of relapse is key. And in addition to improved outcomes, DFMO has been well tolerated with minimal side effects. Children taking DFMO are back in school, playing sports, and have limited clinic visits. I thank FDA for the guidance they've given our group and for its thorough evaluation of the data. I appreciate consideration of treatments for children with rare diseases such as neuroblastoma. Thank you.

DR. LIEU: Thank you so much.

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

MS. SHAW: Good afternoon. My name is Crystal Shaw, and I am speaking today on behalf of my son, Parker, who fought stage 4, high-risk neuroblastoma at the age of 6. I'm not being compensated for my time or my testimony.

High-risk neuroblastoma has a standard protocol that is outdated and very harsh. Parker had unfavorable histology and refractory disease after completing standard upfront treatment. After 10 long months of terrible treatments, he finally completed therapy and reached no evidence of disease status. We were done with treatment, but a choice still needed to be made since there was such a high risk of relapse.

There were three choices given. We could do nothing, enroll in DFMO, or wait a little bit to

see if the vaccine trial was available. We had read a lot about DFMO and spoke to some of our greatest resources, which frankly were other parents who had experience with this drug. Other families shared that this drug was easy and didn't have any lasting side effects. Some shared that their children had decreased hearing while on the drug, but it returned to normal once completing DFMO or sometimes even just by lowering the dose.

For us, it was a no-brainer. The thought of doing nothing was terrifying because our 6 year old had endured so much and we never wanted him to have to relive this nightmare again. DFMO was available at our home hospital and has shown to reduce relapse by 50 percent. Of course, we signed up. Parker already had significant hearing loss from previous chemo treatments, but he did not have any additional loss while on DFMO. He did have mild GI upset for about the first month when starting therapy and slightly thinner hair, but the trial was easy and taken twice daily from our home. After being away from our family on and off for

months, we felt so blessed to have a treatment that was able to be done from home.

Parker was able to take his meds in the morning, go to school, play with his friends, take his meds at night, and most of all, be a normal kid every day. The follow-up visits were easy and never did he have to go inpatient during this trial. After 2 years, Parker completed the trial and remains cancer free today. He will be 17 this month.

As a mother that now has experience with DFMO, I believe that all kids fighting cancer everywhere should be given the opportunity to use DFMO to help keep them cancer free. It is easily taken from anywhere. It does not have long-term side effects and the quality of life these kids get while fighting cancer is essential to their healing. I thank you so much for your time today.

DR. LIEU: Thank you so much.

Speaker number 7, please unmute and turn on your webcam. Will speaker number 7 begin and introduce yourself? Please state your name and any

organization you are representing for the record. You have five minutes.

MS. STEPHENS: Good afternoon. My name is Sarah Stephens, mom of a little girl named Eleanor, who is a neuroblastoma survivor. We are from Central Florida, but I'm Zooming in from Hawaii, as we are here for Eleanor's Make A Wish trip. I would like to start off by saying there is no financial benefit to me for speaking today and I'm not being compensated for my time.

Neuroblastoma was found throughout my daughter's little body at only 3 months old, and she fought hard through her toddler years. Cancer was found in Eleanor's bone marrow, throughout her entire liver, and her adrenal gland, and lymph nodes. She fought as an infant and again, almost two, when her cancer relapsed. Eleanor underwent many rounds of chemotherapy, radiation, intense surgery, rounds of painful immunotherapy, and all of the horrible experiences that come with being a cancer patient.

Well, we were absolutely thrilled with the

news that Eleanor was finally cancer free. The thought that this disease had a good chance of coming back was terrifying. Knowing that survival rates were only around 50 percent from stage 4 neuroblastoma, we have prayed that cancer would never come back. While searching for what we could do to save Eleanor's life, I learned about the research being done on DFMO and how it could increase Eleanor's chance of survival. Because the drug was not yet approved by the FDA, the only way to get Eleanor on DFMO was to have her enrolled in a clinical trial. In order for Eleanor to receive the medication, we would have to travel to Michigan from our home in Florida every 3 months in the first year of the 2-year trial.

As soon as Eleanor finished chemotherapy and immunotherapy, and her counts recovered, we were on a plane to Michigan, and Eleanor enrolled in the DFMO trial in 2019. Eleanor took DFMO for 2 years, 2 times a day, and during the period she was on DFMO, she experienced no side effects. While she was on the drug, her little body began to

heal from her cancer treatment. She began to experience life just as a child should. We gave Eleanor the DFMO medicine and it gave us hope for a future of watching her grow up, hope based in science.

Today, Eleanor has been off of DFMO for 2 years. She remains cancer free. She attends school and is in first grade. She loves to swim, dance, and play tennis, but most of all, loves to spend time with her family. She is thriving. Data has confirmed the DFMO can reduce the risk of relapse by 50 percent when used as a maintenance therapy after remission. More children will live if this drug is approved.

Kids fighting neuroblastoma everywhere, just like my daughter Eleanor, should have the chance to have this evidence-based therapy. We were incredibly blessed Eleanor was given the opportunity to be on the clinical-based trial in which she was guaranteed to receive DFMO and not risk getting placebo, but other kids will die because they do not have access. Children should

never be told there's nothing more that can be done when there is a drug available, increasing their chance of life. I ask you today, as a mom first, but also as a concerned citizen of the United States, to please consider that your approval will help more moms like me get the chance to watch their kids grow up. Every child deserves this chance. Thank you.

DR. LIEU: Thank you so much.

Speaker number 8, please unmute and turn on your webcam. Will speaker number 8 begin and introduce yourself? Please state your name and any organization you are representing for the record. You have five minutes.

MS. JANSHESKI: Thank you. Good afternoon. My name is Rachel Sal Jansheski, and I'm a parent to a child who has received DFMO at a maintenance therapy for high-risk neuroblastoma. I have no relationship with the sponsor and I'm not being compensated for my testimony.

This is my son, Dirk. Dirk was a healthy toddler with an amazing vocabulary and joy for

life. Before July 2019, we would have never guessed that Dirk would have any medical challenges in life, but then he complained of leg pain, and then he stopped walking. He didn't sleep without Tylenol and Motrin, and we knew something was really wrong. It turns out that something was cancer in his abdomen and pelvis, pushing on his blood vessels and lymphatic system, feeding his right leg. By the time cancer was discovered by an emergency MRI, Dirk's pain required having narcotics for management.

In late July 2019, Dirk was diagnosed with stage 4, high-risk neuroblastoma. Dirk was immediately enrolled in Beat Childhood Cancer's DFMO clinical trial. Dirk's neuroblastoma was wrapped around his inferior vena cava and embedded in the psoas muscle. So at the time of tumor resection, after 4 cycles of chemo, only 80 percent could be removed. As a result, Dirk ended up receiving 8 cycles of chemotherapy instead of the traditional six.

Chemo was very hard on his body, and he

acquired BK virus, which left him so weak and frail, and yet the remaining disease remained stable. We had hoped that stem-cell transplant would eradicate the remaining disease. It was so hard on his body. Dirk ended up with moderate-to-severe VOD and had a catheter drain in his abdomen. After stem-cell transplant, Dirk underwent 12 rounds of radiation, and yet the scans were still stable.

Dirk randomized to receive DFMO along with retinoic acid and immunotherapy. By late September 2020, Dirk was due to be done with his therapies, and yet the scans showed stable disease, so an additional 17 doses of radiation were ordered. Finally, as of November 2020, Dirk exited active treatment and remained on DFMO alone. His February 2021 scan showed minimal stable disease in the lymph nodes by his inferior vena cava and in his psoas muscle. Over the next 2 years, we saw his scan results indicate slightly decreased avidity, then resolved avidity in his lymph nodes, and then a smaller tumor in his psoas muscle, to

finally in November 2022, no avidity, no evidence of anatomic or metabolic disease, and finally NED status. This is our experience with DFMO. We saw our son go from minimal residual disease to NED while on DFMO alone. The smile on Dirk's face when he could finally say there is no cancer in his body felt like a gift from above.

Dirk's 2 years on DFMO were years where he could go to school full time. He could continue to build strength and learn to run and climb again. DFMO did not impact Dirk's daily life; however, about one year after exiting active treatment, Dirk started accumulating late effects from other treatments that are standard of care. To date, Dirk has five such late effects: high frequency hearing loss from cisplatin; back pain caused by radiation scarring of the spine; pancreatic insufficiency due to his pancreas being over radiated; specific antibody deficiency causing significant lung, sinus, and ear infections from his B-cell depleting chemotherapies during stem-cell transplant; and iron overload of his

liver due to the 20-plus red blood cell transfusions required to rescue his body from the harsh chemotherapies.

As a parent of a child with high-risk neuroblastoma, I ask you to consider how hopeless we feel when our child is diagnosed and how unfair and dismal the overall survival odds with standard of care seem. We received hope when presented with the opportunity for Dirk to receive DFMO as a maintenance therapy, hope in the form of 7 pills taken daily to be able to reduce the risk of relapse by 52 percent; hope of a treatment that for once wouldn't impact Dirk's quality of life.

I believe all neuroblastoma families deserve that same opportunity to receive DFMO as a maintenance treatment to reduce the risk of relapse while not impacting their child's quality of life. Let's change the story for the next family. Thank you.

DR. LIEU: Thank you so much.

Speaker number 9, please unmute and turn on your webcam. Will speaker number 9 begin and

introduce yourself? Please state your name and any organization you are representing for the record. You have five minutes.

MS. BURNETTE: Good afternoon. First off, I would like to state that I am not being compensated for this testimony. I'm speaking on behalf of myself as a former patient of DFMO. My name is Ashley Burnette. I'm 20 years old from Raleigh, North Carolina, and I'm currently a junior at the University of North Carolina in Chapel Hill. When I was 7 years old, I was diagnosed with stage 4 neuroblastoma. I started chemotherapy immediately and had a stem-cell transplant directly after. During my stem-cell transplant, I was diagnosed with a second type of cancer, non-Hodgkin's lymphoma.

My chances of survival were very low. As a 7 year old I struggled to reach 40 pounds. I was extremely unhealthy, yet I continued with other therapies such as radiation, MIBG therapy, and immunotherapy. After 2 years of fighting, I was finally cancer free. With neuroblastoma patients,

no evidence of disease doesn't always mean you're in the clear. Approximately half of the population of children with high-risk neuroblastoma have a relapse. I wasn't willing to accept these odds. I needed a guarantee that these toxic treatments I endured were enough to keep me in the clear.

For me, this guarantee of a normal, healthy life was DFMO. In 2012, my family and I looked into the possibility of going on the experimental trial. The drug was fairly new at the time, but all the prior results were looking very promising. When I began the trial, the plan was for me to take the drug for 12 rounds of 28 days, and at the end of a year, if my cancer hasn't progressed, I would be considered for another year on DFMO. After a year, I was feeling great and was granted another year of treatment. Over those two years, I was taking 3 DFMO pills every morning and every night. The process was easy and painless, which is something that I can't say about any of the other treatments that I've experienced.

DFMO is a trial targeted specifically for

neuroblastoma patients. While other treatments I went through are targeted at adults with cancer, such treatments can be extremely harmful to a child's body such as mine. Some of the short- and long-term effects of the treatments I went through before I started DFMO include weight loss; loss of an appetite; hearing loss; anemia and need for constant blood transfusions; nausea; severe pain; hair loss; lack of growth; infertility; and more.

Over the 2 years that I took DFMO, I never experienced any side effects from the drug. Throughout the entirety of the trial, no evidence of neuroblastoma was ever seen in any of my scans. This past August, I celebrated 11 years of being cancer free. I have DFMO to thank for the great health and happiness that I've been able to experience ever since I went into remission.

You have been listening to the data today. My story's in those data. My wish is for DFMO to be approved so that children that are experiencing the same thing that I did can have a chance at a normal healthy life, too. Please help save the

lives of so many children by approving this drug. Thank you.

DR. LIEU: Thank you so much, and thank you to all of our open public hearing speakers.

The open public hearing portion of this meeting has now concluded and we will no longer take any additional comments from the audience.

I'd like to call on Dr. Drezner to provide a brief update on our charge to to the committee before we move on to our other agenda items.

DR. DREZNER: Thanks, and thank you to everybody in the open public hearing. I believe we're going to be going into additional questions and discussion, so I just wanted to focus the conversation on the strengths and limitations that are laid out in this slide, which represent our challenge in assessing the statutory requirement for substantial evidence of effectiveness. Thank you.

Clarifying Questions (continued)

DR. LIEU: Thank you, Dr. Drezner.

As we have additional time, we will now

take some remaining clarifying questions. I'll certainly specifically ask our neuroblastoma experts -- and there are numerous ones that are in this meeting -- to please ask clarifying questions, and we will certainly need your comments during our discussion of the questions that are being asked to the committee.

Just as a reminder, please use the raise-hand icon to indicate that you have a question, and remember to put your hand down after you have asked your question. Please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. As a general reminder, 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.

With that, I will open it back up for questions, so Dr. Spratt, your question please.

DR. SPRATT: Thank you so much, and thank you so much for the people that recently just spoke. I'll start, actually, with a little commentary, and then I'll provide a question both to the sponsor, as well as the FDA. But as we already said, the FDA recommended the randomized trial in 2015, and I think all of us on here want to improve cancer patients' outcome. And I think that if an overall survival was shown in any trial with a hazard ratio of 0.32, or in the FDA's sensitivity analysis of 0.16, which is almost a 90 percent relative reduction in death, this would be a very easy conversation. But I think that given any therapy that's approved, it does have some side effects, as well as potential financial side effects.

The vast majority of our therapies that are promising results in single-arm studies do not actually improve outcome, so the question, as posed to us, is, is this sufficient and is it feasible? I'd like to say while we've just heard from patients who received DFMO, greater than 7 out of

10 patients in the control arm of the data submitted did not have relapse, where greater than 8 out of 10 did not experience relapse with DFMO.

The other clarifying point that I just want to make is a lot of the toxic therapies that sound like they've greatly impacted these patients lives, that's not the goal of this therapy because all of those therapies as the frontline standard of care will still need to be given. So I guess the question is, the goal or the criticisms of randomization are cost, time, the rare disease, and equipoise, but none of those impact the accuracy of the results, so if we look at the data presented, is this too rare of a patient population?

As many on here know, there have been dozens of randomized trials in rare disease, even more rare disease across pediatric cancer patients. The control arm trial did enroll 225 patients in a randomized trial and recently completed the ANBL1531 trial. At 750 patients, it took 5 years to accrue a multi-arm randomized trial in high-risk neuroblastoma, so I don't think we can say this is

too rare of a population.

Equipoise, the question is, if this is very promising data, why -- unless this can be given routinely off of trial, this randomized trial would enable this to be given. And also, if these results are indeed accurate, this would be one of the smaller randomized trials because, as I mentioned, the overall survival hazard ratio is 0.32, so not even needing a surrogate of event-free survival, and on the fully adjusted analyses that were done, the sensitivity, the hazard ratio is 0.16.

So I would just like to keep that in mind. This could be a very feasible small trial, and to compare this to the trial that approved immunotherapy, its overall survival hazard ratio is 0.58, so this estimate would be a much larger effect size.

So the question I guess I'm going to give here is, what I don't really understand is that in the DFMO arm, there were 16 EFS events; subsequently, eight of those patients died. That's

about 50 percent where they talk about patients die with relapse. But in the control arm, in this non-randomized study, there were 29 EFS events but 21 of those patients died, so that's 72 percent, and there is a long tail in both of these curves with longer follow-up.

So that's going to be question 1, I guess, for the FDA, as well as the sponsor. And then I would like to know, was any instrumental variable analysis done? Because I didn't see anything that actually is a specific statistical test to account for unmeasured confounding.

The last question for the sponsor is, can you show us or did you perform a completely non-adjusted analysis? Not a 3-to-1 matching and not all. Did you just compare the patients that you have in these two different cohorts to let us see the effect of how much these hazard ratios or treatment effects change?

The final comment is simply, there is yet to ever be proven, unfortunately -- and I wish it was true -- a statistical analysis or method that

can overcome or reliably reproduce randomization. So I think while we can give you a million more analyses to perform, the crux is this has never been shown to be able to be overcome no matter how many analyses we do.

So thank you and, again, to repeat the questions, one, why is the EFS-to-death ratio so much higher in the control arm? Because once you have a relapse, unless there's some other salvage therapy, that's unclear to me. Two, was instrumental variable performed? And three, can you show us the completely unadjusted, unmatched results? Thank you.

DR. LIEU: Thank you, Dr. Spratt.

Maybe we can start with the applicant.

MS. GULLO: Starting with your question about overall survival, we also observed the same difference you're reporting and did further evaluate why the overall survival results actually appear to be even more pronounced than the event-free survival results. I'm going to show a slide with some of our findings.

First, I actually just want to provide a little bit of context. We're evaluating the outcomes in patients that relapsed, and then following them for overall survival in some of the data we're presenting here. But the expected rate of death following a relapse event is closer to 85 percent, and that is consistent with what we saw trending in that direction for the control group of patients that experienced a relapsed event in that primary analysis. In our group of relapsed patients, from the primary analysis, there were 7 deaths among 14 relapsed patients, which is trending toward a a better overall survival result and is part of what is driving the difference we see in the overall survival curves.

In addition, we considered whether perhaps we had just not had enough time to observe death following relapse events in the DFMO group, and we actually found that in the patients that had relapsed that remained alive, we had a median follow-up time of one-and-a-half years longer in the treated group as compared to the control. Then

in the second bullet there, even within the patients that relapsed and then went on to unfortunately die, their time between relapse and death was a median of one year longer in the treated group. So these observations together do appear to even widen the effect that we've seen from the event-free survival when we look at the overall survival result.

We also, at FDA's request, did as much work as we could to evaluate post-relapse therapies to try to understand if they were contributing to the differences we saw here. We did not identify any clear differences in post-relapse treatment; all of the data were limited, particularly in the control group. We also importantly considered whether these same observations remained consistent in the contemporary group, where we would expect all of the evolution and treatment to be accounted for in both groups, and the observations were the same. So while all of these are supportive that the overall survival result, again, is in some way attributable to DFMO, we also know that reducing

the risk of relapse is the most important way to improve overall survival.

Just going back to some of the points that you made, it is the hazard ratios that we find so compelling, and we would agree there is not a statistical test that replicates a randomized-controlled trial, but we have worked with FDA through a lot of different approaches to try to rule out the outcome differences that we're observing as being attributable to some other factor, and we've come up short in explaining it, other than the fact that the patients received DFMO, and that is consistent with the hazard ratios, suggesting approximately a 50 percent reduction in risk and relapse and an even higher risk reduction in death.

I'll go to your question now about overall survival analyses with the overall populations. If we could pull up our core slide, please, showing EFS and OS without the match. And I apologize; I don't have the number in front of me. CO-45, please. Thank you.

This slide was presented this morning, shown again here. The figure on the left is event-free survival and on the right is overall survival, and these are the full groups of patients that met the selection criteria agreed with FDA in the statistical analysis plan without matching. You can see that the results are very similar to the propensity-matched analysis, again with the hazard ratio and EFS being right at 0.5.

DR. LIEU: Great. And the FDA response?

DR. DREZNER: Hi. Can I ask Dr. Mishra-Kalyani to take that response -- or sorry, Dr. Duke first. Can we go to backup slide 48, and then Dr. Mishra-Kalyani.

DR. DUKE: Thanks. This is Elizabeth Duke. This backup slide shows the post-relapse therapies, so I don't think we can say that the post-relapse therapies were similar. We just don't know on the 0032 arm what the number of post-relapse therapies were and what they included.

You have the slide? Sorry.

DR. DREZNER: Yes, backup 48.

DR. DUKE: Great.

So while the number of relapses was known for most patients, the number and type of post-relapse therapies was unknown for the EC arm. I would also note there were differences in follow-up, particularly after 5 years, for overall survival, and the low number of OS events and sensitivity analyses that have fewer eligible patients ultimately decreases our confidence in thorough characterization of the effect size there.

We would be interested in panel members regarding the question about feasibility of randomization, and certainly interested in panel members who have experience with neuroblastoma, their thoughts on that as well. Thanks.

DR. MISHRA-KALYANI: Hi. This is Pallavi Mishra-Kalyani from FDA Statistics. Thank you for the questions. First, actually, could I have slide B-58 up -- thank you -- or backup 58? Your question about instrumental variables is certainly a good one. We did really consider a variety of analyses when considering how to best control for

different types of bias, including confounding and unmeasured confounding. The difficulty with instrumental variables is that first you must establish a variable is an instrumental variable, and that is that it has correlation with the various aspects of your model that you're trying to control for, and in this case, we didn't really have many instrumental variables to consider or to control for. Additionally, analyses including instrumental variables have their own limitations.

I bring this slide back up because there have been numerous discussions regarding how to best control for unmeasured confounding, and certainly FDA considered various methods for looking at what the effect of unmeasured confounding might have been on the results and whether or not our results are likely to be attributable to unmeasured confounders.

The method described earlier by my colleague, Dr. Sinha, and shown here for an unspecified confounder with a hazard ratio of 2, which is a fairly strong effect with respect to

being detrimental on EFS, shown here in this plot is that if we have different prevalences in each arm, we would expect to still see relatively low hazard ratios unless we see a very, very wide difference in the prevalences across arms, which is unlikely.

We can extrapolate from this table that if multiple confounders acted together and had a hazard ratio of 2.0, we would still see such effects. So while we can't directly examine multiple confounders at the same time, we can use these results to understand better if multiple confounders exist at the same time and are affecting our estimation of treatment effect at the same time, what the likelihood is that our results are fully attributable to those confounders.

I also want to bring attention to backup slide 51. These are the Kaplan-Meier curves for our conservative sensitivity analysis, which was previously mentioned, especially with regards to the overall survival analysis. I'll echo my colleague, Dr. Duke's remarks, that with such few

events in the overall survival analysis, it's very difficult to rely on this analysis for an estimation of the magnitude of effect. The directionality, it remains constant or consistent, so for that reason, we rely on this more to support the primary analysis than to be an independent analysis of the effect size.

On the other hand, for the event-free survival analysis, it's important to remember that we did control for various types of measured confounders or sources of bias simultaneously in this analysis, and while perhaps we aren't able to do instrumental variable analyses, it's an important and known feature of adjustment of various types of bias and various concerns simultaneously in the model that other concerns or biases may also be mitigated with such analyses and may be adjusted for with such analyses. So while there may be items, or measured confounders, or unmeasured confounders that were not adjusted for directly in these analyses, we do feel confident that the results of these analyses may have the

side effect, if you will, of also adjusting for various confounders.

DR. LIEU: Thank you so much.

My apologies. I think we're going to have time for one additional question, but we do have two discussion questions and a voting question, which is going to take a significant amount of time. I will ask Dr. Asgharzadeh to ask his question, but may need to leave the other questions potentially for the discussion that we're going to have in the discussion questions, so my apologies to those that still have their hands up.

Dr. Asgharzadeh?

DR. ASGHARZADEH: Good morning. Good afternoon over there. Shahab Asgharzadeh from Children's Hospital Los Angeles. My background is in neuroblastoma. I wanted to make a couple of comments because some of the colleagues here, and FDA also, keep bringing this up that this is a unique circumstance, study, showing great flexibility in regulatory efforts, which I agree with, but I want to emphasize that I hope this is

the beginning of continuing to do this type of study of analyses this way.

The use of a randomized clinical trial in neuroblastoma, for this question, I think we have some ethical challenges that need to be addressed, which we haven't discussed. FDA suggested that there was a missed opportunity to do a randomized clinical trial before publishing the results. I think that would be, actually, unethical not to publish the results, given the rarity of the condition and the data that was generated with that trial.

I don't think it will take 5 years to do a randomized clinical trial to answer this question because this data needs to be matured after the end of the therapy completely, so at a minimum, it's 8 years. And given that these are not studies like a typical adult study, where you're looking for 6 months increase in survival to get FDA approval, these are changes that will affect the child for the rest of their life.

So I appreciate that the ideal way to do

this would be a randomized clinical trial, but I think the guidelines also suggest that we could use the external control trials for this purpose, and there's flexibility, and it should be addressed in this rare population of patients where there are only 400 patients a year that are diagnosed.

I really applaud the FDA and the sponsor for conducting the extra analysis. As I was reading the document, I kept asking, "Well, what about the immortal time period?" But that was addressed; and about the imaging assessments and differences, and that was addressed; the blindness of the response assessment, that was addressed; and the sensitivity issues I think were addressed.

So I guess one question would be -- for, I don't know, the FDA or the sponsor -- the ethics of trying to do a randomized clinical trial in this cohort. In terms of the sensitivity -- and I appreciate that it's hard to do -- ideally, I would have liked to have seen a couple of more analyses with the combination of pre-AST and MYCN and their interactions as a possible request, but given that

you guys also did the extra sensitivities of assuming that there may be some interactions between these factors and still the results are impressive, I don't think that's going to be necessarily a question. But that's something to think about in the future, as what type of guidance would you give for these types of studies and a level of evidence that you want post-analysis to prove these types of studies in the future, and that is all I'm going to say.

DR. LIEU: Would the FDA like to start?

(Pause.)

DR. DREZNER: Hi. Sorry. I was getting the 2:20 notification.

Thanks, Dr. Asgharzadeh. I want to just clarify our position, that we didn't mean to suggest that published results should be delayed. I think we were more referring to the conduct of a randomized-controlled trial prior to a single-arm trial enrolled.

Do you mind just clarifying your specific question so that we can identify the correct person

on the FDA who will take that? Was it about the MYCN sensitivity analyses or more just about the general feasibility or ethics of conducting a randomized clinical trial at this time?

DR. ASGHARZADEH: There are certain prognostic features that are more important, I guess, in terms of relapse, and you could take the totality of all the factors that you want to emphasize as being equitable in designing your propensity, but there are certain ones that you could think about doing an interaction analysis that would, again, give you a little bit more credence that this indeed is not a result of any kind of unknown factors that will affect the survival. The two broad examples was interaction between MYCN and pre-AST response.

DR. DREZNER: Thanks. I will ask Dr. Mishra-Kalyani to take that. Thank you.

DR. MISHRA-KALYANI: Thank you very much for your question. This is Pallavi Mishra-Kalyani, FDA statistics. Certainly, we aimed to take a very scientific approach to the sensitivity analyses

that were conducted. Our main goal was to look at the data that was available, as well as whatever data was available from literature to inform various aspects of our analyses. We didn't directly consider interaction terms, mostly because there perhaps was not too much literature supporting this as a direct or as a type of analysis that would be required in this setting; however, we will take that note and perhaps consider it in the future.

DR. LIEU: Great. And I believe the applicant has a comment.

MS. GULLO: Yes. I just wanted to comment on the question about pre-ASCT and MYCN status. We did not do specific interaction analysis, but the slide we presented before with the -- I'll show it again -- exact match on the pre-ASCT, which has been reported more recently to be more prognostic -- oh, I'm sorry.

Could we share our screen, please?

This is the analysis that we did, one of the sensitivity analyses, where we replaced the

exact match on MYCN with an exact match on the pre-ASCT response. But in this analysis, MYCN is maintained as a covariate in the assignment of the propensity score, so we do achieve good balance on MYCN status while also exact matching on pre-ASCT in this specific sensitivity analysis, which is consistent with the primary.

DR. ASGHARZADEH: Thank you for the clarification. I have no more questions.

DR. LIEU: Thank you so much.

Dr. Kim, my apologies. You're the one person who was not able to ask a question during the clarifying questions. Briefly, would you be able to state your question for either the FDA or the applicant, please?

DR. KIM: Thank you. This AeRang Kim from Children's National. It's a quick question. This is for the applicant. My question was, they demonstrated that DFMO was well tolerated, but about 17 percent of the patients was dose modified or came off for AE. I was just wondering if any subanalyses were done of the outcomes on those

patients that had dose modifications or came off therapy

MS. GULLO: Yes, we did. We did explore that issue, and in the group of patients where those outcomes are available, the 3b primary analysis population, there is no clear difference in patients that discontinued treatment due to adverse events; however, I believe there was only -- sorry. Could I have the data slide on patients discontinuing, please?

Only 6 patients discontinued treatment early due to adverse events or for any reason other than relapse in the primary analysis, and the median duration of therapy in those patients was just over a year, but there were no differences in outcomes in that group.

DR. KIM: And were there any difference in those that were dose modified?

MS. GULLO: No. And again, that was a small group when we consider the group we're evaluating for outcomes.

DR. KIM: Thank you.

DR. LIEU: Does that conclude your question, Dr. Kim?

Questions to the Committee and Discussion

DR. KIM: Yes. Thank you so much.

DR. LIEU: Great.

Dr. Pappo, my apologies. You will certainly have an opportunity to provide some comments during our discussion questions, which are now coming up.

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

After I read each question, we will pause for any questions or comments concerning its wording. We will proceed with our first question,

which is a discussion question. The question is, discuss the strengths and limitations of the externally controlled trial results to support the use of DFMO in pediatric patients with high-risk neuroblastoma.

Are there any questions, comments, or concerns regarding the wording of this discussion question?

(No response.)

DR. LIEU: If not, I will open it up for discussion. I think we're going to really rely on two groups in this panel, and that is our neuroblastoma experts and our biostatisticians. I certainly will just make the comment that in regard to the external control, I agree with all the comments in regards to the need for randomization to truly measure the strength of the evidence, but at the same time, this is probably I think as good as we may get in regards to an externally controlled trial.

But I certainly have significant concerns about setting a precedent for utilization of an

externally controlled trial. I don't want to get us into a situation where the discussion or decision to do a randomized trial is really influenced by the decision of this panel. I think that this is a fairly extraordinary situation, but like I said, I think I would really appreciate the comments of those that know this disease much, much better than me.

With that, I'll call on Dr. Alexander for comments.

DR. ALEXANDER: Well, I mean it's hard not to think that should the FDA move forward, that this isn't precedent setting, so I think it's sort of naive to think otherwise, as much as we may hear assurances to the contrary.

With that being said, I agree that this is a fairly unusual setting and, again, I think both the FDA and sponsor should be commended for how carefully they've looked at the data. I think, Dr. Sturmer, you rightly point out that there were important differences between those that enrolled in 3b and those that didn't and, yes, they can be

propensity matched or propensity weighted, but the concern isn't what you're observing; it's what you can't measure or didn't measure.

I think that some of the discussion has rightly pointed out that there tends to be a focus on could there be a missing confounder that we're not considering; could it be education; could it be performance status and so on, but there's not likely one smoking gun. So I am curious, but my guess is that nobody really believes that this drug reduces mortality by 70 percent and relapse by 50 percent. I certainly don't. I think that it may well have efficacy, but then that generates the question, well, where do we fall? How much do we think is residual confounding and how much is true effect?

So we have any number of potential confounders that muddy the waters: performance status; tumor cytogenetics; income; education; employment; housing; bone marrow response; transplant regimen; surgery during induction; and so on and so forth. I don't know that there's much

more that can be done statistically. I'm not a biostatistician, by the way; I'm an epidemiologist, but I don't know that there's much more that can be done epidemiologically or biostatistically with these data. I think at the end of the day, this I think elevates the importance of the next question, which I think is about the confirmatory evidence. Thank you.

DR. LIEU: Thank you, Dr. Alexander.

Dr. Sturmer?

DR. STURMER: Thank you. Same here. My camera is on now. I'm not a biostatistician, but an epidemiologist, or more specifically, a pharmacoepidemiologist. I have several issues that we don't have time to discuss here, including the 40 percent that were not matching eligible. The crude data that were requested by one of the previous speakers and presented by the sponsor are on the 852, all the comparators, but what I would really like to see is the crude data on those matching eligible, i.e., 500 or so patients, to see what kind of measured confounding was controlled

for and what was the change in estimate. And I have not seen any analysis about predictors of missingness and how they could be related to the risks for the outcomes.

Finally, I still find it staggering, the point I raised, that we have seen little information in the materials about how the patients were recruited into 3b, and I think all of these would be related to potential for confounding, and we heard travel to Michigan during the open session, for example. So this is something that I would have liked to hear much more about.

Matching is not ATE but ATT in this setting, where 99 percent of those treated could be matched. There are just several of these things going through the data that I think are fit for purpose and that I would have wanted to see addressed in a package. Thank you.

DR. LIEU: Thank you, Dr. Sturmer.

My apologies to the applicant, but this discussion will only be the panel members unless specifically called on to have the applicant answer

a question.

We're going to go to Dr. Shaw here. I think we really need the input here of our neuroblastoma experts, specifically, Dr. Kim, Dr. Parsons, Dr. Twist, Dr. Weiss, Dr. Unguru, I think we really need your comments here to guide this discussion, and certainly we'll continue this discussion, but I'm going to ask specifically for some of our neuroblastoma experts to make comments.

But while those comments are being prepared, Dr. Shaw?

DR. SHAW: Yes. Thank you, and I think I'll help you tee up the discussion for our clinical experts. I'm Pamela Shaw, Kaiser Permanente, Washington Health Research. I am a biostatistician. As I think about this question, the strengths and limitations and this concern over could this be confounding, something that is striking to me, this population, are those with high-risk neuroblastoma, and when we look at the estimates for the 90 patients for 2-year survival, 4-year survival, if my memory serves me right, it's

something like 99 percent and 96 percent, so statistically close to 1. So no matter how you weight it, that's not going to vary.

So when we think about confounding, it's can we think of sources of confounding that are driving survival up that high? That's the kind of confounder we would need, and is that plausible? That could be simply confounding to have these really high survival rates, where I think the comparator, external controllers, may be down. Maybe I'm not going to quote that; I can't quite remember.

I think that's the setting here. It's hard to decide. Is this such a high survival that, as we've heard some other panel members, they don't quite believe it, or is it such a high survival that this gives us confidence that there is a treatment effect? And perhaps our clinical experts could talk a little bit about their reactions when they're seeing this group of patients in the 2-year/4-year survival, where we have fairly good follow-up in both groups in that less than 5-year

survival and what they think about these differences in this not randomized trial, but this is a group of people with a high-risk disease and having very good outcomes. So those are the kinds of things I'd like to hear from the clinical experts in this disease area.

DR. LIEU: Thank you, Dr. Shaw.

Dr. Spratt?

DR. SPRATT: Thank you. Yes. I would just comment that if the 4-year results, just to give the numbers, was 96 percent versus 84 percent -- please, the FDA or the statisticians can validate -- I come out with approximately a 54-patient trial would be required. Even if you increase that to 80, it's a much smaller trial than the trials that were in the control arm, that trial that was used.

I still don't think the question that I asked of why in the relapsed patients -- and this goes to what the last speaker just said -- are they dying at such a higher rate than in the relapsed patients in the DFMO? So that speaks to there is

some underlying confounding that is not -- even in all the adjustments and every analysis shown accounting for. So again, if we believe these effect-size estimates, then you need a very small randomized trial. If we don't believe the effect-size estimates, then the question is, can we believe the results at all?

DR. LIEU: Thank you, Dr. Spratt.

Dr. Weiss?

DR. WEISS: Yes. Thank you. I wanted to echo what Dr. Spratt had said before, and also Dr. Alexander and Sturmer. I'm a neuroblastoma physician, and it is very complicated. I don't feel that a randomized trial would be impossible; in fact, I think it's quite feasible. And unlike what Dr. Shaw asked, I don't have patients on this trial, so I can't tell you what I have seen in patients on DFMO. But I have a lot of patients who were not on the trial who also had very similar stories to the moving testimony that people gave of their child's or their own results on DFMO. And that's why we have to do a randomized trial,

because neuroblastoma is weird, and sometimes you have marrow disease at the end of therapy that just goes away, and we don't completely understand that.

So I just wanted to say those as a neuroblastoma expert on the panel.

DR. LIEU: Thank you, Dr. Weiss. That's very, very helpful.

Dr. Asgharzadeh?

DR. ASGHARZADEH: Shahab Asgharzadeh from CHLA. I'm going to, again, respectfully disagree with Dr. Weiss and others. It will not take 54 patients because these data are from patients who have had no evidence of disease at the end of their entire treatment, and we know there is a good percent of the patients that actually have relapsed during therapy. So it's not like all of these data that you see, every patient who starts with induction therapy reaches that level where they could go and continue this. Yes, will it be a smaller number of patients? Probably, but I don't think it'll be 54 patients.

Now, to talk about confounding effects and

why survival may be so good for these patients in the relapse in the trial, there are confounders but the confounders could actually be beneficial because of the DFMO. So one thing that hasn't been discussed or put on the package at all is DFMO has strong activity against a tumor microenvironment in several diseases that has been described. The ornithine levels that are high actually affect the myelosuppressor cells, causing a more anti-immunosuppressive environment. The lowering of ornithine improves T-cell activity.

So the confounding effects that you see may be beneficial effects of DFMO that we don't understand, that's given to these patients when they have lack of disease and an improved anti-tumor effect, which has clearly been shown in neuroblastoma.

Neuroblastoma is a very strange, weird disease. We recently have shown that chemotherapy with anti-GD2 together melts well-established tumors that we've never seen before. This is also a tumor that, in a subset of patients, goes away

and has a complete regression. So it's not far-fetched to think that DFMO has effects beyond what's been described in this application, as inhibiting neurosphere formation, and may actually improve the anti-immune tumor effect or the tumor immune effect of the patient.

So again, I recognize that for statisticians, the randomized-controlled trial is the way to go, but I still, again, agree that the studies that have been done, and the sensitivity studies that have been done, are sufficient to justify use of DFMO in this patient cohort. Thank you.

DR. LIEU: Thank you, Dr. Asgharzadeh.

Just a quick reminder that I think the discussion regarding overall survival is certainly of interest, but here the specific voting question and the discussion questions really center still around event-free survival as the primary endpoint.

Dr. Pappo?

DR. PAPPO: Yes. Thank you for the opportunity to comment on this. I agree with what

has been said before. I don't think that you can do any more matching and more exceptional analysis trying to compare this population to the 0032 population. I think that the sponsor has done an exceptional job, and I think that statisticians, both from the company and the FDA, have basically done an exceptional analysis and the data is very compelling.

My concerns are as follows. First of all, this is a highly, highly selected population. Patients basically do not have to progress during induction; 12 percent of them happens. They don't have to die because of complications and because of transplant. They have to go through all of the cycles of maintenance therapy, immunotherapy, and finally make it there. So you're out there with a very, very small number of patients.

The concern I have is, if this approval goes forward, what are you going to use as your metrics in the future for randomized trials of neuroblastoma? Are you going to basically say this is going to be the new standard for outcome for

controlled-randomized trials, either from CytoPAN or from COG? How are you going to set the bar? How are you going to study this? I mean, is this going to affect -- and this may be, perhaps, irrelevant, because if it's benefiting the patients, who cares? But is this going to be a limiting factor for enrollment in prospective clinical trials that are currently ongoing, or are going to be ongoing, or are families going to say, after they finish immunotherapy, "I want to come off study and I want to be on DFMO for 2 years; thank you very much," and the questions to those clinical trials will never be answered?

So those are some of the concerns that I have. It might be a little bit of a biased opinion, but I just wanted to put that out.

DR. LIEU: Thank you, Dr. Pappo. That's a bit of a question to the FDA, as well.

Dr. Drezner, I believe you wanted to make a clarifying point.

DR. DREZNER: Yes. Hi. I wanted to know if Dr. Mishra-Kalyani wanted to come on just to

make a quick point about overall survival estimates.

DR. MISHRA-KALYANI: Sure. Thank you, Dr. Drezner. This is Pallavi Mishra-Kalyani from FDA statistics. I believe our chair, Dr. Lieu, has just reminded the committee that the endpoint of interest and the primary endpoint in the study was EFS. We caution that the overall survival results must be interpreted, I think, with a grain of salt or with some additional caution because there were not that many deaths overall in the study. There were about 64 deaths overall in the primary analysis; that's the matched analysis. There were a greater number in the weighted analyses that were described in the briefing documents, but in the sensitivity analyses, particularly the most conservative sensitivity analyses, there were only 17 deaths that informed that analysis.

So when there are such few events, we expect greater variability in the treatment effect estimates and much wider confidence intervals. So it's difficult to take those results and inform

assumptions for a new trial.

DR. LIEU: Thank you.

DR. DREZNER: Thanks.

DR. LIEU: Dr. Twist, your question, or, sorry, your comment, please?

DR. TWIST: Hi. Clare Twist from Roswell Park. I'm a pediatric oncologist. I just wanted to echo some of the comments Dr. Pappo, and Dr. Weiss, and others have made. First of all, kudos to the sponsor and to the FDA for a really sophisticated analysis to try to address the propensity scoring and to try to really come up with a control arm that feels as closely matched as possible with an external control.

I do think the data are compelling. I am left with some concern about some of the potential confounding factors that others have mentioned. It is a very selected population now that it is really being looked at. There's also the missing bone marrow data in, I think, 25 percent of the patients in the control arm, and that may just be a CRF data omission, but it does potentially impact the

disease state in practice for those patients.

I also think that the points raised about the recruitment strategy and, again, how were these patients identified and brought onto the investigational trial, I'm not at a center that has access to this trial, but I think we can all recognize that recruitment to some of these trials, certainly you may end up with a very selected population of patients, and that's already been raised by, I think, other investigators on the call. Those are my comments.

DR. LIEU: Thank you so much, Dr. Twist. That's very helpful.

We're going to move on to question number 2, which is also a discussion question, if we could have that question up. Question 2 is a discussion question stating, discuss the strengths and limitations of the additional nonclinical and clinical data to support the use of DFMO in pediatric patients with high-risk neuroblastoma.

I wanted to see if there were any questions or comments in regards to the wording of this

discussion question.

(No response.)

DR. LIEU: Seeing none, I'll open up this question number 2 for discussion, and we'll call on Dr. Alexander to get us started off.

DR. ALEXANDER: Yes. Well, we've talked some about this and had good discussion, so I don't have much more to say about the animal data. I mean, I'm not an animal researcher, and the question of how confident we can be in the animal data seems really mission critical to me.

The only other two points I'll make, I don't know what the confirmatory clinical evidence would be. I mean, the FDA has pointed out these three studies, so we have 002, which was 18 children, a single-arm dose escalation where the drug was given -- where the anti-tumor effect is unclear of DFMO, and it was given as combination therapy with multiple prior treatments. We have 006, which was an expanded access study that included 27 children with high-risk neuroblastoma in remission, where there was no control arm and no

prespecified response criteria or imaging assessments. And then we have Stratum 2, which was 35 patients, but as the FDA reports, and I agree with them, that there's no corresponding external control that can be derived from that. So I don't know what the confirmatory clinical evidence would be that the FDA would point us.

The final point is just that I am disappointed, coming from the outside, not to understand more and not to have had a chance to synthesize what's known about this drug in other cancers. It seems to me that's crucially important. If you ask me do I think that there's substantial evidence at an evidentiary threshold, I'm very, very interested in the entirety of what we know about this drug.

So if it's the case that we should disregard what we know about its failures in other settings because, dot-dot-dot, it would just really be helpful for me to know why I should be confident that the long history of unsuccessful development in other cancers is not a reason that should temper

my enthusiasm for the confirmatory evidence that we're being asked to evaluate here, which again I think just comes down to the animal data, I don't see how these clinical data could be confirmatory, unless I missed something, in which case I'd be delighted for the FDA to point it out.

DR. LIEU: Thank you, Dr. Alexander.

Dr. Cosenza?

DR. COSENZA: Yes. As a toxicologist, I'll just add a few comments on the animal model. I did actually go back. I spent the time and went back to the original publications that the FDA referenced, and the transgenic neuroblastoma model comes from the laboratories of award-winning oncology researchers, particularly in oncogenes. So I think this model is a little unique. It's not a xenograft model; it's more applicable to the status of the disease.

So I think it's a well-established model, and I think the data is supportive in that respect. I can't speak obviously to the clinical evidence, as I'm a nonclinical scientist. But I just wanted

to add that I did go back and review all of that data, so I do think the data can be supportive from a nonclinical perspective.

DR. LIEU: Thank you, Dr. Cosenza.

Dr. Parsons?

DR. PARSONS: I just wanted to add and emphasize my agreement with the second point about the preclinical models. I think the model, by our standards in the field, is a well-conceived and reliable one. It's been used in other studies of neuroblastoma. The biological and preclinical evidence as a whole, to me, are quite compelling for their consistency with the hypothesis and the clinical results. That's all.

DR. LIEU: Thank you, Dr. Parsons.

Dr. Widemann?

DR. WIDEMANN: I just wanted to get back to -- Brigitte Widemann, NCI -- I thought there was a trial 14 that was prospectively looking at exactly the same population and could provide confirmatory results with the 4-year event-free survival, if that is incorrect. This data it looks

like will come out later but could be, I think, very informative and potentially provide additional confirmatory results.

DR. LIEU: Thank you, Dr. Widemann.

Other comments? Dr. Pappo?

DR. PAPPO: At the end, they showed some of the other clinical trials that are ongoing with DFMO, and they showed NMTRC012, and I saw that the estimated completion date for that trial would be 2032. So that just caught my attention a little bit, so I don't think we're going to have a definitive trial. Even in a randomized trial, though it's a little bit different, it's molecularly based, and everybody gets DFMO, and then they get randomized to have maintenance DFMO or not. But even in that setting of a randomized trial, we will not have the answer, ever. The closure date for that trial is 2032, so it was just another comment that I wanted to make.

DR. LIEU: Thank you so much.

Okay. I'm going to summarize as best I can the discussion for questions 1 and 2. In regards

to question 1, with the strengths and the limitations of the externally controlled trial results, I think that there's a sincere appreciation for the effort that's gone in to match the external control as best as possible to the study population that's being investigated.

I think there are significant concerns from the group about setting precedent in regards to utilization of an external control, and there are also concerns and debates of not having consensus in whether or not a randomized-controlled control trial could be performed in the setting; mainly, if the hazard ratio is as robust as is proposed through this application, what the sample size would look like and what the time frame would look like. But overall, it seems like in regards to the external control, there is not significant consensus among the panel in regards to the dependability or reliability of using that, as well as the concerns about what future studies will look like.

In regards to question 2, it seems that the

preclinical data are certainly with a trusted model and provide some strength of evidence, but of course the concern in regards to any preclinical data -- or even the clinical data that were provided -- it's certainly limited in terms of what its true clinical application can be. But I think it does kind of point at least to some believable, at least, efficacy in the model being used, and that that model is believable, but very few comments on the other provided clinical data beyond the external control.

With that summary, any other questions or comments before I move on?

(No response.)

DR. LIEU: Okay. Thank you so much for your comments in regards to both of these discussion questions. We will now proceed to question 3, which is a voting question. Dr. Frimpong will provide the instructions for voting.

DR. FRIMPONG: Thank you, Dr. Lieu.

This is Joyce Frimpong, designated federal

officer. Question 3 is a voting question. Voting members will use the Zoom platform to submit their votes for this meeting. If you are not a voting member, you'll be moved to a breakout room while we conduct the vote.

After the chairperson reads the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, we will announce that voting will begin. A voting window will appear where you will submit your vote. There'll be no discussion during the voting session. You should select the button in the window that corresponds to your vote. Please note that once you click the submit button, you will not be able to change your vote.

Once all voting members have selected their vote, I will announce that the vote is closed. Please note that there will be a momentary pause as we tally the vote results and return the non-voting members into the meeting room. Next, the vote results will be displayed on the screen. I'll read the vote results from the screen into the record.

Thereafter, the chairperson will go down the list and each voting member will state their name and their vote into the record. Voting members should also address any subparts of the voting question, including rationale for their vote.

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

(No response.)

DR. ALEXANDER: Well, I have a question about the question.

DR. FRIMPONG: In regards to the wording of the question?

DR. ALEXANDER: Yes. I'm just wondering are we being asked whether we think there's substantial evidence of efficacy essentially consistent with the statutory thresholds, or is sufficient evidence supposed to suggest some other threshold other than the statutory threshold of substantial evidence?

DR. FRIMPONG: Dr. Lieu, I don't know if we would defer to the review division, if they could provide any clarification.

DR. LIEU: Absolutely.

Dr. Drezner, do you have a comment in regards to the question regarding the voting question?

DR. DREZNER: Yes. Sure. The voting question is intended to really refer to the totality of the evidence that includes both the externally controlled trial and the available supportive data. The question of substantial evidence of effectiveness is considered to be a regulatory determination that we will make, and we'll be utilizing the committee's discussion and conclusion on both the results of the ECT and the nonclinical and clinical supportive data in our assessment. So when we say sufficient evidence, we're asking the totality of the evidence presented; can you conclude that DFMO improves event-free survival?

DR. LIEU: Thank you.

Again, let me read the question into the record, and then bring it up for questions and comments. Has the applicant provided sufficient

evidence to conclude that DFMO improves event-free survival in patients with high-risk neuroblastoma?

Dr. Shaw, you have a comment or a question?

DR. SHAW: Yes. Thank you. Pamela Shaw, Kaiser Permanente. This is a clarifying question. I'm wondering if I'm supposed to interpret this as, has there been evidence provided that DFMO has improved event-free survival in all patients with high-risk neuroblastoma? Just thinking about our discussion leading into this, the trial was in a very highly selected group of patients who did not fail that upfront therapy, et cetera, et cetera. So I'm not sure how to react to this question, if I thought -- I don't know how to interpret this question, what I should be voting on.

DR. DREZNER: Sorry. It's for the intended indication, so patients with high-risk neuroblastoma who have completed and are in remission after upfront multimodality therapy. Thank you for making that clarification.

DR. SHAW: Thank you so much.

DR. LIEU: Thank you.

Any additional questions or comments in regards to the voting question?

DR. PAPPO: So when evaluating this, we take into consideration all the different caveats and all the lack of data that is there. We need to take into consideration the whole totality of the data presented. I also feel a little bit uncomfortable answering the question just like this.

DR. DREZNER: Yes. It's intended to be a totality of the data question.

DR. LIEU: Dr. Alexander?

DR. ALEXANDER: I mean, all of the information that you've given us is pegged to statutory and evidentiary thresholds. I mean, the whole point about generally two adequate and well-controlled -- or sometimes one plus -- confirmatory evidence, and this type of thing increases the likelihood of evidence truly being confirmatory, you've given us all of this information, and I guess it's just a little curious. I understand you're not asking us do we

want this approved, but it's just curious that you're asking this level of sufficiency rather than whether we think that there's substantial evidence, but maybe that's more of a comment than a question.

DR. LIEU: Any additional comments or questions?

DR. DREZNER: I think Dr. Donoghue or Dr. Kluetz are going to chime in.

DR. KLUETZ: Hey. This is Paul Kluetz from FDA, the Oncology Center. We presented the statutory requirements for substantial evidence, including a single adequate and well-controlled trial with confirmatory evidence, and that's what was presented. So if that helps, the question is to be framed around, is this consistent with that approach, a single adequate and well-controlled clinical trial with confirmatory evidence, if that helps.

DR. ALEXANDER: Thank you.

DR. LIEU: Thank you, Dr. Kluetz.

Any additional comments or questions?

(No response.)

DR. LIEU: Okay. If there are no further questions or comments concerning the wording of the question, we will now begin the voting on question 3.

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

(Voting.)

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

(Pause.)

DR. FRIMPONG: There are 14 yeses and 6 noes, and no abstentions.

DR. LIEU: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also include the rationale for your vote. We will start from the top of the list, so we will start with Dr. Kim.

DR. KIM: Thank you. I voted yes, and I voted yes based on the discussion that was had and evidence that was presented. I felt that in the indication that was asked, of patients that had

received upfront therapy, that have gone into remission, in this narrow population of patients, I felt that the applicant and the FDA in their analysis demonstrated a positive effect size. And although some of the unknown biases could not all be accounted for, after adjusting for many of the known and potential unknown biases, the effect size still seemed to have remained.

Of note, the addition of DFMO will not change the outcome in terms of the toxicity less than the late effects of the upfront therapy, but I felt that the data presented did improve the efficacy of event-free survival, and I felt that the nonclinical animal data was also compelling. Thank you.

DR. LIEU: Thank you, Dr. Kim.

Dr. Asgharzadeh?

DR. ASGHARZADEH: I voted yes. I think I made some of my points earlier, but I applaud FDA and the sponsor. I think these types of analyses need to be done in the pediatric cohort, and this may be a good precedent. There are easily

circumstances where we could avoid this, and in certain diseases, there are sufficient patients to do a randomized trial quickly. But I felt in this setting that the evidence shows that DFMO is effective. The preclinical studies are also compelling with the use of TH-MYCN models. So for those reasons, I approved -- or I answered yes to the question.

DR. LIEU: Thank you.

Dr. Alexander?

DR. ALEXANDER: Yes. I'll say this is one of the tougher advisory committees I've participated in, in terms of managing uncertainty. I do believe the product works to some degree, that is, if I gambled, which I don't, and if I had to put my money down, it would be in favor of DFMO. I am hedging my response to some degree insofar as I asked literally the question posed.

I'm not clear that the evidence that we've reviewed meets statutory thresholds, and I also think FDA has to be careful what they wish for and the ways that any favorable decision here may have

significant consequences on future drug development and be precedent-setting. I'm also not confident that an RCT is infeasible, and while on the one hand this may seem like water over the dam, on the other it's actually a contextual factor that -- I think we heard, based on guidance -- should be considered about what constitutes substantial evidence.

I also would echo my prior comment that I really think that I hope that the FDA will consider, as they make any final decision, a more careful assessment of the product in other settings, if only to conclude that those settings are not applicable here because of differences in tumor biology, or study designs, or outcomes, or something, because there is a wealth of data about this product in other settings, and I just can't imagine that a regulatory decision would be made blind to that evidence.

My vote was non-trivially influenced by the comments from our toxicologist and I think another maybe physician or scientist who know the animal

models much better than I do and seem to vouch for their translational merits to humans. I do have concerns about selection effects into Study 3b, but I have a hard time believing -- again, if I had to put my money down -- that selection effects could fully explain the magnitude effects that we've seen. These sorts of advisory committees are always educational, and it's a privilege to be able to contribute and learn from all of you. Thank you.

DR. LIEU: Thank you.

Dr. Shaw?

DR. SHAW: Yes. Thank you very much. Pamela Shaw, Kaiser Permanente. I really do agree with a lot of the sentiments, particularly Dr. Alexander who just spoke, in that this was a difficult decision in terms of managing uncertainty, but we have to make a binary decision here. So I thought it would be good to clarify how I interpreted that the question was, really, is there sufficient evidence for a favorable risk-benefit balance in this highly selected

population?

When I think about that risk-benefit balance, it's kind of a decision theory thing here, where I'm thinking about the probability of this benefit and how strong I think that probability is, and just the reward, if there is that probability and if it is efficacious in this population, which is an unmet need, and a lot of detrimental -- we saw a very poor prognosis for many patients. There is a possibility of a big benefit when we're managing the uncertainty of what that size is and how much selection we think there is.

But just given how much of a reward there could be, that really did weigh in because I think the risks are very low, it's highly tolerated of this immunotherapy, and I do think there was really robust and interesting analyses that were done to address every possible confounder that folks could think of, and were measured, and that definitely weighed favorably for me. So those are just some thoughts, and I appreciate this process. I thought it was a very good discussion today. Thank you.

DR. LIEU: Dr. Twist?

DR. TWIST: I voted no, and I echo other folks mentioning how this was a challenging decision and also really thought that the thoroughness of the analysis was quite impressive. Ultimately, I voted no because I was going back to the guidelines, as I understood them from the FDA, that in order to establish substantial evidence of effectiveness, a single adequate and well-controlled trial must be accompanied by sufficient confirmatory evidence. And particularly for an agent that is thought to work through a cytostatic mechanism, I just was not convinced that what was presented met this benchmark, and that's why I voted no.

DR. LIEU: Thank you.

Dr. Widemann?

DR. WIDEMANN: Yes. Thank you so much. I was very impressed with both the applicant and the FDA with the really tremendous analysis that was performed. I have to admit I would have liked -- and I still believe, why wasn't a

randomized-controlled trial done earlier on, but I think the analysis that was done, including the propensity score and the blinded independent analysis, was really phenomenal and potentially could show us a way for future drug development for other diseases as well.

I do think that the preclinical data was somewhat compelling, as well as the limited clinical data provided, for example, in patients with relapsed disease. I do think that confirmatory studies, in my mind, would be needed. Dr. Alexander raised a few really important points that I think are important, but working in the rare disease space, I do think we will get these questions more. And while this raises for neuroblastoma I think many important drug development questions, I do think it's good they are raised, and hopefully this would be one way for us to approach this jointly. I really appreciate the meeting today and the discussion. Thank you.

DR. LIEU: Dr. Widemann, just for the record, you voted?

DR. WIDEMANN: Yes. For the record, I voted yes for the evidence. Sorry.

DR. LIEU: No worries.

Dr. Gradishar?

DR. GRADISHAR: I voted yes, and I think my response is based on the totality of the evidence, even with the limitations that so many others have pointed out. I work in a space where there are huge numbers of patients, as opposed to this particular indication, and I think the preclinical mechanistic data supports the effect that we saw in the trial, so I was persuaded by that. Then the clinical data, even with the limitation of confounding factors that we don't quite know what they might be, the selectivity, the highly selective group of patients that were in this particular trial, I still see an effect from the drug, and I would certainly concur that it's worthy of approval in this particular setting.

The other influencing thing, I think, is clearly that there's no data set immediately on the horizon that's going to provide any more clarity

with ongoing trials that may be out there, and furthermore, if there were a randomized trial done, even if there is some feasibility to considering it, that is still many years out before we'd have any information. So I voted yes, and those are my comments.

DR. LIEU: Thank you.

Mr. Mitchell?

MR. MITCHELL: Yes. First of all, I want to thank the sponsor and the FDA for all of the work to analyze the data and try to give us the clearest picture. Given the unmet need using the best available evidence, where a randomized-controlled trial apparently isn't feasible for this drug, and given all the sensitivity studies, I voted yes.

DR. LIEU: Thank you.

Dr. Vasan?

DR. VASAN: Hi. Neil Vasan. I voted no. I applaud the FDA and the applicant for their rigorous analyses in their application files. Given the large effect size, I believe a randomized

trial could be conducted, which would rule out other confounders that were discussed. I do want to say that I think that the conceptualization, development and analysis of this application will serve as a model for future drug development, and I would like to thank the patients and their families for sharing their compelling personal stories. Thank you.

DR. LIEU: Thank you.

Dr. Unguru?

DR. UNGURU: I voted yes, and like many of the speakers before me, I struggled. My vote yes, like Doctor Alexander and some others stated, based on how I understood the intent of the specific question we were asked, the research ethicist in me clearly was influenced by two factors beyond the data. One was the patients' and the patient surrogates' interests and values, and the other was equipoise.

I am far from a biostatistician or an epidemiologist, but hearing the thoughtful debate, the well presented information by both the FDA and

the sponsor, as well as the commentators, it seems that there is equipoise. So those combinations of factors, along with how the question was presented, resulted in my vote for a yes. And I applaud the FDA for the willingness to take this approach because, yes, a randomized-controlled trial is our gold standard and should continue to be, but there are extenuating circumstances. So the willingness to think in this manner I think is a good one. Thank you.

DR. LIEU: Thank you.

Dr. Weiss?

DR. WEISS: This is Brian Weiss. I voted no, for all the reasons outlined by Dr. Twist and Vasan. I also want to thank the families that spoke, the patient that spoke, and I do think it was a complete analysis of the data, so thank you.

DR. LIEU: Thank you.

My name is Chris Lieu. I voted yes. I believe that the data for event-free survival is compelling, but I don't believe that the efficacy is as high as what's been reported because of the

lack of randomization, and what I honestly believe is just an inherent bias in an external control that likely overestimates the benefit of DFMO. But I believe the FDA's additional analysis to deal with these confounding variables was compelling and that they were generally consistent with the primary analysis.

Having said that, this is a therapeutic that has relatively lower toxicity compared to what we typically discuss and in regards to other interventions, and I believe that the expected benefits outweigh the risks of treatment here, and I'm not sure we should wait an additional 8 years to answer that question.

Dr. Spratt?

DR. SPRATT: I voted no. I think, as you have stated, the FDA states for substantial evidence. It requires a design which permits a valid comparison with a control. This is an area of my own research, that data consistently demonstrates that non-randomized data agree with randomized trial effect sizes no more likely than

chance alone, and that has been shown in multiple large studies. So you can find instances where they can agree, but it is no more than chance alone here.

So the effect sizes, which even what the chair just stated and many others here, if you cannot rely on what they are and you're using your gut instinct, or that there were certain statistical analyses done to determine benefit, if you can't rely on those estimates, that's a huge problem. And if they're not reliable, it brings in the chance that there is no benefit. And if they are very reliable, which I hope they are for patients because we all want to help these patients, then a very small trial could be done.

Study 3b itself, if it was randomized, if those effect sizes were real, would have been large enough. Because there was no response data shown to strengthen results, that limits my ability to say this is effective. There are no approvals in other cancers that limit the ability for me to determine the result. These animal models, while

they may be good animal models, there is yet in almost any cancer an animal model that translates 1 to 1 into a human; hence, why we do human studies.

I think we need to be very careful. Stating a randomized trial is unethical is very dangerous, and there have been numerous examples we don't have time to state, that we've realized that error. There's been over 75 phase 3 randomized trials in pediatrics in even more rare disease than this, so I do believe it's feasible, and I disagree with multiple people that the overall survival data is not relevant. It is relevant because that is a source to show us that confounding is there.

And lastly, for me as someone who treated pediatric cancer patients for a large part of my career and have children, about 10 percent will say 4-year EFS benefit. That means that if you do not approve this, that's about 320 kids over 8 years that may relapse because they did not get this drug, but if it is something that's approved, that's over 3,000 children that are exposed to

something that has financial toxicity, as well as real side effects. So if a randomized trial was done in 2015 when recommended, as well as stated in the publication by the authors that they would do, then we would have that answer today for all the kids in the country. Thank you.

DR. LIEU: Thank you.

Dr. Conaway?

DR. CONAWAY: Yes. I voted yes. It was a very difficult decision. I eventually voted yes despite lots of misgivings about the lack of an RCT and the potential setting of precedents. Overall, I thought that the extensive analyses, confirmatory data, provided enough evidence of a favorable benefit-risk ratio for this agent on PFS.

DR. LIEU: Thank you.

Dr. Cosenza?

DR. COSENZA: Yes. I voted yes. My vote was largely based on the strength of the preclinical data and the validity of the transgenic animal model. And although preclinical data is rarely used as supportive evidence this way, it

does seem like this is a compelling case to consider doing so. I also think that the analysis of the externally controlled data was fairly rigorous, given the challenges of this type of data and the rareness of the disease. And lastly, as a toxicologist, as others have noted, this certainly is less toxic than other things that we use in treating all types of patients, particularly cancer patients. Thank you.

DR. LIEU: Thank you.

Dr. Nieva?

DR. NIEVA: Thank you. I voted yes. I think the external control coming from a trial population and not a general population certainly gives me a lot of comfort regarding confounders. Also, this is a disease that's really solely treated by people with specialty expertise. I trust those experts to understand the limitations of the data, and ultimately it will be those physicians that should have the option to decide for the individual patient if the data package is appropriate and treatments outweigh the risks.

I'd like to point out I am bothered by the lack of objective criteria by either the agency or the sponsor to make a determination of when a randomized clinical trial can be performed, but I do note that it took 15 years to accrue the referenced 0032 trial compared to 4 years for the DFMO trial. And if the new treatment means that there are more patients who survive who wouldn't otherwise have a delay, I think there's a certain value to that. Slowing drug access has a cost, both in lives, as well as capital investment that's actually required to complete these trials, and tying up 15 years of capital to get that clinical trial done ultimately translates to financial toxicity for the patients.

I would like to compliment the FDA's statistical team for the multiple sensitivity analyses that they've performed, which really, I think, gives a lot of confidence to how we interpret these data sets. Thank you.

DR. LIEU: Thank you.

Ms. McMillan?

MS. McMILLAN: Yes. I voted yes based on the data presented and the discussion, and I actually particularly agree with Dr. Lieu's voting comments. I support this kind of flexible approach for the rare disease population, and I'm pretty confident that it will not inspire an uncontrollable slippery slope of precedents. That's all.

DR. LIEU: Thank you.

Dr. Parsons?

DR. PARSONS: Yes. I voted yes on the basis -- actually, I came in as a bit of a skeptic of this type of trial mechanism and still have some concerns about it. I was very impressed with the data presented, and the plan, and the rigor of the analyses and various subanalyses done by the sponsor, as well as the FDA. In the end, it led me to pretty strongly believe a favorable risk toxicity benefit ratio of the agent.

I do have to say that I think the debate about whether a randomized trial would have been relevant in 2015 is a different debate from whether

I could reasonably think that would be done now, in 2023 to 2024. The former, I think we could have a lot of discussion; the latter about now, I don't think this is a trial that could feasibly be done, given the the data available on these relatively small number of patients. I don't think, ethically and practically, it would likely be a successful trial, so I voted yes on the basis of those thoughts.

DR. LIEU: Thank you.

Dr. Sturmer?

DR. STURMER: Yes. I want to start with highlighting that I do realize that all data presented and discussed are based on real patients, their families, and doctors dealing with a terrible disease and difficult decisions about optimum treatment. This was, again, a very difficult vote, as for others, because [indiscernible] are likely mainly based on lack of randomization. I do think, however, that the data are fit for purpose. Lack of randomization, however, requires slow assessment of selection processes and, unfortunately, I have

not been presented with enough information on selection processes, both into the 3b cohort and into the matching pool for the comparator, to conclude that there is sufficient evidence for an effect. Just to be clear, I do think that all my concerns could be addressed without the need to collect additional data, nor the need for a randomized trial. Thank you.

DR. LIEU: Thank you.

Dr. Pappo?

DR. PAPPO: Yes. I voted no. It was a very difficult decision. I was going to abstain, actually, but I felt that perhaps a vote would make a big difference in how this moves forward or not. I'm still very concerned about the unmeasured confounding variables, and was also still concerned about the wording of the question. When you put the totality of the data together, that sounds like, yes, this is fantastic, but then I started thinking about the repercussions of this. How is this going to affect patients in the future for clinical trials? How is this going to affect their

ability to be enrolled in clinical trials? How is this going to affect the interpretation of data for future clinical trials that may have TKIs or new forms of immunotherapy?

So that's what's making me extremely nervous. And in the absence of a randomized study, I just feel very uncomfortable saying that this drug should be routinely incorporated in the treatment of patients with neuroblastoma if they have achieved a complete response after all therapy and immunotherapy.

DR. LIEU: Thank you so much, Dr. Pappo.

Okay. I'm going to try and summarize all of these comments, which are truly wonderful. I think that the general consensus is that there's a tremendous amount of difficulty interpreting this kind of data in a rare disease, and there's sincere appreciation for the panel for all the work that went into this incredibly robust analysis.

I'll just say, there are some sources of general agreement. It's certainly not consensus, but the general consensus, or agreement, is that

the totality of data appear to support the assertion that DFMO does improve event-free survival, or at least that the results were more likely than not to be something more than just a result of chance. This was given the robustness and the uniqueness, I would say, of the external control, and there's also significant trust in the preclinical model, and I believe the comments in the discussion regarding the preclinical data were honestly instrumental in shaping some of that opinion.

There are clear areas of disagreement within the panel, and that is whether this type of data should really ever be used, given the concern regarding confounders and biases that are just inherent in these types of external controls. Certainly, there's a lot of concern from the group about what the future holds for drug development and what level of evidence the FDA will require in similar situations in the future, and I think there are some concerns about a slippery slope, and then others on the panel that are not worried about that

type of slippery slope.

There's also some disagreement in this group about whether a randomized-controlled trial is potentially feasible and whether it could be done in a timely fashion. But I think we have to appreciate how incredibly difficult of an application this was to discuss for all the reasons mentioned, but a sincere appreciation to the FDA, the applicant, our open hearing speakers, and the panel members for all of the work, discussion, and these incredible comments, and obviously just the desire and the care to provide the best possible therapies for all of our patients.

Before we adjourn, are there any last comments from the FDA?

DR. DREZNER: No. I think we just want to thank everybody for their participation.

Adjournment

DR. LIEU: Thank you so much. We will now adjourn the meeting. Thank you, everybody.

(Whereupon, at 3:35 p.m., the meeting was adjourned.)