FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Virtual Meeting

Friday, October 28, 2022

10:00 a.m. to 2:35 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Philip Bautista, PharmD, MPH

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Christopher H. Lieu, MD

(Acting Chairperson)

Associate Professor of Medicine

Associate Director for Clinical Research

co-Director, Gastrointestinal Medical Oncology

University of Colorado Cancer Center

Aurora, Colorado

David E. Mitchell

(Consumer Representative)

Founder, Patients for Affordable Drugs

Bethesda, Maryland

Jorge J. Nieva, MD

Associate Professor of Clinical Medicine

Section Head, Solid Tumors

University of Southern California (USC)

Norris Comprehensive Cancer Center

Keck School of Medicine of USC

Los Angeles, California

Neil Vasan, MD, PhD

Assistant Professor

Division of Hematology & Oncology

Department of Medicine

Herbert Irving Comprehensive Cancer Center

Columbia University Medical Center

New York, New York

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBER

(Non-Voting)

Jonathan D. Cheng, MD

(Industry Representative)

Head of Oncology Development

Global Drug Development

Bristol-Myers Squibb

Lawrenceville, New Jersey

TEMPORARY MEMBERS (Voting)

Rochelle Bagatell, MD

Professor of Pediatrics

Division of Oncology, Department of Pediatrics

The Children's Hospital of Philadelphia

University of Pennsylvania

Philadelphia, Pennsylvania

Natia Esiashvili, MD

Professor

Department of Radiation Oncology

Winship Cancer Institute

Emory University

Atlanta, Georgia

David Harrington, MA, PhD

Professor of Biostatistics (Emeritus)

Dana-Farber Cancer Institute and Harvard T.H.

Chan School of Public Health

Boston, Massachusetts

Michael Hudgens, PhD

Professor and Associate Chair

Department of Biostatistics

Gillings School of Global Public Health

University of North Carolina at Chapel Hill

Chapel Hill, North Carolina

Michele Jonsson Funk, PhD, FISPE

Associate Professor of Epidemiology

Director, Center for Pharmacoepidemiology

Gillings School of Global Public Health

University of North Carolina at Chapel Hill

Chapel Hill, North Carolina

E. Anders Kolb, MD

Director, Nemours Center for Cancer and

Blood Disorders

Nemours Children's Health

Wilmington, Delaware

Professor, Department of Pediatrics

Sidney Kimmel Medical College at

Thomas Jefferson University

Philadelphia, Pennsylvania

Tobey J. MacDonald, MD

Aflac Endowed Chair for Pediatric Neuro-Oncology

Professor of Pediatrics

Director, Pediatric Neuro-Oncology Program

Aflac Cancer & Blood Disorders Center

Children's Healthcare of Atlanta

Emory University School of Medicine

Atlanta, Georgia

Gianna (Gigi) McMillan, D.Bioethics

(Patient Representative)

Professor of Research Ethics, Graduate Division

Associate Director, Bioethics Institute

Loyola Marymount University

Los Angeles, California

Julie R. Park, MD

Professor of Pediatrics

Division Pediatric Hematology Oncology

University of Washington School of Medicine

Seattle Children's Hospital

Seattle, Washington

Donald (Will) Parsons, MD, PhD

Sidney L. and Donald F. Faust Chair of Pediatric Cancer Precision Medicine
Texas Children's Hospital
Deputy Director, Texas Children's Cancer and Hematology Center
Associate Professor, Department of Pediatrics, Section of Hematology-Oncology
Baylor College of Medicine
Houston, Texas

Nita Seibel, MD

Head, Pediatric Solid Tumor Therapeutics
Clinical Investigations Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute (NCI)
National Institutes of Health (NIH)
Bethesda, Maryland

Brigette Widemann, MD

Chief, Pediatric Oncology Branch

Center for Cancer Research

NCI, NIH

Bethesda, Maryland

FDA PARTICIPANTS (Non-Voting)

Richard Pazdur, MD

Director, Oncology Center of Excellence (OCE)

Director (Acting)

Office of Oncologic Diseases (OOD)

Office of New Drugs (OND), CDER, FDA

Paul Kleutz, MD

Deputy Director, OCE

OOD, OND, CDER, FDA

Gregory Reaman, MD

Associate Director for Pediatric Oncology, OCE

Associate Director for Pediatric Oncology

OOD, OND, CDER, FDA

Harpreet Singh, MD

Director

Division of Oncology 2 (DO2)

OOD, OND, CDER, FDA

Martha Donoghue, MD

Acting Associate Director for Pediatric and Rare Cancer Drug Development, OCE

Deputy Director

DO2, OOD, OND, CDER, FDA

Donna Rivera, PharmD, MSc

Associate Director for Pharmacoepidemiology

OCE, FDA

Amy Barone, MD

Cross-Disciplinary Team Leader

DO2, OOD, OND, CDER, FDA

Gautam Mehta, MD

Central Nervous System Cancers, Pediatric

Solid Tumors, Rare Cancers

DO2, OOD, OND, CDER, FDA

Somak Chatterjee

Visiting Associate

Division of Biometrics V

Office of Biostatistics

Office of Translational Sciences, CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(10:00 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're not speaking. For media and press, the FDA press contact is Chanapa Tantibanchachai. Her email and phone number are currently displayed.

My name is Dr. Christopher Lieu, and I'll be chairing this meeting. I will now call the October 28, 2022 Oncologic Drugs Advisory Committee meeting to order. Dr. Phil Bautista is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. BAUTISTA: Good morning, everybody. My name is Phil Bautista, and I'm the acting designated federal officer for this meeting. When I call your name, please introduce yourself by saying your name and affiliation.

Dr. Lieu?

DR. LIEU: Good morning everybody. My name is Chris Lieu, and I'm a GI medical oncologist at the University of Colorado Cancer Center.

DR. BAUTISTA: Mr. David Mitchell?

MR. MITCHELL: I'm David Mitchell. I'm the consumer representative to the ODAC. I am a cancer patient, and I am founder of Patients for Affordable Drugs.

DR. BAUTISTA: Thank you.

Dr. Nieva?

DR. NIEVA: Hi. I'm George Nieva. I'm an associate professor at the University of Southern California, Norris Comprehensive Cancer Center, and I'm a medical oncologist specializing in thoracic oncology.

DR. BAUTISTA: Dr. Vasan?

(No response.)

DR. BAUTISTA: Hi, Dr. Vasan. Are you able to unmute yourself and introduce yourself for the record?

(No response.)

DR. BAUTISTA: I will come back to Dr. Vasan

once he returns.

Dr. Cheng?

DR. CHENG: Good morning. Jon Cheng. I am the industry rep, and I am a medical oncologist by background, and I work for Bristol-Myers Squibb.

DR. BAUTISTA: Thank you.

Dr. Bagatell?

DR. BAGATELL: Hi. My name is Ro Bagatell. I'm a pediatric oncologist at the Children's Hospital of Philadelphia.

DR. BAUTISTA: Dr. Esiashvili?

DR. ESIASHVILI: Hi. I'm Dr. Natia Esiashvili. I'm from Emory University. I'm a radiation oncologist specializing in pediatric tumors.

DR. BAUTISTA: Dr. Harrington?

DR. HARRINGTON: Hi. This is Dave Harrington, biostatistician, Dana-Farber Cancer Institute and the Harvard School of Public Health.

DR. BAUTISTA: Dr. Hudgens?

DR. HUDGENS: Hi. This is Michael Hudgens, professor of biostatistics, University of North

Carolina, Chapel Hill.

DR. BAUTISTA: Dr. Jonsson Funk?

DR. JONSSON FUNK: Hello. This is Michele Jonsson Funk. I'm an associate professor of epidemiology at the University of North Carolina, and I direct the Center for Pharmacoepidemiology here.

DR. BAUTISTA: Dr. Kolb?

(No response.)

DR. BAUTISTA: Hi, Dr. Kolb. Are you available to unmute yourself and introduce yourself for the record?

(No response.)

DR. BAUTISTA: Alright. We'll come back to Dr. Kolb once he's reconnected.

Dr. MacDonald?

DR. MacDONALD: Hi. this is Toby MacDonald. I'm professor of pediatrics at Emory University, and I direct the pediatric neuro-oncology program at Children's Healthcare of Atlanta.

DR. BAUTISTA: Dr. McMillan?

DR. McMILLAN: This is Gigi McMillan. I am

at the Bioethics Institute at Loyola Marymount University in Los Angeles. I'm professor of research ethics, and I'm the patient representative for this meeting.

DR. BAUTISTA: Thank you.

Dr. Park?

DR. PARK: Good morning. I'm Julie Park. I'm a professor in the Department of Pediatrics at the University of Washington School of Medicine, and I practice as a pediatric hematologist/ oncologist at Seattle Children's Hospital.

DR. BAUTISTA: 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. BAUTISTA: Dr. Seibel?

(No response.)

DR. BAUTISTA: Hi, Dr. Nita Seibel. Are you available to unmute yourself and introduce yourself for the record?

(No response.)

DR. BAUTISTA: Dr. Seibel, I can't hear you.

You might be double-muted.

(No response.)

DR. BAUTISTA: Alright. We'll move on to Dr. Widemann.

DR. WIDEMANN: Good morning. Brigette Widemann. I'm the chief of NCI's pediatric oncology branch, and I'm a pediatric oncologist.

DR. BAUTISTA: Alright. Dr. Vasan, are you able to unmute yourself and introduce yourself for the record?

DR. VASAN: Yes. Hi, everyone. Good morning. I'm Neil Vasan. I'm a breast oncologist and physician scientist at Columbia University, Herbert Irving Comprehensive Cancer Center.

DR. BAUTISTA: And we'll try Dr. Seibel again.

Dr. Seibel, are you available to introduce yourself for the record? You're still muted.

(No response.)

DR. BAUTISTA: Once Dr. Seibel and Dr. Kolb return, we'll ask them to introduce yourselves for the record, but in the meantime, we'll go ahead and

move on.

With that, I'll turn it back to Dr. Lieu, if you will.

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 break or lunch. Thank you.

Dr. Phil Bautista, will now read the Conflict of Interest Statement for this meeting.

DR. BAUTISTA: Hi, all. This is Phil Bautista. I apologize. I forgot to introduce the FDA participants, after which I will do the Conflict of Interest Statement.

So why don't I start first with Dr. Pazdur.

Could you unmute yourself and introduce yourself?

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

DR. BAUTISTA: Dr. Paul Kleutz?

DR. KLEUTZ: Hi. I'm Paul Kleutz, a medical oncologist and deputy director of the Oncology Center of Excellence at the FDA.

DR. BAUTISTA: Dr. Reaman?

DR. REAMAN: Good morning. I'm Gregory

Reaman, the associate director for Pediatric Oncology at the Oncology Center of Excellence.

DR. BAUTISTA: Dr. Singh?

DR. SINGH: Harpreet Singh, medical oncologist, director of the Division of Oncology 2.

DR. BAUTISTA: Dr. Donoghue?

DR. DONOGHUE: Martha Donoghue. I'm a pediatric oncologist. I'm the deputy division director of the Division of Oncology 2 and the acting associate director for Pediatric and Rare Cancer Drug Development in the Oncology Center for Excellence.

DR. BAUTISTA: Dr. Rivera?

DR. RIVERA: Hi. Donna Rivera, associate director for pharmacoepidemiology, Oncology Center of Excellence.

DR. BAUTISTA: Dr. Barone?

DR. BARONE: Good morning. Amy Barone, the pediatric oncologist and the clinical team leader in the Division of Oncology 2.

DR. BAUTISTA: Dr. Mehta?

DR. MEHTA: Good morning. Dr. Mehta. I'm a

neurosurgeon and a clinical reviewer in the Division of Oncology 2.

DR. BAUTISTA: Dr. Chatterjee?

DR. CHATTERJEE: Hi. Good morning. Somak Chatterjee, statistical reviewer in the Division of Biometrics V.

Conflict of Interest Statement

DR. BAUTISTA: Thank you so much.

Alright. I'll go ahead and read the Conflict of Interest Statement.

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

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

being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the 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 the discussion of biologics license application 761176, for 131 iodine-omburtamab solution for injection, submitted by Y-mAbs Therapeutics, Incorporated. The proposed indication, use, for this product is for the treatment of central nervous system/leptomeningeal metastases in pediatric patients with neuroblastoma following standard multimodality treatment for CNS disease.

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

members and temporary voting members to disclose any public statements that they may have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Jonathan Cheng is participating in this meeting as a 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 the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any other financial interest or relationships they may have with the firm at issue. Thank you.

Dr. Lieu?

DR. LIEU: Thank you, Dr. Bautista.

We will proceed with FDA introductory remarks from Dr. Amy Barone.

FDA Introductory Comments – Amy Barone

DR. BARONE: Thank you, Dr. Lieu.

Good morning. My name is Amy Barone. I'm a pediatric hematologist/oncologist in the Division of Oncology 2, and I am the cross-disciplinary team leader for the application for i-131 omburtamab, a radiolabeled monoclonal antibody. I will refer to Y-mAbs as the applicant and to i-131 omburtamab as omburtamab for the remainder of the presentation.

The applicant is seeking traditional approval for omburtamab for the treatment of pediatric patients with neuroblastoma following standard multimodality treatment for CNS disease. Omburtamab is given as an intraventricular infusion through an Ommaya reservoir or similar device, and the proposed dosage ranges from 25 to 50 millicuries based on patient age. Because the application relies on overall survival endpoint,

which is a direct measure of clinical benefit, the appropriate approval pathway is traditional approval.

FDA is bringing this application to the Oncology Drug Advisory Committee to enable public discussion, as we do not have confidence that a treatment effect of omburtamab on overall survival has been established. The evidence submitted by the applicant to support the efficacy of omburtamab relies primarily upon overall survival results from Study 03-133, a single-center, single-arm trial.

Study 03-133 was conducted exclusively at Memorial Sloan Kettering Cancer Center and was initially designed as a dose-finding study not intended to support a marketing application. However, based on preliminary data, suggesting an improvement in overall survival compared to a historical control benchmark, the applicant obtained the rights to commercial development and proposed to use an external control population derived from a neuroblastoma registry to demonstrate that omburtamab improved survival in

patients with CNS relapse neuroblastoma.

Study 101 is a single-arm study initiated by the applicant in order to obtain a multicenter experience. Unlike Study 03-133, Study 101 systematically collected response data in order to characterize the overall response rate of omburtamab, and these data were reviewed as part of this application.

To provide context for this rare disease, I will first provide a brief background on neuroblastoma and how omburtamab fits into the treatment paradigm. I will then provide an overview of the regulatory framework for approval and the use of external controls, followed by an overview of Study 03-133.

Next, I will present the high-level issues related to establishing effectiveness. You will see today what appears to be an improvement in survival for patients treated with omburtamab compared to an external control. However, underlying differences between the control and study populations call into question the

appropriateness of the control chosen as a comparator and the ability to attribute any difference in survival to omburtamab. I will then review the discussion topic and voting question.

Neuroblastoma is the most common extracranial solid tumor in childhood, so only approximately 650 cases are diagnosed in the U.S. per year. CNS involvement is exceedingly rare and typically presents at the time of relapse in about 6 percent of patients. There are no FDA approved or curative therapies, however, patients in the U.S. who are well enough to be treated are often treated with some combination of surgery, radiation, and chemotherapy.

Omburtamab is a radiolabeled monoclonal antibody that binds B7-H3, which is overexpressed on neuroblastoma cells. Beta emission for iodine-131 then induces cellular damage. It is a local therapy delivered directly into the CSF space using an Ommaya reservoir or shunt.

The applicant proposes it is intended to treat the entire CFS compartment, including

micrometastatic disease. It is clear that omburtamab delivers radiation to the CSF space given this mode of delivery, however, the applicant has not provided evidence to support that omburtamab works through elimination of micrometastatic disease in the CNS or provided compelling evidence to support uptake of omburtamab in CNS metastases to the brain parenchyma.

To receive FDA approval, a drug or biologic product must demonstrate substantial evidence of effectiveness through adequate and well-controlled studies. This 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. This application attempts to demonstrate effectiveness based on overall survival data from one single-arm trial, Study 03-133, with supportive response rate data from Study 101.

For oncology studies, survival is considered the most reliable endpoint, as it is a direct

measure of clinical benefit, it's easy to measure, and it reflects safety. However, for a marketing application, overall survival is usually evaluated in the context of a randomized-controlled trial because it is important to distinguish the effect of the drug from other factors intrinsic to the patient and extrinsic factors such as approach to supportive care.

Objective response rate is a unique endpoint we have in oncology that can be assessed in a single-arm study since the effect on that endpoint is a direct measure of the intervention. Tumors do not typically regress on their own, and this is different from overall survival, which can be influenced by many factors.

As discussed in FDA guidance, overall survival should be evaluated in randomized studies, as survival can be impacted by factors other than drug treatment such as natural history disease or patient selection. Overall survival results from externally controlled trials can be uninterpretable, as differences between the study

and control populations may impact survival and designs for these trials can be very complex. Randomized studies minimize the effect of these known and unknown differences.

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 well-defined natural history, a high degree of similarity with regards to baselines in these characteristics and concomitant treatments, and evidence of change in the established progression of disease such as tumor shrinkage.

Patients with neuroblastoma have an undeniable unmet medical need, however, the natural history is not well characterized due to its rarity, and we have analyses from published literature and additional data from this application suggesting that survival has improved over time; the major review issues from this application, stem from important fundamental

differences in the external control, particularly with regards to concomitant treatment; as well as a lack of robust evidence to demonstrate that omburtamab shrinks CNS or leptomeningeal metastases.

Moving on to regulatory history, the applicant considered a randomized-controlled trial infeasible based on a suggested overall survival improvement in patients treated on Study 03-133 compared to a historical overall survival benchmark rate reported in the literature.

Early on, we cautioned on the complexity of the proposed external control design and consistently highlighted that the ability to interpret the data would largely depend on the comparability of the populations and the ability to isolate the treatment effect of omburtamab from other therapies. Throughout the many meetings we had with the applicant leading up to the submission, we stated that response rate data, including duration of response, would also be needed to establish effectiveness.

Again, Study 03-133 was a single-arm, single-center trial with a primary endpoint of overall survival. Protocol recommended treatment for CNS disease prior to receiving omburtamab included surgery, chemotherapy, and radiation. As we advised the applicant in prior meetings, the receipt of so much intensive treatment prior to administration of omburtamab would be an important prognostic variable when matching to a control and would likely make it difficult to determine if any effects on survival are due to omburtamab and not to those treatments.

The external control used for this study is derived from the Central German Childhood Cancer Registry, which includes almost all children diagnosed with cancer in Germany. Patients were selected who were thought to be most similar to those included in Study 03-133, particularly with regards to treatments received for their CNS disease. Eighty-five were identified who received treatment of any kind for their CNS relapse.

As you saw on the last slide, recommended

study treatment included three types of therapy. Due to sample size constraints, the applicant designed the control to include patients who received at least two types of treatment rather than three, one of which was radiation.

To further address the sample size issues of the control and because we did not know if treatment outcomes had improved over time, we encouraged the applicant to include outcomes from the control dating back to enrollment starting in 1990. This is in contrast to Study 03-133, which did not open until 2004.

This slide presents a summary of the applicant's primary analysis, which appears to show a marked difference in survival for patients treated in Study 03-133 in green compared to the external control in gold. When interpreting overall survival comparisons between the study and the control, it is important to keep in mind the extremely small sample size in the control population, 29 patients, which raises uncertainty regarding the apparent differences between arms.

You will note the confidence intervals for the hazard ratio are wide with the upper bound exceeding 1. If there is a survival difference, we question if that difference is due to omburtamab.

Patients in Study 03-133 had to be healthy enough to not only get to a tertiary center but to withstand intensive treatment of surgery, radiation, and chemotherapy, and to then have a reservoir surgically placed for the treatment with omburtamab. FDA's review of the data has also identified several other key differences in the population that would affect survival outcomes. It is possible, or even probable, that the combination of these factors is responsible for the difference seen here. You will see in Dr. Mehta's talk later that as we attempt to control for some of these factors, the curves nearly overlap.

FDA has identified three key issues regarding the level of evidence to demonstrate that the difference in survival, if any, is due to omburtamab. You will hear more about each of these in the subsequent slides and in Dr. Mehta's talk.

Briefly, the first and most important issue is that the external control is not a relevant comparator, and because of this, comparisons of survival are not reliable. We can also sometimes rely on response rate to establish effectiveness, however, this application does not provide reliable evidence of CNS or leptomeningeal responses to omburtamab.

Several key differences between the populations are highlighted here, and you will hear more detail about each one in Dr. Mehta's talk. Although the external control captures many key pieces of information regarding treatment of patients with neuroblastoma, we have the opportunity to intensively interrogate the data and, unfortunately, our review has identified important differences, rendering the registry population not fit for purpose as an external control.

Patients in Study 03-133 received treatment for their CNS disease that was generally more intensive than the treatment documented in the control. As mentioned earlier, the external

control data are not contemporaneous with the dates of enrollment in Study 03-133. Based on the data provided in this application, it does appear that survival in patients with CNS neuroblastoma has improved over time, but this is something we were not sure of prior to the review of the data. There are also unknown and unmeasured differences that have the potential to impact survival such as differences in the clinical care in the U.S. and in Germany.

The second major review issue is a direct result from the first review issue. In cases where an external control population is not sufficiently comparable to the study population to be considered fit for purpose, we would typically not review the data any further, as comparisons between dissimilar populations would not be interpretable. However, recognizing that regulatory flexibility is appropriate given the high unmet medical need, we decided to further analyze the data to see if this application could be salvaged.

As Dr. Mehta will describe in more detail in

his talk, we conducted multiple sensitivity analyses and saw that the differences in survival between the study and control populations were attenuated with hazard ratios approaching or exceeding 1 in many cases. These results reinforce that any apparent difference in survival cannot be reliably attributed to omburtamab.

However, it is important to keep in mind that we are in a very unusual situation where all the analyses you will see presented today by both the applicant and the FDA are post hoc descriptive analyses. We each chose different analyses populations and statistical methods, and you will notice that the results of the various analyses and the conclusions that can be drawn from them can be very different depending on the approach taken.

These differences in results across analyses highlight the high degree of uncertainty associated with relying on this external control to establish a causal role for omburtamab in any observed differences in survival between the populations.

Finally, although the analyses presented by

FDA reflect an approach that we consider fair, balanced, and scientifically rigorous, it is important to remain cognizant of the limitations in interpreting any analysis due to the known and unknown differences between the population to confounding, and to the small sample sizes of the external control. We do not think that any statistical method can successfully mitigate the uncertainty created by these limitations to allow comparisons between the population.

Finally, early on in development, we expressed concern that the ability to interpret the data would largely depend on the comparability of the populations, and given that uncertainty, we stated that robust response rate data would be needed to provide evidence of efficacy of omburtamab.

You will recall that the applicant provided response rate data from Study 101. Of the seven responses reported by the applicant, only four were confirmed by a second scan; and upon closer examination, we identified issues with the

characterization of each of these responses, making it difficult to draw reliable conclusions about the presence of a response in some cases, and in other cases, that an observed response was due to omburtamab given the close temporal relationships between administration of omburtamab and other CNS-directed treatments, particularly radiation. You will hear more detail on this from Dr. Mehta.

When considering these three major review issues, we have strong reservations regarding whether the applicant has provided sufficient evidence to demonstrate that a difference in survival, if any, is due to omburtamab. There are clinically important differences between Study 03-133 and the external control population derived from the German registry.

These differences are likely to have impacted survival, and this casts doubt that the external control is an appropriate comparator. If we determine that it is not an appropriate comparator, then this application would not contain an adequate well-controlled trial, which is

regulatory requirement for approval.

The results of FDA sensitivity analyses illustrate that as we attempt to adjust for these differences, differences in survival attenuate. Furthermore, the divergent results presented by the applicant and FDA highlight that the results of these post hoc survival analyses are dependent on patient populations and statistical approaches selected, and that there is an underlying high degree of uncertainty associated with drawing conclusions regarding the effectiveness of omburtamab based on these comparisons.

Finally, in situations where an improvement in a time-to-event endpoint such as overall survival has not been demonstrated, we can sometimes rely on a clinically meaningful and durable effect on response rate to establish effectiveness. However, this application does not provide reliable evidence of CNS or leptomeningeal responses to omburtamab.

Although we can be amenable to the use of a robust external control to establish effectiveness

in certain circumstances if the external control is an appropriate comparator, it is important that children with CNS and leptomeningeal relapse neuroblastoma, and their families, have confidence that drugs approved for this disease are effective, as well as safe.

We appreciate that you are here to provide your perspective on this application today. FDA requests discussion regarding the ability of the data provided to isolate the treatment effect of omburtamab from the effects of multimodality therapy and to discuss if additional data are needed to assess the treatment effect of omburtamab.

We ask you to consider if the applicant has provided sufficient evidence to conclude that omburtamab improves overall survival. We are acutely aware of the need for regulatory flexibility and are willing to accept a reasonable degree of uncertainty when assessing effectiveness, given the high unmet medical need of pediatric patients with neuroblastoma. At the same time, it

is important that we think about the degree of uncertainty that is acceptable, particularly because omburtamab has toxicities that are not negligible.

It is our responsibility to ensure that drugs we approve have a favorable benefit-risk balance, but we cannot make that determination without evidence to show effectiveness. Despite our best efforts to leverage the existing information, at this point in time we think that additional data are needed to establish the effectiveness of omburtamab, and we are willing to work with the applicant and the stakeholder community to identify the best path forward to generate this information for patients and their families. Thank you.

DR. LIEU: Thank you, Dr. Barone.

Before we move on to the applicant presentations, I do want to give Dr. Seibel and Dr. Kolb an opportunity to introduce themselves for the record.

Dr. Seibel?

DR. SEIBEL: Hi. This is Nita Seibel. I'm a pediatric oncologist in the clinical investigations branch at CTEP at the NCI.

DR. LIEU: Thank you, Dr. Seibel.

And Dr. Kolb?

(No response.)

DR. LIEU: Dr. Kolb, are you able to introduce yourself for the record?

(No response.)

DR. LIEU: Okay. We will try and come back to Dr. Kolb after the presentations.

DR. BAUTISTA: I apologize, Dr. Lieu.

Dr. Kolb, you'll need to connect yourself to the audio, at your earliest convenience. We'll come back to you.

Sorry, Dr. Lieu.

DR. LIEU: Alright. We'll continue to proceed.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that

it is important to understand the context of an individual's presentation.

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

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have 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 Y-mAbs Therapeutics' presentation.

Applicant Presentation - Rikke Lilleso

MS. LILLESO: Good morning. My name is Rikke Lilleso, and I'm the vice president of Global

Regulatory Affairs at Y-mAbs. Thank you for the opportunity to present our data today. We will start with a few words of introduction of our company by Thomas Gad, the founder, CEO, and president of Y-mAbs.

Applicant Presentation - Thomas Gad

MR. GAD: Thank you, Rikke.

My name is Thomas Gad, and it's a pleasure being here today. Our daughter Daniella, picture here, was diagnosed with systemic high-risk neuroblastoma in 2006 just before she turned 2 years old.

After looking for treatments worldwide, we finally found our way to Memorial Sloan Kettering, where Daniella received a GD2 antibody for her systemic disease and was declared in full remission in 2007. Two years later, she was diagnosed with an isolated CNS relapse of neuroblastoma and entered into Trial 03-133, receiving omburtamab, which led to more than 14 years of remission.

After I experienced what families go through mentally and financially in order to get access to

these potentially life-saving drugs to save their children, I founded Y-mAbs in 2015, a company dedicated to conducting research in ultra-rare pediatric diseases where no approved therapies are available. Our main goal is to make treatments available close to home and give all children access to treatment. Thank you.

Applicant Presentation - Rikke Lilleso

MS. LILLESO: Thank you, Thomas.

Omburtamab has a long clinical development history. In 2001, MSK cleared the IND, and Trial 03-133 was initiated in 2004. Y-mAbs obtained the rights to omburtamab in '15. The product then received breakthrough therapy, orphan drug, and rare pediatric disease designations. To support regulatory approval, Y-mAbs initiated the multicenter Trial 101, which is still ongoing. The BLA was admitted in March of this year following extensive feedback from the FDA.

Omburtamab is a monoclonal antibody that binds to B7-H3, which is highly expressed on neuroblastoma with minimal expression on normal

tissue. The radiolabeled antibody binds and destroys tumor cells by beta emission, including any measurable or micrometastatic CNS disease, and that is important to note because following post-relapse therapy, not all patients have measurable disease, but they may still have micrometastatic disease. The radiolabeled antibody is delivered directly into the CSF by an Ommaya catheter, which bypasses the blood-brain barrier. This allows the antibody direct access to tumor cells in the entire CNS and the leptomeningeal surfaces.

The clinical trial supporting the BLA, 03-133 and 101, are the only interventional trials ever done in neuroblastoma patients with CNS or leptomeningeal metastases. Because it is not feasible to conduct a randomized trial in this rare and life-threatening disease, these were single-arm trials. Therefore, we compared the data from the pivotal Trial 133 to an external control arm.

Based on these trials, our proposed indication is treatment of central nervous system,

leptomeningeal metastases in pediatric patients with neuroblastoma following standard multimodality treatment for CNS disease. This population reflects the patients included in the primary analysis, the MG2 populations that you will hear about later. The proposed dosing regimen is two age-based doses administered 4 weeks apart.

Today we will share with you that despite multimodal treatment of surgery, radiotherapy, and chemotherapy, neuroblastoma with CNS or leptomeningeal metastases is associated with a poor prognosis, so there's a pressing need for new treatment options. In consultation with the FDA, we defined an external control arm for comparison to Trial 133, and so we'll hear today why the external control arm is fit for purpose.

Trial 133 showed a clinically meaningful 42 percent improvement in overall survival compared to the external control arm, and the results of Trial 101 are consistent and supported for overall and progression-free survival. Furthermore, it demonstrated single-agent activity.

The most common AEs were laboratory values related to myelosuppression, and these were manageable. In the context of this life-threatening and very rare disease with no approved therapies available, it's appropriate to exercise regulatory flexibility. Based on the totality of evidence from the two trials, we conclude that there is substantial evidence of effectiveness and omburtamab demonstrates a positive benefit-risk profile.

Next, Dr. Kim Kramer, the primary investigator in Trial 133, will describe the disease background and unmet medical need. She has studied omburtamab at Memorial Sloan Kettering for more than 20 years. Then, Vignesh Rajah and René Christensen from Y-mAbs will summarize the efficacy and safety data from the two clinical trials and discuss the comparison to the external control arm. Finally, Dr. Daniel Morgenstern from the Hospital for Sick Children will provide his clinical perspective on the data.

Thank you for your attention. I will now

turn it over to Dr. Kramer.

Applicant Presentation - Kim Kramer

DR. KRAMER: Good morning. My name is Kim Kramer, and I'm attending pediatric oncologist at Memorial Sloan Kettering Cancer Center and professor of pediatrics at Weill Cornell Medical Center. I'll describe the disease background and the unmet need in pediatric patients that have CNS metastases from neuroblastoma. By way of disclosure, I'm a paid consultant for and hold options to purchase shares of Y-mAbs Therapeutics.

Neuroblastoma is a rare embryonal tumor that represents 6 percent of childhood cancers. The average age at diagnosis is 1 to 2 years, and only a small percentage of these patients will develop CNS or leptomeningeal metastases, typically at relapse, not at initial disease presentation. As you can see, these are typically very large ugly tumors that cause life-threatening problems: massive headaches, vomiting, seizures, pending brain herniation, and death. These tumors are very difficult to treat, and patients often progress

very rapidly.

So let me walk you through a patient journey. Out of approximately 600 children diagnosed with neuroblastoma annually in the U.S., about half have had stage 4, high-risk disease, and of those, we can cure about 50 percent. But what happens to the other 50 percent?

Many of these patients will have recurrent or progression of the systemic disease, but a small percentage, estimated to be 3 to 6 percent, will relapse in the brain. That represents only 9 to 18 patients per year in the U.S., so it is quite rare. And by and large, most of these children will have isolated CNS disease with no evidence of disease elsewhere, suggesting that the brain is indeed a sanctuary site for neuroblastoma.

When a patient first presents with CNS relapse, conventional therapy is offered. It often includes surgery, chemotherapy, and radiation therapy, but keep in mind that none of these therapies are specifically approved for this indication and, unfortunately, despite all of this

intensive therapy, these aggressive brain tumors tend to progress, and many patients die within months. That is why we developed radioimmunotherapy with omburtamab.

To put this into perspective, I'd like to show you the most recent data from the SIOP database published by Berlanga in 2021. This is a very important publication and provides a reliable estimate of overall survival in this population, based on patients treated between 2002 and 2015.

The overall survival in 53 patients with first CNS recurrence was 4 months, and the 3-year survival rate was only 8 percent. A small subset of patients who were able to receive multimodal therapy, depicted with the green arrow, fared somewhat better with a median survival of 14.5 months and a 3-year overall survival of 21 percent. So yes, multimodality treatment delays death, but the prognosis for cure is still poor.

This is where the addition of radiolabeled therapy to standard multimodal therapy plays an important role. First, we had a target. B7-H3

turned out to be a fantastic target because it is expressed on the vast majority of neuroblastomas and other pediatric embryonal tumors, and yet has limited expression on normal tissues, so we have a great target. We also have an antibody, omburtamab, specific for this target. We have an isotope, i-131. We have a method of delivering it intrathecally to target and kill tumor cells in the CNS. The ultimate goal is to eradicate residual measurable or micrometastatic disease, and hopefully increase the chance of cure.

So what have we learned about compartmental radioimmune therapy over the past 25 years? Well, we've learned that it works well across the spectrum of CNS lesions to help eliminate residual tumor after surgery and conventional radiation therapy.

Here are two examples. On the left is a bulky hemorrhagic metastases causing midline shift with impending herniation, and on the right, a patient with innumerable inoperable, supratentorial and infratentorial parenchymal lesions. Both of

these patients were successfully treated with multimodal therapy plus omburtamab and have remained disease-free for more than a decade.

Importantly, by using targeted radioimmune therapy, the conventional radiation dose has been significantly lowered over the years and significantly lower than that used for other pediatric brain tumors, limiting the long-term crippling side effects associated with conventional external beam radiation.

Imaging studies show that following intraventricular administration, the radiolabeled antibody is distributed throughout the thecal space, which maximizes the possibility of targeting residual disease in the parenchymal leptomeninges or the CSF space.

Here seen on PET images are 2, 24, and 48 hours post-injection, and importantly, on the right, as you can see in these MR and PET images, the antibody does effectively target parenchymal lesions, highlighted here by the arrows. This is a patient with a frontal parietal B7-H3 positive

tumor, showing clear uptake of the radiolabeled antibody while sparing the rest of the brain, something conventional radiation therapy is unable to do.

Administration of omburtamab is also fairly easy and convenient compared to the aggressive conventional multimodal therapies that I've described. It can be delivered by an Ommaya catheter to children as young as 6 months by a physician or nurse practitioner while the patient is awake at the bedside, and patients often go home later the same day. And let me just say, the Ommaya catheter, invented in the 1960s, has been used routinely for over 50 years to deliver CNS-directed therapies, and it is very safe.

So in conclusion, CNS neuroblastoma is a rare and devastating disease, and even with the best available multimodality treatment, prognosis for cure remains poor. As systemic therapies for neuroblastoma improved, it highlighted that the CNS is a sanctuary site that poses an impediment to cure.

There is no targeted CNS-directed therapy approved for these patients, therefore, there remains a high unmet need for effective agents, particularly ones that allow us to decrease the intensity and the side effects of existing treatment modalities. Administration of radioimmune therapy into the CSF is feasible, and the adverse event profile is completely predictable and manageable. Most importantly, omburtamab is an effective agent that improves overall survival and increases the chance of cure.

So why are we here today? Children with CNS neuroblastoma deserve a chance for cure and the opportunity to live a normal life. These are some of my young patients who have done very well and are now adults. They've gone on to do incredible things, such as going to college and getting married. Thank you, and I will now turn it over to Dr. Rajah.

Applicant Presentation - Vignesh Rajah

DR. RAJAH: Thank you, Dr. Kramer.

Good morning, everyone. My name is Vignesh

Rajah, chief medical officer at Y-mAbs Therapeutics. I'll present the efficacy and safety data from our two registration trials, and my colleague, Dr. Christensen, will present the comparison of our pivotal trial, 03-133, to the external control arm.

As you heard previously, the clinical development of omburtamab was based on two single-arm trials. Trial 03-133, initiated by MSKCC, is the largest single trial conducted in this patient population. This study enrolled 109 neuroblastoma patients with CNS/leptomeningeal metastases over a 14-year period. All of them are included in the evaluation of safety, and the data from 107 of these were used to support the efficacy evaluation.

Trial 101 is an international, multicenter trial that was designed by Y-mAbs with input and feedback from FDA to demonstrate the reproducibility of the data from 03-133. This trial has enrolled 50 patients and is close to accrual, and 32 patients included in the planning

from analysis of efficacy.

There were two parts to the Trial 03-133, a dose escalation and a cohort expansion. Each part evaluated omburtamab given in two cycles, initially for the dosimetry dose of 2 millicuries, followed by a treatment dose. Part 1 evaluated the toxicities and maximum tolerated dose. Treatment doses were escalated from 10 to 80 millicuries, and patients received the same treatment dose in both cycles.

In part 2, the expansion phase, all patients were given the selected treatment dose of 50 millicurie to assess the efficacy and safety. The treatment doses were reduced depending on age. The primary endpoint was overall survival at 3 years and the second endpoint was CNS/LM progression-free survival at 12 months. The CNS progression-free survival was evaluated only retrospectively by the investigator and was not independently reviewed, so we have not included this in the presentation.

Trial 101 was a single-arm, multicenter

trial. Patients followed a similar treatment regimen as in 03-133. The primary endpoint was CNS/LM progression-free survival at 6 months, and secondary endpoints were overall survival at 12 months and objective response rate at 6 months. Other endpoints included safety and PK.

The short-term follow-up was at 26 weeks when assessments for CNS/LM, progression-free survival, and objective response rate were made. Long-term follow-up was done twice a year to assess overall survival and safety. Data was collected from five sites in the U.S., including major centers such as MSK, LA Children's, Nationwide, Riley, and MD Anderson. There were also two sites in Europe and one in Japan.

An interim analysis included data from 32 patients who were enrolled until October 2020. Additional patients have since been recruited, and based on prior FDA input, we have included assessment of the 50 patients enrolled. So all the data I will share with you today is based on this total study population.

The key inclusion and exclusion criteria in Trials 03-133 and 101 were quite similar. Key points to highlight is that in 03-133, in addition to 109 neuroblastoma patients, the trial also enrolled 68 patients with other tumor types and had metastasized to the CNS. Also, eligible patients may have had active malignancy outside of the CNS. It's important to note that the majority of patients, 73 percent, have isolated CNS relapse only.

Trial 101 enrolled patients with high-risk neuroblastoma and have relapsed with CNS and leptomeningeal metastases. They may have also had stable systemic disease not requiring chemo or immunotherapy. Key exclusion criteria was similar for both trials, as shown. No restriction or number of prior recurrences were enforced in these two protocols, as goal was to be as inclusive as possible. Prior CNS-directed radiotherapy or chemotherapy must have been completed at least 3 weeks before study entry.

Shown here are baseline characteristics of

107 neuroblastoma patients in Trial 03-133 who received the treatment dose and 50 patients in 101. The patients enrolled have similar baseline characteristics. Median age was 4 to 5 years with an upper range of 13 and 11, respectively, and a mean body weight of approximately 17 kilograms. The majority of these children were male and white.

Here are key disease characteristics in each trial. With regard to the sites of CNS/LM metastases, this was assessed in Trial 03-133 at the time of CNS/LM relapse and was assessed in Trial 101 at treatment baseline. About half the patients in 03-133, 48 percent, had unifocal parenchymal lesion; 15 percent had multifocal; 9 percent had leptomeningeal; and 8 percent had both parenchymal and leptomeningeal lesions.

In Trial 101, among the 40 percent of patients with evaluable disease at baseline, there was a fairly even distribution between parenchymal, leptomeningeal, and mixed lesions. The remaining 60 percent of patients in 101 did not have evaluable disease at baseline, as assessed by

independent review of MRI scans. About half the patients in both trials had MYCN amplification, and most patients had received prior treatment with surgery, radiotherapy, and chemotherapy for their CSF recurrence.

Here are the results of the primary overall survival analysis in our pivotal trial, 03-133. The survival time was calculated from the date of first diagnosis of CNS/LM metastases until death or until the latest date confirmed alive. At median follow-up of age of 2 months, the 3-year overall survival rate was 57 percent. This is a primary efficacy endpoint. Median overall survival was 51 months.

These results are extremely encouraging, particularly given that very few deaths occurred beyond 5 years, 41 percent of patients remained alive beyond 8 years, and some have survived more than 14 years; something that we would not expect to see in this poor prognosis population. CNS/LM progression-free survival was consistent with these results with a 22-month median PFS.

Moving now to the efficacy results in the multicenter Trial 101, the primary endpoint was CNS/LM progression-free survival defined as time from the first omburtamab treatment to CNS/LM progression, or death from any cause. At median follow-up of 23 months, the 6-month CNS/LM progression-free survival rate was 75 percent. And here are the overall survival results. The 12-month overall survival rate was 79 percent. Similar to the previous study, we observed a consistent pattern in the PFS and overall survival curves.

We also sought to compare the overall survival outcomes across both trials. To do so, we had to use time from CNS relapse as the index date in both studies. You can see that the results from Trial 101 in a multicenter setting are consistent with and supportive of the efficacy seen in 03-133, with similar overall survival rates at 12 months, 91 percent and 92 percent, respectively.

We were also able to assess objective response rate in Trial 101 using RANO brain mets

criteria for parenchymal lesions and EANO-ESMO criteria for leptomeninges lesions. Among the 20 patients with evaluable disease, there was a total of 7 patients that showed a response and 7 patients with stable disease. Median response duration was 143 days for all responders, with about 280 days -- about 9 months -- for the complete responders. Five patients had progressive disease.

These swim lanes show the clinical course for those patients designated as responders or complete responders based on the type of lesion. The majority of these patients had an interval of 4 to 15 weeks between completion of that prior radiation treatment, black triangle, and the baseline scan before omburtamab treatment. This interval is sufficient washout time to begin seeing the effect of omburtamab.

In addition, the majority of these patients had an interval of 3 to 8 weeks between completion of prior chemotherapy regimen, orange triangle, and the baseline scan. This is also adequate washout

time to begin seeing the effect of omburtamab. The duration of response improved these patients, both with isolated leptomeningeal disease, and was more than 2 years. This is particularly noteworthy, as patients with leptomeningeal disease are much more difficult to treat and tend to have a poorer prognosis in general.

I will now show a little bit more detail in one of these patients just to demonstrate the single-agent effect for omburtamab at an individual patient level. This patient had evidence of evaluable parenchymal and leptomeningeal lesions at the time of baseline scan. Radiotherapy was given 15 weeks prior to this baseline scan and chemotherapy was given 5 weeks before the baseline scan. The patient did receive systemic anti-GD2 monoclonal antibody as consolidation treatment for systemic disease 5 months after baseline. This antibody treatment does not cross the blood-brain barrier, and therefore does not impact the CNS lesion.

As you can see from the graph on the right,

there was a reduction in size of the tumor from about 30 millimeters in sum diameter at baseline to undetectable, but complete response at 26 weeks. The MRI images illustrated regression of the parenchymal lesion, consistent with the evidence presented earlier, showing clear penetration of the parenchymal lesion. The evaluation for the leptomeningeal lesion at week 26 was also assessed as a response, as the EANO-ESMO criterion. These results strongly indicate a single-agent effect of omburtamab.

In summary, Trial 03-133 represents the largest clinical trial in this population, enrolling approximately one-third of all U.S. patients with neuroblastoma and CNS or leptomeningeal metastases during the trial period. It demonstrated a 3-year overall survival rate of 57 percent and a median overall survival of 51 months. This is for all patients in first recurrence, but also second and higher recurrence, patients known to have poorer prognosis.

Trial 101 demonstrated similar results in a

multicenter setting, with a one-year overall survival rate of 79 percent from start of omburtamab treatment. It also demonstrated evidence of single-agent activity in both parenchymal and leptomeningeal lesions. Some of these were also long-term survivors.

So how do we put this data into context and evaluate the benefit of omburtamab when added to standard treatments? Given the ultra-rare mix of the disease, using an external control arm to establish the relative effectiveness is considered appropriate. Therefore, to support the efficacy assessment, we compared the survival data from the 03-133 with that of an external control arm, and my colleague Dr. Christensen will now take you to that analysis.

Applicant Presentation - René Christensen

DR. CHRISTENSEN: Thank you, Dr. Rajah.

I'm René dePont Christensen, head of biometrics at Y-mAbs. I will show you why we at Y-mAbs believe that a control group that is fit for purpose has been identified. From an extensive

search, including discussions with Children's Oncology Group, COG, we found only two comprehensive repositories for patient-level data from neuroblastoma patients with CNS/LM metastases in existence, the German registry data from Cologne and the SIOPEN data.

The data from the Study Center for Neuroblastoma in Cologne, Germany was determined to be the most suitable to allow comparisons with 03-133. The German patients came from three nationwide single trials in stage 4, high-risk neuroblastoma studied in 1990, 1997, and the last one, including patients from 2004 to 2015. These trials had a coverage of 99 percent of the relevant patient population.

A total of 1,338 patients with stage 4 neuroblastoma were registered in three German trials. We applied the key eligibility criteria from Trial 03-133 and narrowed this down to just 120 patients who have CNS or leptomeningeal disease. The search criteria primarily selected patients in first recurrence after primary systemic

neuroblastoma, and 93 percent of patients fulfilled this criterion. To avoid the inclusion of the frailest patients, we limited the external control arm population to 85 patients who were treatable for the CNS/LM metastases.

The German patients not able to receive treatment demonstrably had an extremely poor prognosis with a median OS of approximately 1 month. A subgroup of 35 patients received a reasonable level of multimodal treatment defined as two or more in the Berlanga paper and in concordance with most patients in Trial 03-133. The primary analysis was restricted to this subgroup with recurrent modality group 2, or MG2, including patients able to receive radiotherapy and at least one other treatment modality, either surgery or chemotherapy.

Ultimately, we directly compared the overall survival of 89 patients in 03-133 with 34 patients in the external control arm for whom we had complete data. The analysis plan for the comparison was developed through several

interactions with the FDA. As requested by the FDA, we used propensity score methods, and we were able to balance all prognostic factors available in various populations.

What you see here are the weighted values for each population. We were able to include a number of important prognostic factors in the model: age at neuroblastoma diagnosis and MYCN amplification; time from neuroblastoma diagnosis to relapse; and time from relapse to start of treatment.

We also adjusted for differences in treatment intensity the number of post-relapse treatment modalities administered, as well as the exposure to surgery were included. Radiotherapy is given to all modalities and include patients by definition, and so was chemotherapy in the weighted comparison. We were not able to include all relevant prognostic factors directly in the model, however, we were able to assess the possible impact of these.

Firstly, the level of complete surgical

resection was comparable across groups. We were not able to include surgical radicality in the model because we only have the direct information in the German data. However, in 03-133 modality group 2, 51 percent of patients had a uniform focal parenchymal lesion, and these types of lesions are most likely to be completely resected.

In the external control arm modality group 2, 52 percent of patients achieved at least macroscopic complete resection and 29 percent of surgeries were also microscopically complete. Secondly, the distribution of systemic disease was similar across the three groups. Presence of systemic disease or pattern of relapse was measured at the time of CNS relapse in the external control arm and at time of first omburtamab infusion in Trial 03-133.

Due to differences in timing, it was not technically possible to incorporate the variable in the model, however, we may reasonably assume that patients in 03-133 with systemic disease at time of infusion likely also had systemic disease at time

of relapse. Given this assumption, as we can see in the table, 25 percent of patients in 03-133 had both CNS and systemic disease compared to 20 percent in the external control arm. Given this similarity, we do not expect this variable to dramatically change the outcome of the analysis, and that has been confirmed in the sensitivity analysis.

Thirdly, the FDA has encouraged Y-mAbs to supply additional data as a consequence to look into a number of recurrences. This subgroup was already defined in the 03-133 protocol and reported in the trial report. Ninety-one percent of the external control arm patients were in first recurrence, whereas only 58 percent of patients in 03-133 were treated at first recurrence.

Due to the skewness, the variable cannot be incorporated in the statistical model, but we looked at the subgroup of patients within MG2 treated at first recurrence for both Trial 03-133 and the external control arm, and I will show these results later.

Finally, this table shows the treatment intensity is comparable between groups within modality group 2. The most marked difference is the use of craniospinal irradiation, which is not used in pediatric patients in Germany; but all external control arm patients received CNS-directed focal or whole brain radiotherapy.

Moreover, there's no evidence that craniospinal irradiation is associated with any better outcomes compared with other radiotherapy modalities in the treatment of CNS/LM metastases from neuroblastoma. In support of this statement, no survival differences were observed in Studies 03-133 and 101, favoring craniospinal irradiation over other irradiation methods.

Based on these data, we conclude that modality group 2 in both 03-133 and the external control arm populations are comparable to an extent that supports a comparison of overall survival. We have evaluated all available sources for external patient level data, and through alignment of eligibility criteria and balancing the propensity

score methods, we have established a comparable external control arm.

Important prognostic factors not included in the propensity score model can reasonably be considered to be similar between groups. Treatment intensity was subject to regional differences but still comparable. Regarding the number of prior recurrences, presence of systemic disease as well as the surgical radicality data suggests that these external control arm patients are similar or may even have a more favorable prognosis than the 03-133 population.

Now, I will take you through the results. This is the primary results from our propensity score weight comparison of the 03-133 population, the green curve, and the external control arm, the orange curve. This is restricted to modality group 2 with aligned index dates for survival. Importantly, we see a hazard ratio of 0.58 and a 3-year overall survival rate of 54 percent versus 31 percent, in favor of omburtamab.

The hazard ratio is highly clinically

meaningful, especially in this very severe disease with no targeted treatment options. In the context of a rare disease, the draft FDA guidance, demonstrating substantial evidence of effectiveness, encourages flexibility in determining substantial evidence when the sample size is limited. It states that a p-value higher than the conventional 0.05 might be acceptable in some cases, and a level of 10 percent has been used in other rare indications.

We submitted the data to various prespecified sensitivity analyses, which all showed results consistent with the primary analysis. The first sensitivity analysis applied imputation. We also accounted for immortal time bias by pushing the index date for 03-133 subjects to the date of first omburtamab infusion, index date D, and the magnitude of the treatment effect is maintained. We also varied the population by looking at the much smaller subgroup of patients who received all three modalities of treatment. Of course this has low statistical power, but the magnitude of the

effect is, again, maintained.

As an exploratory analysis on the assumptions, we included presence of systemic disease as a covariate in the model, and the result remained consistent with the primary analysis; and finally, we restricted the population to those only treated as first recurrence in 03-133. It is evident that even when subjected to a strain of sensitivity analyses, the treatment effect consistently points in the same direction, favoring omburtamab.

And here, as promised, are the Kaplan-Meier curves for the patients treated at first recurrence. This analysis includes 50 patients from 03-133 and 29 patients from the external control arm, modality group 2, after propensity score weighting. In addition, it compares index date A in the external control arm to index date D in Trial 03-133. This accounts for immortal time bias.

The hazard ratio is 0.42 with a nominal p-value of 0.007. So when limiting our study

population to patients in first recurrence, corresponding to the selection criteria for the external control arm, as well as for the SIOPEN data, the effect in favor of omburtamab is even more convincing.

Finally, to address concerns related to era of therapy, we excluded patients from German study NB90, starting in 1990, enrolling patients for 1997 from the external control arm. Please recall that the coverage of the German trials was 99 percent, so these curves show the actual development in the natural history of the disease in Germany.

We observed a substantial change in treatment and maintenance of primary neuroblastoma in the NB90 to the NB97 protocol, whereas the changes from NB97 to NB2004 were limited. This may indicate a change in care of neuroblastoma patients in general in the period between the two early trials. Eligibility criteria were similar between NB97 and the NB2004 protocols, and there's no indication of change in treatment paradigm, leading to improved survival for patients in the latter

protocol. So there's no objective reason to exclude patients from the NB97 protocol, thereby jeopardizing the sample size even further.

As you can see, the treatment effect remains significant with a hazard ratios 0.48. We conclude that for patients in first occurrence, the analysis is robust with respect to immortal time bias, as well as a reasonable definition of era of therapy.

The FDA briefing document raises three major concerns regarding the fit-for-purpose assessment. We find these to be relevant and we can address them. Treatment intensity was comparable. The most marked difference was the use of craniospinal irradiation in 03-133 versus focal/whole brain irradiation in the external control arm. However, there is no evidence to support any differences in efficacy between these types of radiotherapy in neuroblastoma. Also, there is every reason to believe that in Germany, the single largest economy in Europe, generally, CNS/LM metastases would be treated until there's absolutely no options left.

Immortal time bias was handled proactively

by introducing the next index date A plus D in the sensitivity analysis. You were presented with an overall picture of analysis maintaining a clinically highly relevant magnitude of effect also when taking immortal time bias into account.

With regard to era of therapy, we have seen that there's an indication of a shift in management of patients between 1990 and 1997, but no evidence to single out the start of 03-133 in 2005 as being especially relevant. As shown, despite reduced sample size, the analysis within the subgroup of patients in first recurrence strongly favors omburtamab. Importantly, this analysis is robust with respect to immortal time bias, as well as era of therapy.

In conclusion, we evaluated all available sources for external patient-level data, and we were able to identify a high-quality external control arm that we believe is fit for purpose. Prognostic factors included in the model were sufficiently balanced, and those not included are unlikely to materially change the outcome of the

analysis in a negative direction.

We demonstrated a highly clinically meaningful improvement in overall survival with a hazard ratio of 0.58. The comparison also showed meaningful improvements in median overall survival and a 3-year overall survival rate. All sensitivity analyses showed a consistent magnitude of the treatment effect favoring omburtamab.

For patients treated at first recurrence, we demonstrated that there was a large, significant robust effect of omburtamab when added to conventional treatment. Even when taking immortal time bias and era of therapy into account, we see a hazard ratio of 0.48, which given the unmet need should be considered very substantial.

Thank you. I will now hand it back to Dr. Rajah.

Applicant Presentation - Vignesh Rajah

DR. RAJAH: Thank you, Dr. Christensen.

Now I will present a short summary of the safety data for omburtamab from our two studies. There were a total of 109 neuroblastoma patients

from Trial 03-133 and 50 patients from Trial 101 that were included in the safety evaluation. In terms of treatment exposure, in Trial 03-133, the majority of patients received 50 millicurie as a therapeutic dose or the recommended dose depending on age. Fifty percent of the patients received 2 doses and slightly less received one dose. In the 101 trial, a total of 30 patients received two treatment doses and 20 had one treatment dose.

In both studies, the most commonly reported reason for patients receiving only one dose was grade 3 or 4 lab abnormalities from myelosuppression, and there were protocol-defined criteria for a second dose. The protocols did not allow for a second dose if they had persistent grade 4 myelosuppression. If it was grade 3, it was at the investigator's discretion.

Furthermore, in Trial 101, the protocol allowed for a delay in the second dose for up to 8 weeks at the discretion of the treating physician, so a higher percentage received 2 doses in this trial. This mirrors more closely with what

could be expected in clinical practice.

When we look at the overview of the safety profile, almost all patients had at least one treatment-emergent adverse event, with most events being non-serious, and the majority of clinical AEs were of grade 1 or 2. The majority had grade 3 or more lab reported AEs, about half the patients had serious adverse events, and 10 to 14 percent of patients had adverse events that led to drug discontinuation as per protocol. The majority of this was related to lab abnormalities for myelosuppression, but the clinical impact of these SAEs was minimal. In Trial 101, one patient with CNS disease progression died from an intracranial hemorrhage.

This slide shows all the grade 3 or more adverse events. The commonest AEs were lab abnormalities from myelosuppression, which were all predictable and well-managed. It's standard supported measures such as transfusion of blood products. Among the clinical AEs, the notable reports were those of secondary malignancies, acute

myeloid leukemia and myelodysplastic syndrome in 03-133 and intracranial hemorrhage in Trial 101. When we look at the serious adverse events, the most common was thrombocytopenia and neutropenia. Despite this in both trials, there were only two reported case of febrile neutropenia and one reported case of sepsis out of a total of 159 patients.

As noted previously, there were 3 patients with myelodysplastic syndrome and two with AML. There was also one recent case of papillary thyroid cancer in the 101 study. It was not possible to make a direct causal link to omburtamab because these hematological malignancies are known risks in patients who have been heavily pretreated with prior radiotherapy or chemotherapy. Even if identified as a potential risk, it is generally accepted that the risk of secondary malignancy is far lower than the risk of CNS disease progression.

In the 101 trial, there were 4 patients with intracranial hemorrhage. In all four cases, CNS disease progression was observed. One case

resulted in death. It is well documented that intracranial hemorrhage is a recognized manifestation of CNS disease progression in neuroblastoma, which can be fast growing and hemorrhagic, even with normal platelets.

So in summary, the most common AEs were related to lab value defined myelosuppression. Grade 3 and 4 AEs were very manageable with standard supportive measures. And in conclusion, in the context of this serious disease, the safety profile of omburtamab is considered acceptable, and the overall data supports a favorable benefit-risk balance.

Thank you for attention, and I'll hand it over to Dr. Morgenstern to provide his clinical perspective.

Applicant Presentation - Daniel Morgenstern

DR. MORGENSTERN: Thank you, Dr. Rajah.

My name is Daniel Morgenstern. I'm a staff pediatric oncologist and co-leader of the neuroblastoma program at the Hospital for Sick Children and an associate professor at the

University of Toronto. In terms of my disclosures, I provide a consultancy to Y-mAbs Therapeutics, as well as to EUSA Pharma; Clarity Pharmaceuticals; AG Bayer [indiscernible], and Oncoheroes Biosciences, and I want to provide some clinical thoughts on the data you've seen today.

First, I think it's important to appreciate that CNS neuroblastoma represents a very rare disease, so obtaining data on these patients presents many challenges. What's clear to me, as you saw earlier based on the published data from SIOPEN, is that patients with first CNS recurrence of neuroblastoma typically have a very poor prognosis, even with multimodality therapy. Those with the best prognosis, who receive two or more treatment modalities, had a 3-year survival rate of only 21 percent. And if we compare that to the German registry data restricted to modality group 2 at first recurrence, with a similar intensity of treatment, the outcomes are broadly comparable, with a 3-year overall survival rate of 27 percent.

Clearly, these are still inadequate outcomes

despite surgery, chemotherapy, and radiotherapy, and it's important to also remember that patients with CNS neuroblastoma are typically excluded from studies of novel agents. Therefore, there is a clear need for a targeted, CNS-directed therapy.

When we compare these historical results to that which was observed in Trial 03-133 in a similar cohort of patients of first recurrence, the data suggested the addition of targeted radioimmunotherapy with omburtamab provides meaningful clinical benefit.

One could ask if the data from 03-133, which was a single-institution study conducted at MSK, are generalizable or if there might be some potential selection bias in the patient population that was enrolled. And here I think the data from Trial 101, a multicenter study conducted at five U.S. sites, including MSK, as well as three sites outside the U.S., are helpful. Of the 50 patients treated on Trial 101, 26 were enrolled at sites other than MSK, and as you already saw in the presentation, the overall survival of patients

enrolled on 03-133, on the left, is very comparable to that observed in Trial 101, on the right.

When we look at the comparison of 03-133 to the external control arm, you can see an improvement in overall survival with a hazard ratio of 0.58 and a p-value of 0.0544. I think the median survival of 4 years is also quite striking. It's notable that the overall survival hazard ratio was more dramatic when the comparative analysis was restricted to patients treated at first recurrence.

With regard to Trial 101, it further supports the findings from 03-133 and demonstrated quite consistent overall survival in a multicenter setting. Trial 101 also provides some objective response data. Now, these data can be somewhat challenging to interpret because of the small patient numbers and because patients had received surgery, radiotherapy, and other modalities prior to omburtamab, but the gap between radiotherapy and omburtamab administration was often several months, including for patients achieving an objective response. So I think it's unlikely the delayed

effect of external beam radiotherapy would have contributed to the observed responses.

Finally, with regards to safety, the adverse events, which are mainly myelosuppression, are predictable and manageable, so in my mind, the overall evidence does support a positive benefit-risk.

I think it's also reasonable to ask questions about whether it might be possible to obtain additional data, and obviously it would be lovely to imagine that we could undertake a randomized-controlled trial to definitively confirm the benefit of omburtamab when added to other therapies; but as we've heard, I think that this is clearly infeasible given the rarity of this disease and the length of time required to accrue enough patients. In addition, it will be practically challenging at this point to randomize patients to an arm that did not contain omburtamab.

We could also ask if there's a better comparison data set available, and here probably the biggest challenge is identifying patients with

true CNS relapse. Most existing trial databases for outcome studies, including those conducted by the Children's Oncology Croup, COG, don't collect details on sites of relapse. In addition, interrogation of the SIOPEN database identified only 53 patients with confirmed CNS relapse from over 1100 patients with recurrent disease, a smaller cohort than that which was available from the German registry.

So in summary, there is no CNS-directed therapy approved for CNS neuroblastoma. I think the totality of evidence from 03-133, the comparison with the external control arm, and the supportive data from the multicenter trial support the efficacy of omburtamab for CNS neuroblastoma in the context of multimodal therapy. It's not feasible to conduct a randomized trial, and there are no suitable additional external data sources. So ultimately, we have to make a judgment based on the best available data rather than some theoretical ideal.

Importantly, the toxicity is manageable, and

omburtamab can be safely administered. And therefore, on balance, I believe the benefit of omburtamab in patients with CNS neuroblastoma outweighs the risk, and omburtamab should be made available as an additional treatment option for clinicians to use treating their patients with CNS neuroblastoma.

Thank you for your attention, and I'll now hand it back to Dr. Rajah.

DR. RAJAH: Thank you, Dr. Morgenstern.

In conclusion, the studies we have presented today for omburtamab considered the only prospective interventional data with CNS/LM disease from neuroblastoma and with more than 14 years of follow-up in the 03-133.

Omburtamab has shown a compelling and a clinically meaningful efficacy with an acceptable and very manageable safety profile. In the context of this very rare and life-threatening disease, we believe it is entirely appropriate, as per the FDA's own guidance, to apply a degree of flexibility in the evidence being evaluated and in

determining efficacy, based on the overall weight of evidence presented. Thank you for your attention.

DR. LIEU: Thank you very much.

We will proceed with the FDA presentation, but before we do that, I just wanted to give Dr. Kolb another opportunity to introduce himself and say his name into the record.

DR. KOLB: Yes. Hi. This is Andy Kolb. I'm a pediatric oncologist at Nemours Children's Health, and I apologize for the technical difficulties early on.

DR. LIEU: No worries at all. Thank you so much, Dr. Kolb.

We will now proceed with the FDA presentation.

FDA Presentation - Gautam Mehta

DR. MEHTA: Thank you, Dr. Lieu.

Good morning. I'm Gautam Mehta, a neurosurgeon at the FDA. The application for iodine-131 omburtamab in patients with neuroblastoma and CNS or leptomeningeal metastases

was submitted by Y-mAbs Therapeutics, which I will hereby refer to as the applicant. This slide lists the members of the FDA multidisciplinary review team, and my presentation reflects our collective input.

The applicant's proposed indication is for the treatment of central nervous system or leptomeningeal metastases in pediatric patients with neuroblastoma following standard multimodality treatment for CNS disease. The product is given through intraventricular infusions spaced 4 weeks apart. The proposed approval pathway is through traditional approval based on a primary endpoint of overall survival.

In my presentation, I will first present a summary of the design of Study 03-133 and the use of an external control as a comparator. We will discuss FDA's major efficacy issues, which include critical differences in the trial and external control populations; issues with the reliability of comparisons of survival; and the lack of supportive response rate data from Study 101. We will also

briefly discuss key safety considerations for the use of omburtamab in patients with neuroblastoma and CNS or leptomeningeal metastases.

Before we begin, we would like to reiterate a point brought up in Dr. Barone's presentation. Omburtamab is delivered by an Ommaya reservoir, or shunt, to reach the intraventricular and CSF space within the brain. Despite its intended use, there is limited mechanistic possibility with intraventricular therapy using omburtamab to treat CNS parenchymal metastases.

The applicant's briefing document describes that omburtamab will reach and target B7-H3 expressing tumors in the entire CSF compartment. However, more than 70 percent of patients in each trial with known tumor locations experience relapse that included CNS parenchymal metastases. These are not part of the CSF compartment.

It has been well established through several decades of preclinical and drug delivery research that intraventricular or intrathecal administration of drugs into the CSF results in only limited brain

penetration. To date, the applicant has yet to provide robust, nonclinical, or PET evidence to support that this therapy indeed reaches its intended target within the CNS parenchyma. For example, in regard to the single PET image we just saw in their presentation, the applicant has not provided FDA with contrast enhanced imaging to determine whether the uptake we see in the PET image corresponds with a tumor in the parenchyma rather than a tumor in the ventricle or the CSF space.

With that context, and as we begin to discuss the data submitted to the current application, I want to provide a bit of background on the regulatory requirements for approval. To qualify for traditional approval, evidence of effectiveness for an application can either be supported by two adequate and well-controlled trials or one adequate and well-controlled clinical trial with confirmatory evidence. This application aims to fulfill the latter requirement, with one trial supported by confirmatory evidence.

As we heard from the applicant, the primary evidence of effectiveness for omburtamab was derived from a single clinical trial, Study 03-133, a single arm, single-center trial with a primary endpoint of overall survival. This was initially an investigator sponsored trial without registrational intent. Of note, tumor responses were not systematically addressed in this trial.

The initial results of this trial were submitted to FDA in 2017 in support of a breakthrough therapy designation request, based on a comparison with an analysis of the literature review. This preliminary comparison suggested a large treatment effect for omburtamab in this population, and the available literature at the time suggested that treatment outcomes had not improved over several decades.

Based on this information, we decided to grant breakthrough therapy designation, however, the threshold for granting a breakthrough therapy designation is very different from the regulatory requirement for approval of the drug. Breakthrough

therapy only requires preliminary clinical evidence that a drug may provide a substantial improvement over available therapy. To support an approval, we require substantial evidence from an adequate and well-controlled trial, which I will discuss later today; and this is important because as we heard from Dr. Barone, time-to-event endpoints are generally not interpretable in the context of the single-arm trial.

To address this and provide context for interpretation of overall survival data from this single-arm study, the applicant proposed use of an externally controlled trial. Factors that supported the use of an externally controlled trial design included the lack of a clear available therapy as a control and the high unmet medical need in this population.

The applicant identified the Central German Childhood Cancer Registry as a large potentially suitable known data source with patient-level data documenting the outcomes of children with neuroblastoma and CNS relapse. This included over

95 percent of children diagnosed with cancer in Germany between the years 1990 and 2015. Patients were followed until they were 18 years old, and this data set included 800 patients with stage 4 neuroblastoma. Among this cohort, 120 patients experienced a CNS relapse and were included as the source population for the external control.

To assess the marketing application for a drug product, including one based on an external control, FDA requires several conditions to be met. As we discussed earlier, the application must include the results of one or more adequate and well-controlled trials. The results of such adequate and well-controlled trials, or comparisons, must then demonstrate substantial evidence of effectiveness. Once effectiveness has been established, applicants have to show that a drug product is safe, and we use this information to perform a comprehensive benefit-risk assessment.

For this application, we will show that there are multiple layers of uncertainty that raise significant doubt regarding whether treatment with

omburtamab improves survival in patients with neuroblastoma and CNS or leptomeningeal metastases, and whether the available response rate data are reliable to support claims of effectiveness.

So far, you've heard the applicant's approach to addressing our initial concerns, however, FDA has the following ongoing major efficacy review issues. First, because of clinically important differences in the trial and external control populations, we are limited in our ability to interpret their comparison.

Second, we will show through multiple sensitivity analyses that the comparisons of survival in this case are not reliable due to substantial bias and small sample size. Finally, we've identified serious issues regarding the response rate data that limit their ability to verify anti-tumor activity.

The combination of these issues suggests that differences in survival observed between the two populations may be due to significant differences between these populations themselves

and may not be attributable to omburtamab. We'll focus on this first point for now, on the comparability of the trial and external control populations.

Looking at the regulations, a trial using an external control can be considered adequate and well controlled under certain circumstances. However, a fundamental requirement is that the control group be designed appropriately to represent a comparable set of patients or populations.

Before we discuss the data and its comparability, you'll notice that the numbers in our efficacy analyses differ from those presented by the applicant. The comparative analyses presented by both sides today are post hoc, retrospective analyses, and there can be several ways to approach this comparison. Regardless, it's essential that we focus the efficacy analyses to specifically include patients treated at the proposed recommended dose.

Prior to the submission of the BLA, we had

advised the applicant that our evaluation of efficacy would be limited to these patients. Additionally, we've included patients without missing data or specifically complete cases because these are the patients that the comparative analyses are based on.

Finally, given the many uncertainties introduced by use of an external control in the non-randomized nature of this comparison, throughout the course of our interactions with the applicant, we advised that multiple sensitivity analyses would need to be conducted as part of our global assessment of this application. In other words, we would not rely on any single analysis, and the results of analyses attempting to adjust for identified sources of bias would need to consistently support a causal role for omburtamab on any improvement in survival in order to support an approval. Using these multiple analyses, we've taken a step-wise, scientifically based approach to understanding this comparison that I will present to you today.

Now looking at the data, when we compare patients in the current trial who received the proposed recommended dose of omburtamab and patients in the registry, it appears that key baseline covariates of age, MYCN amplification, and the time to CNS relapse are very similar, however, there was a large imbalance in the number of patients who received post-CNS relapse therapy other than omburtamab. All trial patients received at least one modality of therapy compared to only two-thirds of patients in the registry, meaning that in the registry, over a third of patients did not receive any conventional therapy for the CNS relapse at all.

As we heard from the applicant, to improve the comparability of the analysis, the trial and external control populations were further limited to patients who received radiation therapy, as well as at least one other modality of therapy. This described the majority of patients in the trial with no missing data, the 77 patients, and only 34 patients in the external control. These

populations of 77 and 34 patients represent the primary analysis populations for this application.

To better understand differences and prior treatments in these two populations, we can look at the treatment protocol that was generally applied to the patients in Study 03-133 after diagnosis of CNS relapse but before receiving omburtamab. Patients would first undergo maximal resection if possible, followed by irinotecan, then craniospinal irradiation, and finally chemotherapy consisting of irinotecan and temozolomide. After multimodality treatment was completed, patients would have an Ommaya reservoir placed and only then receive omburtamab.

If we focus in on radiation therapy, there's a clear imbalance in the timing and type of post-CNS relapse treatments received. We already saw that nearly all patients in the trial received CNS-directed radiation therapy compared to just a fraction of the external control. But even when we limit our analyses to patients who did receive radiation therapy in the external control, there

are still differences.

For example, the median time from relapse to first radiation therapy was over 3 times longer in the external control population. Perhaps most importantly, almost all patients in the trial population received craniospinal irradiation. We do not have details on the type and dose of radiation therapy received in the external control, but we do know that no patient in the CGCCR registry received craniospinal irradiation.

No randomized studies to date have demonstrated the utility of craniospinal irradiation in this population, however, a handful of studies, including one from the primary study site, Memorial Sloan Kettering, have suggested that this type of radiation may increase the chances of long-term survival. Based on these studies, there remains a concern that the type of radiation therapy may have affected survival outcomes in Study 03-133 and the external control.

We also observed an imbalance in the frequency and type of post-CNS relapse

chemotherapies received. Again, almost all trial participants received chemotherapy compared to 88 percent in the highly selected primary analysis subgroup of the external control. In the trial, most patients received a regimen including temozolomide and irinotecan. In the external control, most patients received topotecan and etoposide-containing regimens, and no patients in the primary analysis received either temozolomide or irinotecan.

Again, no data exists formally comparing these chemotherapy regimens in patients with CNS or leptomeningeal neuroblastoma. We do know, however, that both temozolomide and irinotecan are active in CNS tumors and have frequently been used as chemotherapy backbones for experimental trials in relapse neuroblastoma.

Finally, we do not even know the full extent of treatment intensity received for CNS relapse by patients in Study 03-133. For example, post-omburtamab therapies were not systematically recorded in this trial. In fact, in the more

recent Study 101, which did systematically capture such therapies, 68 percent of patients received some post-omburtamab therapy for neuroblastoma. Altogether, there's likely a large unmeasured imbalance in overall treatment intensity in the trial and external control populations.

FDA has major concerns that the proposed external control population is not fit for the purpose of comparison to Study 03-133. There are fundamental known differences between these populations, such as the type of radiation therapy or chemotherapy received, and although we do not have robust data to understand how these different non-omburtamab therapies affect outcomes, these differences alone could be responsible for any difference in survival reported by the applicant.

Due to the non-randomized nature of Study 03-133, there may also be unknown differences between populations. For example, we do not know if there are any factors particular to the single center or the fitness of patients to travel to Memorial Sloan Kettering that affected how patients

were selected for this trial. Additionally, since patients had to undergo pretreatment and Ommaya reservoir placement, patients for the single-center, single-arm trial were likely to be healthier than the general patient population with CNS relapse for which this drug is intended.

There are other possible differences that we cannot fully characterize such as overall treatment intensity for CNS relapse, differences in anti-cancer and supportive care in the U.S. compared to Germany, and the type of radiation therapy received in the external control. Overall, these issues firmly undermine our ability to attribute any comparative treatment effect to omburtamab.

So we've just outlined some important differences which call into question whether the external control data are fit for the purpose of comparison to Study 03-133. However, given the unmet need in this rare disease space, where regulatory flexibility is appropriate, we attempted to see how the known biases in this trial might be

addressed by sensitivity analyses.

Our approach started with identifying major sources of bias and later controlling for these factors. The source of the bias we will discuss today include population selection, differences in the study time periods between the two arms, and index date selection. Again, as I've previously described, these are only some aspects of bias encountered in this comparison.

Population selection was an important factor in the applicant's analysis and can have an effect on overall survival. As described earlier, when we looked at the overall source populations, it was a clear imbalance in the therapies received in the trial and external control populations.

The applicant constructed modality groupings to attempt to control for these differences. Again, group 1 is patients who received at least one post-relapse therapy, including surgery, chemotherapy, or radiation therapy. Group 2 is that primary analysis population with patients who received post-relapse radiation therapy and at

least one other modality of therapy. And finally, group 3 is patients who received radiation therapy, surgery, and chemotherapy. This last population, group 3, is likely the most similar to Study 03-133 because the majority of patients in the trial received all three modalities of treatment.

When we looked at survival in the external control across these subgroups, not surprisingly patients who received more modalities of treatment survived longer, with a median OS of over 16 months for group 2 and a median OS of nearly 30 months for group 3. With these additional treatments, it becomes more challenging to attribute survival to omburtamab, and it also means that as the control population became more like the trial population, with more therapies received, patients in the control survived longer.

Overall, the choice of modality group 2 for the primary comparison was driven by the practical considerations of balancing the similarity of treatments received and sample size concerns that would arise if instead we chose the more similar

group 3.

Another potential source of bias that we focused on was the effect of treatment era on survival. The trial and external control populations were not contemporaneous. The first diagnosis of CNS relapse in Study 03-133 was in September of 2005. To address sample size issues, and because we did not know if treatment outcomes had improved over time, we encouraged the applicant to include outcomes from CGCCR patients dating back to the start of the registry in 1990.

As you can see, half the patients in the primary analysis population of the external control were diagnosed with CNS relapse before Study 03-133 even started. Again, we looked at survival in the external control arm based on these subgroups, and we found that survival varied greatly depending on the treatment era, with control patients in the era of contemporaneous of the trial that September 2005 and onwards, surviving a median of over 31 months from diagnosis, over 20 months longer than patients diagnosed in a previous era before the trial. This

suggests that patients who are diagnosed in a contemporaneous era may be better matched to the patients in Study 03-133.

Another source of bias is the choice of index date or where to anchor the start of survival analyses. In an externally controlled trial, this can be complex and can affect how we interpret survival. In a randomized trial, we generally measure survival starting from the date of randomization. Survival is then measured until the patient dies or the time they were last known to be alive.

In an externally controlled trial, this is more complicated because no data for randomization exists. An equivalent trial start date may not exist in each arm. In the experimental arm, in this bottom figure, we're interested in measuring the solid blue area, the survival time from the receipt of experimental therapy to the time of death, or the time the patient is last known to be alive. In the external control, there may not be an equivalent start date of experimental therapy

available, so another index date must be chosen as a start for survival analyses, which could either be the date of diagnosis or the date of last therapy.

In the current study, the applicant has proposed the date of last type of therapy received as the index date in both groups, and this is a variation on the red arrows on the bottom figure. Importantly, in the trial arm, this comes before receipt of omburtamab, and this has important implications for how survival is measured, which favors survival in patients from Study 03-133 over the external control.

This choice of index date, the date of last type of treatment received, creates bias because patients in the trial must have survived from this index date to the start of omburtamab treatment, this blue striped area, to receive the study drug. Essentially, on the study, a death cannot have occurred during the striped period, which is a median of 3.1 months on the trial.

Looking at the external control, 18 percent

of patients died within the stripe time, or 3.1 months after the applicant's proposed index date, meaning even if they were eligible to receive omburtamab on the trial, almost a fifth of patients in the external control may not have even survived to the start of omburtamab treatment. This creates an unfair comparison that is biased towards longer survival in the treatment group for patients who received omburtamab.

In summary, we found that each of these factors could strongly affect interpretation of survival. For population selection, external control patients who received more treatments were more similar to those in Study 03-133 and also live longer. Additionally, external control patients diagnosed in the era contemporaneous with Study 03-133 live longer than patients diagnosed before Study 03-133 began.

Finally, use of the applicant's proposed index date for the survival analyses, the time of last type of post-CNS relapse treatment received, favored survival in Study 03-133 due to the choice

of index date. These issues are highly relevant to the analysis of external control data as major sources of bias. However, there may be additional biases and potential confounding that may be present in the study, leading to further inability to clearly observe the effect of omburtamab.

Having identified these major sources of bias, we used several approaches to mitigating differences in the populations, including some that the applicant presented earlier, to gain better clarity. The applicant's primary analysis adjusts for only some concern that was associated with selection bias using two methods: the restriction of the analysis population to modality group 2 or patients who received radiation therapy and one other modality of therapy and propensity score based weighting.

This approach improves the comparability of the analyses populations with respect to receipt of prior therapies and by balancing the observed distributions of measured patient characteristics across groups, respectively. However, as noted in

the previous slides, FDA's analysis of Study 03-133 and external control populations indicated that there were several other sources of bias. Therefore, FDA's approach to the statistical analyses included additional techniques to adjust for these observed differences across populations.

To address bias introduced by differences in study time periods, we limited the comparison to contemporaneous patients. This additional sensitivity analysis was not performed by the applicant. Additionally, for the survival analyses, we address the impact of index date selection by using the proposed index date for the control. Again, that's the date of last post-CNS relapse treatment modality received and the start of omburtamab treatment in the trial population. This index date approach was included among sensitivity analyses performed by the applicant but was not conducted in a contemporaneous subgroup.

But this slide presents the applicant's primary analysis but limited to patients treated at the proposed recommended dose. This primary

analysis includes only patients in modality group 2. Limiting to those patients with radiation therapy plus at least one other modality of therapy makes the populations more comparable, however, it's important to recognize that this adjusts for only some aspects of selection bias, and we know that there are other major prognostic differences across populations, including treatment era.

We can increase the similarity of the two populations by controlling for treatment era when considering patients with CNS relapse in the same era as those in Study 03-133. Thus, 2005 to the present, the Kaplan-Meier curves cross and the hazard ratio is now 0.9 with a wide confidence interval extending over 2. Here, the observed difference in survival is reduced, however, the sample size is now extremely small, with only 17 patients in the control arm.

In an additional sensitivity analysis, starting with this more comparable contemporaneous population, we can limit the impact of the choice of index date by calculating survival time from the

initiation of omburtamab treatment in that trial population. Again, this analysis uses modality group 2, a contemporaneous subgroup, and the start of omburtamab treatment for the start of survival analyses in the trial arm. Here, the Kaplan-Meier curves continue to come closer together with the hazard ratio now above 1 and a similarly wide confidence interval. In this case, we cannot actually rule out that omburtamab has no effect on survival. Again, the sample size here remains very small because the external control source population was also quite small.

Finally, it is important to recognize that the results presented in these last three slides may still be subject to additional bias and confounding, resulting in imbalance comparisons to survival since we know that patients in Study 03-133 received more intensive, non-omburtamab treatments for CNS relapse than patients in the external control.

In summary, there are several factors that lead us to conclude that survival analyses from

this externally controlled trial are unable to establish a treatment effect for omburtamab. The survival analyses were limited by major biases closely related to that fact that the original source data were not fit for purpose. And when we adjust the analyses to create more similar populations, this results in very small sample size and greater uncertainty regarding estimation of treatment effect, although it is still clear that there are diminishing differences in overall survival as the treatment and control populations become more similar.

We performed several other analyses not presented today which also supported that the observed survival difference was not robust when adjusting for bias or model assumptions. Perhaps most importantly, we still cannot control for important baseline prognostic factors such as less intensive radiation therapy received and overall less intensive CNS relapse treatment in the control, which fundamentally undermines any scientific attempts at comparison.

You may remember the applicant presented forest plots showing multiple individual sensitivity analyses to address specific concerns of bias, one by one. However, these biases occur simultaneously and are not isolated concerns in data from real-world patients. This is why we believe the most scientifically accurate approach is a step-wise method that compounds statistical approaches to more rigorously addressed multiple sources of bias together and is reflected in the comparisons that we have presented today.

Finally, as Dr. Barone discussed, we must remember that these analyses, as well as the applicant's, are post hoc. Depending on varying assumptions and approaches, one can drive strikingly different conclusions from the same data when conducting retrospective analyses. Overall, the results of these retrospective sensitivity analyses highlight substantial uncertainties in determining that any difference in survival between the two populations is a causal effect of omburtamab.

Our last major issue is the lack of supportive response rate data from Study 101 to verify anti-tumor activity. Because of the limitation from the survival data from Study 03-133, tumor response data from Study 101 were critical to support efficacy in the setting. As Dr. Barone explained, overall response rate is a unique endpoint in oncology that can be interpreted in a single-arm study, as the natural history of such tumors is not to regress on their own. Again, this is very different from overall survival, which we just saw can be influenced by many factors.

Unfortunately, as I will describe in detail, fundamental issues in baseline and response assessment limited our ability to confirm that omburtamab has anti-tumor activity in neuroblastoma with CNS or leptomeningeal relapse. Looking back at our regulatory framework, a single adequate or well-controlled trial needs to be supported by confirmatory evidence; and as we heard from the applicant, in this case we're relying on supportive data from Study 101.

Study 101 was designed specifically to provide such supportive data in the form of overall response rate. Again, this was a single-arm trial, however, unlike 03-133, it was multicenter. Tumor responses were measured at 5, 10, and 26 weeks by imaging and were assessed by blinded independent central review. RANO brain metastases criteria were used to assess parenchymal lesions, and EANO and ESMO guidelines were used to assess leptomeningeal disease.

To provide context, again, it's important to recall that this therapy was studied in the setting of a multimodality recommended regimen that included surgery, chemotherapy, radiation therapy, chemotherapy again, and then omburtamab. Unlike in Study 03-133, in Study 101, this was protocol specified.

Given this heavy pretreatment, it is not surprising that the majority of patients had minimal or no CNS leptomeningeal disease at baseline. Ninety-eight percent of patients were CSF cytology negative and 60 percent had no

evidence of disease per blinded independent central review. This left just 20 patients with any CNS or leptomeningeal disease on imaging at baseline.

Per blinded review, there were seven responses in this group of which four were confirmed, and I'll describe later why confirmation of response is important. However, in reviewing the clinical data and the imaging responses, there are critical limitations with each one of these responses.

First, there were fundamental issues in baseline assessment. All reported responders with leptomeningeal metastases had negative CSF cytology at baseline. Additionally, clinical signs and symptoms were not incorporated into the disease assessment. This is important because per EANO and ESMO guidelines, without positive cytology and clinical data, none of these patients who qualify as having confirmed or even probable leptomeningeal disease at baseline. In fact, these patients can only be classified as having possible diagnoses of leptomeningeal disease at baseline.

Additionally, there are issues with washout of prior therapies or inadequate time from prior therapies to the baseline scan. Half of the confirmed responders received radiation therapy or chemotherapy within 30 days of their baseline scan. This limited washout of prior therapies creates uncertainty regarding attributing any contribution of effect to omburtamab in these cases.

We saw a prime example of this issue of contribution effect just now in the applicant's presentation. In this single example they chose to highlight, they showed us MRIs from the patient with a complete response, and it occurred only after the patient received systemic therapy that was subsequent to the receipt of omburtamab. In that case, given the timing of treatment, it's impossible to cleanly attribute the response to omburtamab.

Furthermore, there were issues in response assessment as well. Only 4 patients had confirmed responses. RANO brain metastases criteria, which were reviewed by the applicant, require

confirmation of partial response and complete response in non-randomized trials to ensure that these responses are not due to measurement error, and this is consistent with RECIST and other well-accepted response criteria as well.

This was another issue with the case the applicant presented in their slides, which had no confirmation of response. In further limiting this confirmation of response issue in the trial, most of the reported confirmed responders received systemic therapy between their initial response and the scan demonstrating confirmation. As clinicians, this is concerning because it limits our ability to attribute confirmation response to the effects of omburtamab with now additional concerns for measurement error and the limitation, that even if a response is real, it may not be durable.

Finally, leptomeningeal disease and recently treated CNS parenchymal disease can be challenging to measure precisely. This was borne out in Study 101, as there was disagreement between

primary reviewers in all seven reported responses, requiring adjudication, and this next point is particularly concerning. In most of these cases, the second reviewer actually recorded no evidence of disease at baseline. This lack of agreement raises further concern for measurement error in these cases.

To summarize, measurement of tumor responses in this trial was challenged by issues in both baseline and response assessment, providing no reliable evidence to support anti-tumor activity in this setting. There was inadequate diagnosis of leptomeningeal disease. Concomitant therapies created uncertainty in determining the contribution of effect of omburtamab. There was a lack of true confirmed responses, and there were serious concerns for measurement errors.

This left no unequivocal tumor response in Study 101. And even if one or two of these responses were, in fact, real, this limited overall response rate would be insufficient to support efficacy in this setting. This is especially

concerning, given the applicant's stated mechanism of action that omburtamab will reach and target B7-H3 expressing tumor cells in the entire CSF compartment, including micrometastatic CNS disease.

We discussed earlier that there's limited biologic plausibility with intraventricular therapy for CNS parenchymal metastases because these metastases simply do not exist in the CSF compartment. Of particular concern, 71 percent of patients in Study 03-133 at CNS relapse, and 70 percent of patients in Study 101 who had any recorded disease at baseline, harbored CNS parenchymal metastases. And it's been well established that CSF administration of drugs results in limited brain penetration to reach such parenchymal metastases, and the applicant has provided no conclusive evidence to support otherwise.

Furthermore, there's no clinical evidence to support the treatment and targeting of micrometastatic disease in these studies. Only one patient had positive CSF cytology at baseline, and

this patient developed progressive disease. Altogether, there appears to be no clear evidence of anti-tumor activity following the applicant's stated mechanism of action in these patients.

Finally, although we ask you to consider efficacy in your discussion today, there are safety risks with this product for the given indication. Generally, these include risks from radiation exposure and non-trivial risks associated with placement and use of an Ommaya reservoir shunt.

Observed risks include those related to myelosuppression; chemical meningitis; infusion-related reactions; neurotoxicity; and late effects from radiation exposure. More than 40 percent of patients in each trial experienced serious adverse events. Finally, about one-fifth of patients did not receive a second dose due to adverse events.

As clinicians ourselves, we deeply understand the critical need for better treatments in this disease, however, in review of the available data, we identified fundamental issues

that limit the ability to construct an adequate and well-controlled trial that is capable of demonstrating that the addition of omburtamab to intensive multimodality treatment improves survival.

The external control population does not appear to be sufficiently comparable to the trial population due to clinically important differences. These differences fundamentally undermine any attempts at comparison, and we can see evidence of this when we attempted to identify and adjust for some of these differences.

The analysis we presented illustrate the comparisons of survival are not reliable due to known substantial biases in the small sample size of the external control. Adjusting for bias resulted in survival curves that crossed with hazard ratios approaching and exceeding 1.

Again, these are all retrospective analyses, and as we saw from the applicant, depending on how you do the analyses, you can arrive at different conclusions. However, we strongly believe that the

additive approach we took to adjust for some of these important known sources of bias is the most scientifically appropriate approach and result in a more accurate assessment of survival in the two populations.

Finally, we do not appear to have the necessary support of evidence in the form of response rate data to demonstrate that there is anti-tumor activity with omburtamab in this population. What we do know is that there are risks with this treatment, including surgery from an Ommaya reservoir placement and the risk of toxicities that may result in additional hospitalizations or interventions.

The applicant's suggested that we need to make a judgment on the best available data rather than a theoretical ideal. We firmly agree that it is important to make the most of the data that are available, and that is why we decided to be flexible in considering use of an external comparator, and why we have worked so closely with the applicant to see if it was possible to use the

external control data from the German registry to evaluate whether omburtamab improves overall survival.

Although this is not the conclusion we hoped to reach when we started reviewing this application, after very careful consideration of these data, we do not think that they're sufficient to establish effectiveness of omburtamab; and this is important because children with this serious cancer do not just need more treatments, they need treatments that work.

Keeping in mind the complex issues you've heard today, in your discussion, we ask that you consider whether data provided by the applicant isolate the treatment effect of omburtamab from the effects of multimodality therapy for CNS or leptomeningeal relapse, or if additional data are needed.

We will also ask you to vote on the following. Has the applicant provided sufficient evidence to conclude that omburtamab improves overall survival?

And now, I'll turn it over to the chair, Dr. Lieu. Thank you.

Clarifying Questions to Presenters

DR. LIEU: Thank you for that presentation.

We will now take clarifying questions for both Y-mAbs 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 your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

So we'll open up the floor now for clarifying questions for the presenters.

Dr. Hudgens?

DR. HUDGENS: Hi. This is Michael Hudgens, University of North Carolina.

I had a question for Dr. Mehta related to slide 35, which looked at the impact of adjusting or controlling for the era, the treatment era, and based on that slide, it appears that makes a huge difference in these analyses if we restrict just to the contemporary era.

I would like to hear a comment on how this analysis differs from the seemingly -- the conclusion that one would draw from the applicant's analysis that adjust for era, specifically on their slide that's labeled CE-28, where they also seem to adjust for calendar time and come to a very different conclusion.

DR. DONOGHUE: Thank you, Dr. Hudgens.

I was wondering if we could bring the slide up that Dr. Hudgens referred to, that shows contemporaneous populations. I think it was -- was it slide 16? Let me look and see which one it is.

Gautam, do you know?

DR. MEHTA: I believe slide 35, please.

DR. DONOGHUE: Thirty-five. Okay.

(Pause.)

DR. DONOGHUE: While we're bringing the right slide up, Dr. Mehta, do you want to touch upon this? And then we can also ask others in our review team to address the differences.

I think the primary reason for differing conclusions is we had different methods of adjusting for the treatment era, which we can go into a little bit more detail on.

DR. MEHTA: Yes. Thank you, Dr. Donoghue.

We took a different approach than the applicant, as you pointed out, to adjusting for the treatment era, and the way we approached this is we wanted to follow a logical progression in terms of matching these two cohorts to the time that they were treated.

The applicant presented patients who were selected based on Trial NB97 in 2004 to be compared to the Study 03-133 population. So those were patients who were diagnosed from 1997 and onwards.

We thought that it would be most appropriate to select patients who were diagnosed from 2005 and onwards because this was the same era as the patients in the trial. And I think there are several reasons that could account for the differences in survival in these groups, and that may not just be limited to treatment, but it may also be limited to changes in diagnosis, screening, and management that may have occurred during that time.

I think I'll hand it over to Dr. Mishra-Kalyani for the stat's perspective.

DR. MISHRA-KALYANI: Hello. This is Pallavi Mishra-Kalyani from FDA statistics. You mentioned that these results are quite different from the applicant's results presented. We don't feel that the applicant's approach to creating a contemporaneous subset of the external control is scientifically rigorous. They include two of the three national protocols, NB97 and NB90, but if you examine the Kaplan-Meier curves, both NB90 and NB97 have steep drop off almost immediately after

enrollment, indicating that prognostically these patients may be quite different at baseline.

We feel both of these groups should likely be excluded if we were to make the decision based off of the national trial protocols because when deciding which patients are similar enough for comparison, we really should be considering factors at baseline, and those are related to both prognosis and contemporaneity of the patients in their diagnosis.

As Dr. Mehta mentioned, we believe our approach to addressing treatment era is more objective because we selected patients from the specific time period in which they would have been eligible for the analysis population of Study 03-133. This, thus, ensures comparability in terms of time of diagnosis to the study population.

There are some additional differences between this analysis and the one presented by the applicant on the slide that you mentioned, CE-28. That slide also only included patients at the first relapse. However, our analysis in that particular

population of patients at first relapse drastically reduces the sample size of the overall population because we're also still controlling for the other known sources of bias to making them more similar in respect to time and potential follow-up, in addition to disease stage; so we only have a total of 60 patients.

We can agree that the results are interesting, but the small sample sizes and other residual uncertainties that we have described, with regard to the comparison to the external control data, still exists, and so the strongest inference we can really make from those subgroup results is that they are hypothesis generating and should be explored further with additional data.

DR. HUDGENS: Yes, that answers my question.

DR. LIEU: Thank you, Dr. Hudgens.

Dr. Nieva?

DR. NIEVA: Thank you. This is Jorge Nieva from USC. I'm a little confused on FDA's slide 17 in showing that the median time from RT was short in Study 03-133 relative to the external control,

and then trying to reconcile that with the long list of treatments, including resection and irinotecan, craniospinal irradiation, that would typically be delivered to the patients prior to the start of therapy.

So the resection and irinotecan, was that really being done in less than 21 days in the study population or is there some error there?

DR. DONOGHUE: Thank you for the question. We're presenting a median here, and as you can see, there is a bit of a range as well, a relatively wide range, from the median time from relapse to first receipt of radiation in Study 03-133. There isn't an error in our calculations, however. There is no error.

DR. NIEVA: Okay. Thank you.

My other question is for the company.

The concern about selection bias and the data coming from a specialized center in New York, and then in other specialized centers in the multicenter trial, is being compared to whole country data. And my question is, for the

treatment of patients in Germany, what is the concentration of the patients being treated? Are they all typically treated at one or two specialized centers or is the treatment of neuroblastoma distributed among multiple low-volume centers? Thank you.

DR. RAJAH: Dr. Rajah, Y-mAbs.

In Germany, there are three national protocols that's constituted the German data that we submitted, and the centers that were treated with these treatments were a number of hospitals distributed throughout the country. So these were population trials and involved a number of centers scattered throughout the country.

I think on the other point around the selection bias, potentially at MSK, we don't believe there's any suggestion that MSK patients get any better or fitter than those outside MSK. I'd like to share a slide that shows the survival difference in MSK and outside MSK just to illustrate that from 101, there was no selection bias in these treatment-free patients.

Slide up, please. This slide is for the Trial 101, which is a multicenter study, and it shows that there was no difference between overall survival between MSK and non-MSK sites. Furthermore, 03-133 had very broad inclusion criteria as well, and I also say an additional point that this supports the broad inclusion that roughly about 90 patients in the 03-133 were eligible to receive multimodal treatment, and that represents approximately one-third of the overall population of patients with CNS/leptomeningeal metastases in the U.S. There's a similar proportion that about one-third of patients was also eligible to receive multimodal treatment in other external data sources such as the German data, as well as the SIOPEN data.

So it kind of tells you that a majority of the patients who were able to receive multiple treatments and we were able to recruit in the trials were included in 03-133. Thank you.

DR. NIEVA: Thank you for that response.

Just in follow-up, do you have any similar

data comparing outcomes of MSK-treated patients to other population-based registries, say, in the state of New York or other regional databases that may give us a sense that this is not a specialized center effect?

Thank you, and that concludes my questions.

DR. RAJAH: Dr. Rajah here; Y-mAbs.

Dr. Morgenstern would like to expand on this.

DR. MORGENSTERN: Daniel Morgenstern, Hospital for Sick Children. I think the challenge is the lack of other available data sources because the site of relapse is generally not a data element that is captured in most databases, including population registry. So although we'll know about a patient having relapse disease, it will not be possible to identify them as having CNF relapse.

DR. NIEVA: Thank you.

DR. LIEU: Dr. Donoghue, do you have a comment?

DR. DONOGHUE: I do actually. If it's ok, we would like to provide a little bit more context

for the slide that Y-mAbs just presented, looking at outcomes of patients in Study 101 who received treatment at Memorial Sloan Kettering versus those who did not receive treatment at Memorial Sloan Kettering. So I'd like for us to have Dr. Mehta respond to that, and then following his brief response, I'll see if Dr. Chatterjee has anything to add. Thank you.

DR. MEHTA: Are we able to have that slide up from Y-mAbs?

DR. RAJAH: Slide up.

DR. MEHTA: Thank you.

From a clinical interpretation standpoint, there are some limitations in this analysis looking at Memorial Sloan Kettering versus other sites. The primary concern is that the data are still immature to make inference, and we can see from the patients in the non-MSK site that there is a fair amount of early censoring. So it's still early to make inferences from this analysis.

I'll ask Dr. Chatterjee from statistics to comment as well.

DR. CHATTERJEE: Hi. This is Somak Chatterjee from FDA statistics.

To elaborate on Dr. Mehta's point, the median follow-up time for patients who are treated at MSK was 29.5 months with 38 percent deaths, while the median follow-up in non-MSK site was just 18 and a half months with 15 percent deaths. This also includes that MSK patients are almost 50 percent of the total population, and I believe the treatment center of MSK was opened early as well, so this data is immature and not robust enough for interpretation of OS analysis.

DR. DONOGHUE: Thank you, Dr. Chatterjee for that, and thank you, Dr. Lieu.

DR. LIEU: Thank you.

DR. WIDEMANN: Yes. Thank you. Brigette Widemann. I have a question as it relates to craniospinal irradiation.

Is this considered standard in neuroblastoma with leptomeningeal parenchymal disease in the United States, or is this more related to the protocol that was followed?

DR. RAJAH: Dr. Rajah, Y-mAbs, here.

Craniospinal irradiation was used in the majority of the patients in 03-133 for the treatment of neuroblastoma, although there were some patients in both 101 and 03-133 that did not receive craniospinal irradiation. So these individuals who did not receive it received other forms of clinical radiation.

I will invite Dr. Morgenstern to comment on that craniospinal irradiation is considered standard treatment for neuroblastoma.

DR. MORGENSTERN: Daniel Morgenstern, Hospital for Sick Children. I think the bottom line is that there are no national guidelines for the management of CNS recurrence neuroblastoma, so practice probably varies between institutions based on local practice. I think for most clinicians, some form of radiotherapy would be considered routine, but the details I think would vary on individual patient, the age of the patient, and likely individual local practice. Thank you.

DR. WIDEMANN: Thank you.

DR. LIEU: Dr. Donoghue, do you have a comment from the FDA?

DR. DONOGHUE: Thank you. I guess we would just add that we agree at this point in time, we don't think there is a well-defined standard of care with respect to craniospinal irradiation in the United States, at this point.

I would point out that for the interpretation of the radiation received in the external control, we did not have details with respect to the type of radiation received beyond -- in some cases, most likely they are whole brain irradiation or focal irradiation, but we do not have details regarding how it was administered in the external control either. Thank you.

DR. RAJAH: Dr. Rajah, Y-mAbs. May I comment on this?

DR. LIEU: Yes, please.

DR. RAJAH: In the Germany database, it's correct that we don't have specific data relating to what dose of radiation was administered to those patients with CNS relapse. However, what we are

able to say is when we look at the protocols in the latter two studies, particularly in the national protocols, they do recommend to the investigators typical radiation doses that can be administered for various systemic metastases; and in that vein, it includes a recommendation for spinal cord lesions up to 30 gray.

Although that doesn't indicate exactly what dose is useful in CNS lesions, it leads us to suggest that perhaps the dose that was given to many of these patients was considerably higher than what was used at MSK, and we believe the radiation dose ranged between 18 to 20 gray.

This is important from a safety perspective, as was alluded to earlier on. There are concerns about cumulative radiation exposure in many of these patients in the long term, and there's plenty of evidence that has been published, that notably a cohort of patients from St. Jude's, they looked at adult survivors of childhood ALL patients, and they were able to show strong correlations of patients with severe neurocognitive impairment related to a

dose of 24 gray or above verses 18 gray.

The reason why this is important also is because omburtamab, purely by its mechanism of action, where it delivers a payload directly to the tumor cells expressing B7-H3 at a cellular level, possibly enables reduction in damage to normal tissues, and therefore enables a dose of CSI to be lower while still maintaining the efficacy.

I just wanted to add this point to say that we believe that although the doses from the German registry, or German database, we don't have definitive data, but there's indication from the protocol that they were a higher cumulative radiation compared to the MSK data. Thank you.

DR. LIEU: Thank you.

Dr. Donoghue, do you have a comment?

DR. DONOGHUE: Yes. I'd like to ask Dr. Mehta to provide a little bit more background on what we do know about craniospinal irradiation.

Could you please bring up backup slide 11?

DR. MEHTA: Thank you, Dr. Donoghue.

There are not a lot of data to support any

specific type of radiation therapy in this particular setting, but as the applicant alluded to, in an early cohort reported out of St. Jude's, two long-term survivors had received craniospinal irradiation. There's also been a couple studies that have been published from Memorial Sloan Kettering on craniospinal irradiation, and I've included data from one of these retrospective studies that compares their experience with focal irradiation versus craniospinal irradiation, which suggested improved survival outcomes with the latter.

You can see the median survival times at the bottom here, but it's important to recognize that the change to using craniospinal irradiation at their site coincided with the use of radiolabeled antibodies as well, which included omburtamab. And here we're running into the same problem we faced with this application in reverse but, again, are limited by the retrospective study design in terms of taking anything away from this.

DR. DONOGHUE: Thank you, Dr. Mehta.

DR. RAJAH: Dr. Rajah, Y-mAbs. If I may just add to this.

I'd like to show a slide showing similar data from 03-133 for those patients who received CSI versus patients who did not receive CSI. As I alluded to earlier, there were 10 patients in 03-133 who did not get CSI, and when we analyze the overall survival results, granted, there's a small number of patients from 03-133; when we compared that to those taking no CSI, the KM curves, Kaplan-Meier curves, were very similar, as you will see very shortly from the slide here.

But when we look at the patient characteristics, there did not appear to be any notable differences in the baseline patient or disease characteristics that might explain why the CSI patient did not do any better. And this similar picture of lack of difference was also replicated when we looked at the 101 patients as well.

So in conclusion, what we're saying is CSI is not expected to make a dramatic difference or is

a key driver of the survival advantage seen. What does drive the survival advantage is a combination of multimodal therapy plus omburtamab. This is what drives the overall survival in these patients. Thank you.

DR. LIEU: Dr. Donoghue, do you have a comment to this? And then I think we need to move on to the next question.

DR. DONOGHUE: Sure. Thanks.

I think I would just emphasize the lack of a really robust sample size in these comparisons. I don't think that you can make good inferences from that data. Thank you.

DR. LIEU: Thank you for that discussion.

Dr. Vasan?

DR. VASAN: Hi. Neil Vasan, Columbia University. I had a question for the applicant around the FDA slide 70 and 71 on this assessment that patients had really minimal CNS disease at baseline and that the cytology was almost close to 100 percent negative.

I was wondering if the applicant in the CSF

patients had done any additional characterization, any more sensitive analyses of micrometastatic disease, for instance circulating tumor DNA of MYCN, for example.

DR. RAJAH: Dr. Rajah here from Y-mAbs.

There were a number of patients in the 101 that were indicators of no measurable or no evaluable diseases. This can either mean no evidence of disease or it can mean no disease that was detectable by the MRI imaging scan.

In 03-133, all the patients had baseline scan at the time of CNS relapse diagnosis, whereas in the 101 study, all of the patients had the baseline scan just prior to omburtamab after they had received all of the multimodal therapies. So these were patients who had already received surgery, debulking the tumor, followed by radiotherapy and chemotherapy, which is why we see a higher proportion of patients who have no measurable disease in the 101. However, we do note that many of these patients will still have minimal residual disease and micrometastases that will go

on to relapse and have a poor prognosis.

As evidenced by even other patients in the German registry or the SIOPEN, despite multimodal treatment, these patients still go on to relapse and now have a poor prognosis. Even in the 101, we see that. So I think that's a strong rationale to have a therapeutic strategy very similar in both those with measurable disease and no measurable disease.

As far as the CFS cytology and the proposed suggestion that we can use DNA as a validated surrogate, at the moment there are no validated markers to use this, but this is being investigated ongoing at the moment. At the moment, what we have is a qualitative assessment of CSF cytology. In other words, a lumbar puncture requiring the presence of tumor cells, it is qualitative and the sensitivity is low.

I should also add, to refer to one of the slides that the agency presented, it is well known in neuroblastoma. It is very unlikely to see neuroblastoma cells from CSF samples, so it is not

surprising in this particular tumor that the CSF cytology was negative. What we have to go by is the firm evidence of disease at baseline. We have MRI scans in 20 patients with measurable disease, indicating presence of leptomeningeal parenchymal lesions. Thank you.

DR. LIEU: Thank you.

I know that we still have several clarifying questions yet to be asked. For those of you with your hands raised, there will be time after the open public hearing session to return to these clarifying questions, so I believe we'll do that.

So for right now, we will take a quick 30-minute lunch break. Just a reminder to all panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break. We will reconvene at 1:00 p.m. Eastern time. Thank you very much.

(Whereupon, at 12:35 p.m., a lunch recess was taken.)

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

(1:00 p.m.)

Open Public Hearing

DR. LIEU: Welcome back, everybody. We will now begin the open public hearing session.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your participation in the meeting.

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

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

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

(No response.)

DR. LIEU: Speaker number 1, are you available? You may be on mute.

(No response.)

DR. LIEU: Okay. I believe we'll come back to speaker number 1 at a later time.

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

MS. SOLLOWAY: Yes. Good afternoon. Can you hear me?

DR. LIEU: Yes, we can hear you.

MS. SOLLOWAY: Thank you very much. My name is Elise Solloway. My husband, Joseph Solloway, joins us as well. We have no financial relationship with anyone involved in this hearing.

There are no words that are more terrifying to here than, "Your child has cancer." On March 8, 2004, those words were said to my husband and me.

Jenna, my perfect, beautiful 23-month-old daughter was sleeping all the time. She wasn't really eating and she was no longer able to walk. Knowing that she was sick but obviously not realizing how sick, we took her to our pediatrician who prescribed antibiotics for an ear infection and sent us on our way.

The symptoms persisted, so a few days later, we returned to him, and seeing that she could no longer walk, his words to us were, "Let's do a quick CT scan just to rule out the scary stuff." Well, the scary stuff turned out to be our reality, and she was eventually diagnosed with stage 4, high-risk neuroblastoma. We were instantly thrown into the world of childhood cancer.

Jenna endured 5 rounds of chemotherapy, many rounds of localized radiation, and 2 tandem stem cell transplants. She was a rock star with the cancer clearing from her body before her first transplant. Even though she spent so much time inpatient, she was unaffected. She continued to play, take walks in the halls, and even reach her

learning milestones. By Columbus Day of that same year, her frontline therapy was completed, she had no evidence of disease, and we were sent home to recover and quarantine for the winter.

One year later, on an early Tuesday in October, we received a call from Jenna's daycare that she was dancing and spinning around, and while spinning vomited. Naturally, this was very concerning, so we immediately took her back to our pediatrician who ordered a brain MRI. The results showed two large tumors in her brain, one in the left frontal lobe and one in the back. We were admitted and began chemo the next day.

With a CNS relapse of this magnitude, the conversations turned to palliative care and getting her through the [inaudible - audio break]. We refused to accept this approach, and we began our worldwide search for new trials. While we were inpatient, another neuroblastoma mother told me about a phase 1 trial that had just recently opened at Memorial Sloan Kettering. This was the 8H9 antibody therapy, a trial for neuroblastoma

patients suffering from brain relapse. We finally had hope.

In order for Jenna to qualify for this trial, she had to have another round of scans to make sure the rest of her body was clear of cancer cells. She also had to have a surgery to biopsy and debulk the tumor. At the conclusion of this surgery, we were told that she should be able to qualify for this trial, and we were absolutely elated. Once we had the final approval, we packed our bags and headed straight to New York.

With our first visit to Sloan Kettering and meeting the neuroblastoma team, we knew immediately that we were in the right place to fight this disease. After being at MSK for some time, it became clear to us, through whispers and innuendos, that those kids who were there for the 8H9 trial were the lucky ones. The parents were calling this a slam-dunk for brain relapse.

While we don't remember many of the specific details of her treatment leading up to the 8H9 injections, we can say that she had chemotherapy, a

dual craniotomy done over the course of 2 days, and whole brain and spine irradiation, and an Ommaya placement. Naturally, Jenna had her fair share of low platelets, various infections, and even a little leak of CNS fluid all over her baseball cap.

So here we finally were at the 8H9 injections. Looking back at all the treatments that Jenna had gone through, the 8H9 immunotherapy was the least invasive, and dare I say the easiest thing that she had to endure. It's hard to imagine that something that seems so innocuous to us has had the greatest impact on her being with us today. Even though our memories of the actual 8H9 treatment are dramatic, we want to firmly stress that we believe that this trial is the reason that Jenna is cured of neuroblastoma. I want to emphasize that the brevity of those words cannot be overstated. The simple fact that we don't have a lot to express having undergone this therapy is a testament to its efficacy and impact on our family.

Today, Jenna is a beautiful 20-year-old high school graduate. While she does suffer from many

late-term effects from her cancer treatment, we strongly feel that those effects are not from this therapy but rather from all the traditional chemo and radiation she had before this trial. On more than one occasion, leading doctors in their field have commented that they haven't seen many people having had as much cancer therapy as Jenna has had, but she's here, she's healthy, and she's able to lead a wonderful happy life.

I thank you for your time, and I solemnly hope that you approve this request so that other children may have the chance that Jenna has been given. Thank you.

DR. LIEU: Thank you for those comments.

Speaker number 3, your audio is connected now. Will speaker number 3 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. ZUCKERMAN: Thank you very much. Can you put my slides up, please?

I'm Dr. Diana Zuckerman, president of the National Center for Health Research. We scrutinize

the safety and effectiveness of medical products, and we don't accept funding from companies that make those products. Our largest program is the Cancer Prevention and Treatment Fund.

My expertise is based on postdoctoral training in epidemiology and public health; my previous policy positions at congressional committees with oversight over the FDA; my previous position at the U.S. Department of Health and Human Services; and as a faculty member and researcher at Harvard and Yale.

I'll just zoom through this one. You know what these studies are looking like. We have a single-center, single-arm trial and an interim report of a multicenter also single-arm study with a small number of patients, seven responders according to the sponsor, but only three have been confirmed, and a primary endpoint that hasn't been mature yet.

In terms of safety, 19 percent of the patients were permanently discontinued due to an adverse reaction in Study 03-133 and 28 percent in

Study 101, and 3 percent of these were due to chemical meningitis and one case of fatal intracranial hemorrhage. For shortcomings, obviously there was only one completed study. It wasn't randomized, it wasn't blind, and it didn't have a good control.

In terms of the external controls, the children in the external control had more intensive prior treatment. There were population differences, as well as treatment differences. And because overall survival for these patients has improved since the control data were collected and since there was a very small sample of control data, the problem is we don't know what to do with these controls. We can't assume that they're similar enough to be experimental group, and for that reason the overall survival differences can't be reliably attributed to the drug.

In addition, "the application does not include reliable response rate data." That's a direct quote from the FDA. No patient in Study 101 demonstrated a response that can be unequivocally

attributed to the drug, and the overall response rate data in Study 03-133, there was none, and it was just limited overall response rate data in Study 101.

These are heartbreaking stories, and we want these children to get the treatment that they need, but it's also important that FDA continue to be a gold standard. So when we look at the FDA summary that the comparator is too dissimilar to the subjects in the experimental treatment and there's no reliable information on tumor response rate, therefore the submitted study cannot be considered an adequate and well-controlled trial necessary to establish effectiveness, and that by law is a requirement for the FDA.

So there is an unmet need and the data are inadequate. I guess my first question is, why isn't this an accelerated approval application, and are the data even good enough for an accelerated approval application?

We want to help these children, and these children deserve help, but it's also important that

the FDA continue to have their standards. So the question here is, if the sponsor is so interested in helping these patients, why didn't they conduct a randomized, double-blind, controlled trial? Even a small one would have been better than an uncontrolled trial. And what's the incentive to conduct a well-designed study for this company, or any other company, if a poorly conducted study with questionable findings results in approval? When the FDA approves a drug based on inadequate data, all companies, not just the company involved in this particular review, all companies lose the incentive to conduct well-designed studies.

The bottom line is patients deserve better, and we're not doing patients any favors if we approve treatments that aren't proven to work. But these children do need treatments, and that's why the FDA has an expanded access program, and that's the way to give patients access to experimental drugs. That access, expanded access, is usually free, it's carefully monitored, and most important, the families and the patients understand that it's

an experiment, and they know that they're taking a risk, and they are freely choosing to do that. So why should they be paying for a drug that's really still an experimental drug?

The bottom line is -- I can't believe I have to say this -- without an appropriate control group, it's not possible to provide evidence that patients and doctors are really needing to make informed decisions, and in this case, unfortunately, the preponderance of evidence doesn't support approval.

Thank you very much for the opportunity to speak today.

DR. LIEU: Thank you for those comments.

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

MR. UNGER: Mark Unger. I'm representing my family. Our son Louis was diagnosed with stage 4 neuroblastoma in November 2001. After one year of treatment at Memorial Sloan Kettering, which I

abbreviate as MSK, he was declared NED or no evidence of disease. The key fact of this outcome was the use of innovative mouse antibodies developed at MSK to activate our son's own immune system to kill the neuroblastoma cells.

In 2003, he relapsed with a tumor in his brain. This impacts about 10 percent of all neuroblastoma kids. We were told by Nai-Kong Cheung, the head of the neuroblastoma oncology team at MSK, that Louis had, quote, "zero chance of survival with this type of relapse." After this horrific shock, we began the standard treatment protocol for a brain relapse.

First, the golf ball size tumor was removed surgically from our 5-year-old son's brain, followed by months of radiation to eradicate any remaining cancer cells. We knew this treatment was effective in the short term, but within 1 to 2 years, the cancer would always return. If Louis would receive more radiation treatments then, it will result in severe and irreversible cognitive losses. There will be no life-saving options left

for him at that time.

My wife and I began frantically researching possible treatments that could save our son. We scoured the clinicaltrials.gov website and called doctors around the world for help. The answers were mostly, quote, "We are so sorry." Among very few options was a phase 1 clinical trial at MSK that used the same antibodies we received in his initial treatment but were modified for use in the brain. As the brain has no immune system, these novel antibodies were radiolabeled with very small amounts of radiation. The goal of this treatment was essentially to create guided missiles to search and destroy any remaining neuroblastoma cells in the brain and spinal fluid.

We decided to enroll Louis in this trial. We knew it was a long shot. Dr. Kim Kramer, who led the MSK trial, managed our fears with a kind heart and reassuring expertise. Louis would be the only child to join the trial and number 14 overall. It was a risk we had to take. The alternative was not an option. When the drug was administered into

his brain, the antibodies would attach themselves to the neuroblastoma cells in the spinal fluid and brain. The miracle drug would then release a small amount of radiation and kill any remaining neuroblastoma cancer cells.

He received 4 intrathecal treatments over the next year and a half with minor side effects. The cancer never returned. Today Louis is 24 years old and very proud to be the trailblazer of this treatment. He is the first survivor of this always deadly relapse. MSK has been using Louis' protocol for all neuroblastoma brain relapse patients since Louis' success.

This treatment as presented before you today is now the standard of care at MSK with a survival rate of over 60 percent. It has now been over 17 years since Louis completed this treatment and, sadly, only wealthy parents who can afford to come to MSK in New York can receive this life-saving procedure. I implore the panel to approve this treatment today so it can be administered everywhere in the U.S. and save countless children,

regardless of their ability to pay.

I'd like to make this real for all of you. Imagine if your 3-year-old child or grandchild was diagnosed with stage 4 neuroblastoma tomorrow and was struck with this relapse. You would move heaven and earth to get this treatment because the alternative is zero chance of survival.

My son Louis also wanted to say a few words.

"Hello. My name is Louis Unger. I was diagnosed with stage 4 neuroblastoma at age 3 in 2001. I was finally declared free of cancer in 2008. I have been through a lot, way more than any child should have to. I do not wish for any other child to go through the same. The words 'zero chance of survival' put an incredible burden on my parents and loved ones that I also wish to share with no other.

"This is a chance to cure cancer and make the impossible reality, not just for me, but for every child and family inflicted by this. Without this clinical trial, I would not be alive today, so I write this for you [indiscernible], and I humbly

ask for your approval. Thank you. Louis."

Clarifying Questions to Presenters (continued)

DR. LIEU: Thank you for those comments.

I wanted to give speaker number 1 an opportunity to provide comments if they've joined the call.

(No response.)

DR. LIEU: Okay. Just a reminder for everybody just to keep yourself on mute if you're not speaking.

I certainly want to thank all the open public hearing speakers. The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience.

I do want to move back to the remaining clarifying questions, as I know that we had some prior to the break. Just as a quick 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 gentle reminder, it would be helpful to acknowledge the end of your question with a thank you, and end your follow-up question with, "That is all for my question," so we can move on to the next panel member.

So moving on in the order in which we saw the hands, I want to move to Dr. Bagatell Berg for your question.

DR. BAGATELL: Hi. This is Ro Bagatell from Children's Hospital Philadelphia. My question was in regard to the applicant's slide number 37.

One of the boxes on the far left said that for the control group, the patients too frail to be treated were excluded, which I'm guessing was an effort to try to deal with the fact that the patients who were mainly involved in the clinical trials had to be well enough to travel to participate, as well as to have an Ommaya placed, and everything else that's been mentioned.

But it wasn't clear to me what the criteria -- like what does it mean to be too frail? How was that defined? I'm assuming there had to be some objective criteria to exclude what looks like a reasonable number of patients there in the orange boxes.

DR. RAJAH: Dr. Rajah, Y-mAbs. I'm going to ask Dr. Christensen to comment.

DR. CHRISTENSEN: René Christensen, Y-mAbs. Slide up, please. While we wait, the criterion for excluding patients too frail was simply that they did not receive any treatment, and the frailty was substantiated by the fact that they had an overall survival of less than a month, a median overall survival. Thank you.

DR. BAGATELL: Thank you very much for clarifying. I think that gets to the point that was made by the FDA reviewer, though, that the comparator group, it takes out the people who died quickly. So that gets to that immortality biased piece, but then included are patients who maybe got some therapy but not necessarily as many therapies

like surgery and radiotherapy.

So I guess we just have to keep that in mind, that some of those patients were retained, then it was really only the patients in the worst clinical condition who were excluded from the control. Thank you.

DR. LIEU: Thank you, Dr. Bagatell.

Dr. Harrington?

DR. HARRINGTON: Thank you. We heard two messages, different messages, from the FDA and the applicant's proposal about the period for the washout of prior therapies. It's important to know whether the treatment might have started soon enough that they would have a lingering effect. I guess I would like clarification from both the FDA and the sponsor about why they apparently feel differently about that.

DR. RAJAH: Dr. Rajah of Y-mAbs. Maybe I kick off the answer. As alluded to in that presentation we gave earlier, the majority of the patients had an interval of 4 to 15 weeks.

Slide up, please. This is between the trial

radiotherapy and the baseline scan. Some of these patients had a period of 4 to 15 weeks, which is almost 4 months. This is sufficient washout time for the radiotherapy and it begins to affect omburtamab. I know this can vary a lot from patient to patient, but generally speaking, it is considered that this is adequate time; and the same for chemotherapy as well. I think it was 3 to 8 weeks interim period between the last chemotherapy and the baseline scan. So based on this, we believe the interval is adequate time for washout. Thank you.

DR. HARRINGTON: Thank you.

If I possibly could hear from the FDA about why they felt it was not reasonable.

DR. LIEU: Dr. Donoghue?

DR. DONOGHUE: Thank you, Dr. Lieu.

I will turn to Dr. Mehta, and he can address this question. Thank you.

DR. MEHTA: Thank you.

Can I have the FDA backup slide, please? And let me just quickly select the slide.

I think the important note here is that there were very few confirmed responders, and in these cases, we had to take a very close look at what the time from these other therapies were to the baseline scan. There have been studies that have shown that the effects of radiation therapy can take longer than 60 days to fully manifest, and what we saw in this slide, which is our analysis of the four reported confirmed responses in Study 101, is two of these responses -- so this is patient number 2 and patient number 3 -- had inadequate washout of their prior therapy prior to the baseline scan.

So if we look at patient number 2, for example, they had radiation therapy 30 days prior to their baseline scan, and patient number 3 had a 19-day washout period from chemotherapy; so not even 3 weeks, and also received radiation therapy just 29 days before their baseline scan. So this limits our interpretation of that baseline scan and understanding the effect of different treatments on any responses that we do observe.

DR. HARRINGTON: Thank you.

DR. LIEU: Thank you.

Dr. Esiashvili?

(No response.)

DR. LIEU: Dr. Esiashvili, I think you are muted.

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

DR. LIEU: We can hear you.

DR. ESIASHVILI: Yes. So I'm a radiation oncologist at Emory. I have a question for the applicant.

Since we have heard their argument for, really, no contribution from CSI to outcomes with their patients, what's the rationale of keeping this even reduced-dose CSI in Study 101 while these children are young, and they will be exposed to the long-term side effects from this approach?

DR. RAJAH: Dr. Rajah, Y-mAbs. Let me just clarify the question. As I understand, it was the rationale for not reducing the CSI dose?

DR. ESIASHVILI: Sorry, for keeping

craniospinal irradiations in current Study 101.

DR. RAJAH: Dr. Rajah, Y-mAbs. I'd ask Dr. Kramer to comment on that, please. Thank you.

DR. KRAMER: Kim Kramer from MSK. I really appreciate the thought that's going into craniospinal irradiation because as I see it, in our long-term survivors, the long-term effect of craniospinal irradiation, even low dose, are the reasons our patients deal with neurocognitive deficits or short stature. So anything we can do to decrease the craniospinal irradiation dose is welcomed by all of us.

There are no mandated CSI doses that have to be given before omburtamab, and even going back into 03-133, if a patient's age was young enough that we felt even low dose -- and by low dose, I'm talking significantly lower than that which would be offered to a typical child with another kind of common brain tumor, medulloblastoma. But age is taken into consideration, and therefore patients might not get craniospinal irradiation. Prior radiation therapy to initial neuroblastoma bulky

disease, commonly next to the spine, is also considered.

So while we have generally recommended what we consider a low dose, if feasible, there are definitely instances where we will not advise that patients get craniospinal. Thank you.

DR. RAJAH: Thank you.

DR. ESIASHVILI: Thank you.

DR. LIEU: Thank you.

Dr. Jonsson Funk?

DR. JONSSON FUNK: Hello. This is Michele. Thank you so much for all the information you've shared today. I am also thinking about the treatments that we heard that patients have gone through, leading up to the therapy. I just want to have a clear sense of what that timeline is. From the time that the recurrence is identified, what are the different procedures and treatments, both in the individuals who are receiving therapy and what that timeline and events look like for patients who have not received this therapy?

Since it appears that there's a very steep

survival curve in that initial period after the diagnosis, I would imagine that the duration of that and the number of activities and procedures that one has to go through could essentially form a pretty strong funneling or filtering process, selecting for patients who are able to ultimately get the treatment.

DR. RAJAH: Dr. Rajah, Y-mAbs. Can we show the slide of the swim lanes, please?

Slide up. I hope the slides will help illustrate the points that I want to make, and I hope they address your questions.

These are the 5 patients that are classed as complete responders as per the RANO criteria and the EANO-ESMO criteria. The two patients right at the top with the yellow boxes were those being a response for the EANO-ESMO, and those with the red squares in the bottom-three patients were those being a complete response for the RANO brain mets criteria.

In terms of the [indiscernible] intervening treatments, I mentioned early on about the trial

radiotherapy and the chemotherapy treatments, indicated by the orange and the black triangles, but I also want to address the treatments received post-omburtamab.

So there were 2 patients that received chemotherapy that was after the first response assessment. The first patient received temozolomide and the second patient received temozolomide and/or irinotecan. Both of these patients were after the 10 weeks of their period and before the 26 weeks, and both of them had a response assessment prior to this chemotherapy. One of them was a complete response and one of them was a partial response.

The other two patients, you can see the fourth patient and the fifth patient down. Both of them had received naxitamab. It's an anti-GD2 systemic monoclonal antibody. Neither of these patients -- this drug does not enter the blood-brain barrier and does not affect the CNS lesion.

The core slide that I presented earlier on

in the patient with the MRI images in the graph showing the reduction in size, that was a patient indicated at the bottom of the slide here. In that particular patient, the antibody therapy was given almost 5 months after the omburtamab treatment, so the effect that this would have had on subsequent survival, our response rate is negligible.

I think the important point here I want to stress is that whilst some of these patients did get chemotherapy, when you look at those patients that did, all of them had prior evidence of a response, either complete response or partial response, which importantly is evidence of single-agent activity.

This is the most important message from this particular swim-lane slide, answering the question, does omburtamab have effect on an individual patient level? Does it show activity to show that omburtamab works? And as I hope I have highlighted in the cases that are outlined, there is evidence of single-agent activity. Notably, I would say those two patients right at the top, you'll see had

a duration of response in excess of 2 years; one of them 2 and a half and the other 3 years. In this particular indication, this is particularly notorious to treat. This is very compelling evidence, further again, to demonstrate omburtamab works. Thank you.

DR. JONSSON FUNK: Apologies for the interruption. I meant to specifically ask about the time prior to omburtamab treatment, and I'm looking, for instance, at slide 24 from the sponsor -- 64. It's labeled as CE number 4, but it comes at number 24 in your deck.

I'm thinking about the time leading up to screening, and how the time prior to screening and ultimately initiation of therapy, what are the timelines and activities that patients essentially have to give up in order to ultimately receive the therapy of interest?

DR. RAJAH: I'll ask Dr. Morgenstern to answer that question.

DR. MORGENSTERN: Daniel Morgenstern, Hospital for Sick Children. I think the answer is

that it will vary quite a lot, depending on the individual patient circumstances. Within the 101 trial, there were recommendations for treatment prior to receiving omburtamab, but it would have varied from patient to patient the details of exactly what they received.

Clearly, for instance, not all patients will receive surgery because surgery would not be appropriate for patients with only leptomeningeal disease, and clearly the duration of the radiotherapy would also very between patients, depending on whether they're having craniospinal radiotherapy, whole brain, or focal. So I think it's difficult to answer the question. In general, it will vary from patient to patient. Thank you.

DR. LIEU: Dr. Donoghue, does the FDA have a response?

DR. DONOGHUE: Thank you. We thought we just might provide some additional clarification to try to answer the question. So first, I'd like Dr. Mehta to respond, and then after that, Dr. Rivera, please.

DR. MEHTA: Thank you, Dr. Donoghue.

Could we have the FDA main slides up, please? I will just show you the timeline recommended pretreatments for CNS relapse that patients received before omburtamab. As you'll note from Dr. Morgenstern's response, this is obviously individualized for every patient, depending on what type of disease they had and different characteristics, but this was the general recommended paradigm, and this is within the protocol of Study 101.

Generally, this is a 12-week pretreatment regimen, so about 3 months, which is very close to that issue of immortal time that we brought up earlier with the index dates, the median time between CNS relapse and the data of startup omburtamab treatment with 3.1 months in the Study 03-133 population.

I might ask Dr. Donna Rivera to briefly comment on that.

DR. RIVERA: Thank you, Dr. Mehta.

I'd like to expand additionally on what we

see as a specific design issue, and that is immortal time, which has been described by Dr. Mehta as the period of study follow-up during which, by design, the study outcome cannot occur. So thinking about this, it's when the index date precedes treatment and all treated patients have to have survived this period in order to be included in the study. This bias can be introduced when periods of immortal time are differentially excluded from the analysis, inducing a form of what is categorized as selection bias.

In this study, the absence of an ideal index date and varying effect sizes upon the different sensitivity analysis are of concern. When a study is designed for that follow-up, it includes a period of time where participants in the exposed group cannot experience the outcome. They're essentially immortal.

Then there's a lot of concern around avoiding inappropriately misclassifying or excluding this immortal time, so this type of bias has been shown to systematically lead to an

apparent protective effect of a study treatment, and propensity score weighting does not address this bias. Thank you.

DR. RAJAH: Dr. Rajah, Y-mAbs. If I may address this point by inviting Dr. Christensen to comment on this, and also using that to address radiotherapy, which was raised early on by the panel member and director of Y-mAbs.

Dr. Christensen?

DR. CHRISTENSEN: René Christensen, Y-mAbs. Slide up, please.

Of course, immortal time bias, as pointed out and also described very well in the briefing document, is an important factor and cannot be adjusted in the propensity score analysis but can be handled -- as it was handled both in the FDA analysis and in the Y-mAbs analysis -- by using the differential index dates, of index date A in the general population and index date B, which is the time of omburtamab infusion in 03-133, thereby eliminating any immortal time bias on a subject level.

What we see here are the curves for the patients featured in first recurrence, and I would like also to comment on that in light of the FDA's emphasis on having a step-wise approach to handling and adjusting for various factors in one analysis. We agree completely, and we have done this in this analysis.

First of all, as mentioned, we have adjusted for immortal time bias by using the differential index dates. Secondly, we have adjusted for era of therapy, era of therapy guided by the natural history of the disease in Germany, evident in the difference in management of patients described in the early protocol compared to the total length of protocols.

Instead of dismissing patients before 2005, because the 03-133 trial happened to start that year, dosing patients, we leaned towards that being guided by the natural history. Additional to what the FDA did, we also adjusted for the very important confounder of number of prior relapses by focusing on the patient in first recurrence.

Evidently, the German population is made primarily out of patients in first recurrence, and also if you look to the SIOPEN data, that's patients in first recurrence.

So we present an analysis here where we take that confounder into account. And as always, when you don't take a confounder into account, you see a picture that can be very misleading, and we see that in the FDA analysis. Here we see what happens when you take that confounder into account. Dismissing this adjustment for this confounder as simply hypothesis generating when accepting other less well-defined confounders such as the era of therapy cut in 2005 seems very inconsistent.

In light of this being the data in existence, we are not able to go out and confirm any of these with additional data. That's simply not possible, but you should have the same level of acceptance towards various confounders used. And here we take all the steps in this analysis, and the natural history seen in the German population is very well underlined by -- slide up,

please -- what we see in the SIOPEN data.

Please recall, also with reference to the era of therapy, the SIOPEN data was collected from 2002 going forward, so we actually have a very detailed and in-depth understanding of the natural history of the disease, which is confirmed both in the German data and the SIOPEN data. And when taking all steps into account in the analysis, we see a clear advantage of adding omburtamab to multimodal treatments.

Also noticeably, please see that the patients are stabilized at the beginning of the period. For a period of 2 months, both the patients in the German population and in 03-133 are stabilized by treatments to an equal amount. And we feel that dismissing a hazard ratio of 0.48 to debatable regional differences and conventional therapy regimens seems unnecessarily dismissive.

DR. RAJAH: Thank you.

DR. JONSSON FUNK: Thank you for your comments. And looking at the slide that you have presented now on the right side, you note that the

two groups are essentially stable and there are no events happening in the first 3 months.

Do you have a further explanation of why the treatment benefit would appear suddenly and dramatically in month 4?

DR. CHRISTENSEN: Yes. René Christensen, Y-mAbs. What is apparent is that both groups are stabilized after the index date by the treatment received, and I invite Dr. Morgenstern to comment on the clinical.

DR. MORGENSTERN: Daniel Morgenstern, Hospital for Sick Children. I think what it shows is that the patients' disease has been stabilized by the multimodal therapy that they have received either prior to omburtamab or without the use of omburtamab. And I think it's also important to note that the reference data on here is the start of the last modality of post-CNS therapy, and therefore during those initial periods when the lines are horizontal, patients may still be receiving active therapy.

DR. CHRISTENSEN: One additional comment.

For the German population, it's the start of the last therapy. For the omburtamab population in 03-133, it's the infusion time, start of infusion time, thereby modifying immortal time bias. Thank you.

DR. RAJAH: Thank you.

DR. LIEU: I see that you have a comment, Dr. Donoghue; maybe a brief one so we can get to the questions.

DR. DONOGHUE: Hi. Yes. Thank you, Dr. Lieu. We'll be brief, but we would like to add a little additional clarification to help more fully answer the question posed.

If you could bring up our backup slides, and Dr. Mishra-Kalyani, could you speak, please?

(No response.)

DR. DONOGHUE: I'm not hearing you, Pallavi. Are you on mute? Dr. Mishra-Kalyani?

(No response.)

DR. DONOGHUE: I'll go ahead and take part of this while she tries to get back on.

Again, we took different approaches to

address this for immortal time bias, as can be seen on this slide. We took a couple of approaches to doing this.

Oh, Dr. Mishra-Kalyani's back on.

Do you want to jump in for analysis?

DR. MISHRA-KALYANI: Yes. I apologize. Can you hear me now, Dr. Donoghue?

DR. LIEU: Yes, we can hear you.

DR. DONOGHUE: Oh, I still don't hear anything.

DR. MISHRA-KALYANI: Great.

DR. DONOGHUE: I'll call your attention to the third row down, where we took the approach of excluding the 18 percent of patients that we estimated would have died during that period of immortal time, and as you can see, when we do so, the hazard ratio is 1.03 with a range between 0.45 and 2.35.

So there are multiple ways, as you note, to adjust for immortal time and to attempt to adjust for various sources of bias. As we mentioned during Dr. Barone's talk, we took different

approaches to doing so. We feel that ours is the more rigorous approach. Just the fact that when you use different approaches you can get drastically different results that can have you draw different conclusions, only speaks to the uncertainty behind this data.

Additionally, in terms of looking at the temporal differences in the populations, we did not agree with the applicant's approach of only excluding the very earliest trial that comprise the German registry, and we, again, felt that basing our adjustment for temporal bias, based upon the actual date and time where patients were diagnosed with CNS relapse, was more appropriate.

DR. RAJAH: Dr. Raja, Y-mAbs. I would like to respond to that, if I may.

(Crosstalk.)

DR. MISHRA-KALYANI: This is Pallavi Mishra-Kalyani from FDA statistics. I'd like to just briefly add. I'm sorry that my telephone got disconnected earlier.

I'd like to highlight something mentioned by

Dr. Donoghue here. In general, these set of analyses that we have chosen, each analysis was dictated by the science and the data of this application. We didn't take things that were necessarily the most convenient for ourselves or for the applicant. We picked what made the most sense based on epidemiologic and statistical methodology and what would be appropriate for this data set.

As Dr. Donoghue mentioned, and Dr. Mehta, and Dr. Barone, we used the date of Study 03-133 for the external control population. When we considered immortal time bias, we looked at several sensitivity analyses, only two of which are presented here. All of our analyses indicated that with greater adjustment for the bias, the results were greatly attenuated for overall survival. They approached or actually became greater than 1 in hazard ratio.

Ultimately, this shows us that the choices in the analysis population, or corrections for known bias, when done appropriately, result in very

different treatment effects, and this highlights the uncertainty regarding this data and the treatment effect of omburtamab.

Finally, I would just note that we're not indicating that any one of these analyses definitively describe the treatment effect of omburtamab, but rather that they indicate that we cannot accurately or definitively characterize the treatment effect of omburtamab, and therefore, we must recognize that it's not well established from this comparison.

DR. RAJAH: Dr. Rajah, Y-mAbs. We'd like to respond to that, if I may.

Dr. Christensen, please?

DR. SINGH: Dr. Lieu, this is Harpreet Singh, the director. I think it's really time to close this particular topic. We've both spent an inordinate amount of time discussing this particular point. There are other hands raised. I think we've made -- each side has had more than adequate time to address this particular point. I think we should move on.

(Crosstalk.)

DR. RAJAH: Dr. Rajah [indiscernible].

(Crosstalk.)

DR. LIEU: I agree. Why don't we move on to Dr. MacDonald's question, and if we have time, we can come back to this because this is, obviously, a contentious issue. This will certainly come up in the discussion, I'm sure.

But, Dr. MacDonald, your question?

DR. MacDONALD: Thank you. Toby MacDonald, Emory University. The question is for the Y-mAbs team, and it's apropos, I think, given the challenges we've all heard in the interpretation of the clinical data.

I just wanted clarification whether there are any preclinical data demonstrating clearly the mechanism of action, the efficacy of the drug when given alone, and whether there's a survival advantage seen over whole brain irradiation in preclinical models of neuroblastoma. I think this would be highly complementary and would help in the interpretation of some of the data. Thank you.

DR. RAJAH: Dr. Rajah, Y-mAbs. I would like to ask Dr. Kramer to answer that, please.

DR. KRAMER: Thank you. Kim Kramer from MSK. We have published a rhabdomyosarcoma xenograft model that expresses B7-H3 and showed localization of the drug with the tumor and improved survival. Those data are published by Shakeel Modak, et al.

In addition to that, there was the preclinical non-human primate study that gave the drug into the CSF. Those were non-tumor bearing, non-human primates, but demonstrated a relatively safe profile, a huge as well as long-term monitoring of these animals over several years. Thank you.

DR. RAJAH: Thank you.

DR. MacDONALD: My concern is the whole brain irradiation, and in particular the effect over that. Are there any models in which the animals received, for metastatic CNS disease, whole brain irradiation and compared that to the addition of the drug? Thank you.

DR. KRAMER: Kim Kramer from MSK. No, that was never one of the treatment plans proposed in the preclinical studies. Thank you.

DR. RAJAH: Thank you.

DR. MacDONALD: Thank you.

DR. LIEU: Thank you, Dr. MacDonald.

Dr. Kolb, your question?

DR. KOLB: Yes. Thank you. This is a follow-up from Dr. MacDonald's question as well, and this is for Dr. Kramer.

In the data from Dr. Modak and your work in the primates, do you have any response to the FDA's comment about the mechanism specifically for parenchymal disease? Thank you. That'll be the end of my question.

DR. KRAMER: Thank you. Kim Kramer from MSK. On PET imaging, there's definitely uptake seen in bulky tumor rhabdomyosarcoma models. We do know that when tagged to i-131, the path length of that isotope in general is millimeters, so part of the rationale in recommending additional therapy -- whether that's surgery or radiation

therapy -- prior to getting omburtamab is to get those tumor sizes down to a mind-set that the i-131 could target micrometastases. Thank you.

DR. LIEU: Great.

I wanted to see if there are any additional clarifying comments before we moved on to the panel discussion.

DR. RAJAH: This is Dr. Rajah, Y-mAbs. We want to just come back, and we have a comment on the sensitivity analysis that was shown [indiscernible].

DR. LIEU: If we can just make this quick because, again, I think we've --

DR. RAJAH: I agree, too.

DR. LIEU: -- discussed this a lot, but yes.

I see that Dr. Donoghue also has a comment, so I'll open up the floor for just a few minutes of comment just to wrap this up, but let's please be efficient in our use of time and discussion. Thanks.

DR. RAJAH: We will do.

Dr. Christensen?

DR. CHRISTENSEN: Yes. René Christensen, Y-mAbs. Slide up, please.

We definitely agree with the FDA that analysis should be done to high scientific standards, and we truly believe that we do the same. We have a team of very famous [indiscernible] statisticians and epidemiologists at hand. The analysis you see here, again, in contrast to the FDA analysis, takes the important confounder, number of prior relapses, into account, which shifts the image. That is a textbook example of what happens if you don't take a confounder into account. Also, please regard the natural history of this population. Thank you.

DR. LIEU: Thank you so much.

Dr. Donoghue, a brief comment?

DR. DONOGHUE: Thank you.

I was just going to ask Dr. Stephanie Aungst just to comment very briefly on the nonclinical data in case there is any -- I think we need to clear just a few things up.

Dr. Aungst?

DR. AUNGST: Hi, Martha. This is Stephanie Aungst for the FDA. Can everybody hear me?

DR. DONOGHUE: Yes.

DR. LIEU: Yes.

DR. AUNGST: I'm the nonclinical reviewer for this application. The applicant did show tumor uptake into subcutaneous rhabdomyosarcoma tumors in brain that was after intravenous administration of the radiolabeled omburtamab. They also did show brain scan penetration after convection-enhanced delivery for the radiolabeled drugs, but that was directly to the brain stem. However, they haven't provided any nonclinical evidence to support uptake into the brain tissue or tumors after administration directly to the CSF space. Thank you.

DR. LIEU: Dr. Donoghue, any additional comments from the FDA?

DR. DONOGHUE: No, I'll stop there. Thank you very much, Dr. Lieu.

DR. RAJAH: Dr. Rajah, Y-mAbs.

[Indiscernible]. Thank you.

Dr. Kramer?

DR. KRAMER: Thank you.

Kim Kramer from MSK. Slide up on the distribution of the antibody in patients as assessed [indiscernible] by imaging after injection in the various organs.

DR. RAJAH: Please start to show the slide of the system [indiscernible] absorbed dose. You have the slide showing the organ absorbed dose? Thank you.

(Pause.)

DR. RAJAH: Slide up.

DR. KRAMER: Over a panel -- here we are; slide up -- of approximately 20 different organs, we showed the total absorbed treatment dose of omburtamab, and this was in 22 patients by spect imaging, serial spect imaging after injection.

As you can see here, the highest total absorbed dose was in the liver and the brain, followed by very low activity at all in any of the remaining organs. However, all of the absorbed

dose in terms of centigray per millicurie were well below what known radiation toxicity limits for these organs are. Thank you.

DR. LIEU: Thank you.

Dr. Donoghue, do you have a brief comment before we move on to the discussion?

DR. DONOGHUE: Yes, please.

Just very quickly, I'd like to turn to Dr. Fotenos. Could you please pull up our backups?

And then while we're doing that, I just want to comment that the absorbed dose that was shown really reflects what is occurring in the intracranial space, not in the brain itself, due to the methodology used to assess that.

DR. FOTENOS: Thank you, Dr. Donoghue.

This is Andy Fotenos. I'm the clinical team leader and nuclear medicine physician in the Division of Imaging and Radiation Medicine in the Office of New Drugs.

I'd like to start by drawing attention to the public set of images in the lower panel. In this panel, you can see 6 stats [indiscernible]

plus two unweighted magnetic resonance images acquired at multiple time points from the same healthy individual. The baseline image in the lower left was acquired before contrast image administration and the images to the lower right were acquired after investigational intrathecal administration directly into the cerebral spinal fluid of the small molecule gadolinium-based contrast agent.

Comparing post- to pre-contrast imaging, you can clearly see that the predominant areas of small molecule transit and brightening are limited to the peripheral leptomeningeal compartment and not to the central nervous system parenchymal compartment. The pattern is consistent with cerebrospinal physiology.

The upper panel shows that the applicant acquired imaging on delivery of their product to target leptomeningeal in central nervous compartment under Study 03-133, including potentially highly informative pre-therapeutic i-124 positron emission tomography and magnetic

resonance imaging data from over 40 patients. Notably, none of this data has yet been submitted to the application for review.

Particularly, across all CNS tumor lesions from over 40 patients administered i-124 omburtamab for pre-therapy imaging, the number with uptake and the degree of uptake remains unreported. In sum, the internal radiation delivery to the leptomeningeal compartment is likely higher and more consistent in radiation delivery to the central nervous system compartment.

Questions to the Committee and Discussion

DR. LIEU: Thank you, everybody, for those comments and for answering all of the clarifying questions, and to our panel as well.

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 comment. We will now proceed with the questions to the committee and panel discussion. I would like to remind all 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 comment concerning its wording, then we will open the question to discussion.

May I have the question for discussion placed up onto the presentation? Wonderful.

For discussion, discuss whether data provided by the applicant isolates the treatment effect of omburtamab from the effects of multimodality therapy for central nervous system/leptomeningeal metastases relapse or if additional data are needed.

Are there any questions about the wording of the discussion question?

(No response.)

DR. LIEU: If there are no questions or comments concerning the wording of the question, we will now open the question to discussion, and I'm happy to start us off.

Obviously, I am not a pediatric oncologist. I think seeing this data, I obviously have a lot of

desire to see more therapeutics in, obviously, a rare disease that obviously needs additional therapeutics. I do want to state that I think we're -- and I hate to call on people, but I do think the opinion here of our statisticians, Dr. Harrington, Dr. Hudgens, as well as our epidemiologists, Dr. Jonsson Funk, will be extraordinarily helpful here because I think, as you've heard with the clarifying questions in particular, that the statistical analysis of this data is fraught with a lot of confounders and would love the impression from the panel, and obviously those that have more expertise in this disease.

My concern is regarding the external controls. I'm thrilled to see real-world data and for that to be presented to the FDA, and for us to be considering it, but I do have concerns about the applicability of the external controls in regards to how we're supposed to interpret that survival data in regards to the treatment data. But certainly, we'll open it up to the panel. Those that desire to make comment, please raise your

hand, and I'll call on you.

Dr. Nieva?

DR. NIEVA: Thank you. Jorge Nieva from USC. I think I very much wanted to believe the survival differences that were shown, but in looking at the adjustments for confounders, this really looks to me like this is a lot of selection bias, and unfortunately we don't have any data that isolates the treatment in the absence of a lot of other treatments, and we don't have good response rate data that's not inconsistent among different reviewers.

I'm very much bothered by the fact that the best picture that we've had showing a response was a picture that was confounded by intervening chemotherapy, and all these things I think make me want to see more data. Thank you.

DR. LIEU: Thank you, Dr. Nieva.

Dr. Park?

DR. PARK: Hi. This is Julie Park from the University of Washington, and thank you very much for the opportunity to ask questions and speak.

I think there was a very thorough discussion about the confounding differences between the external control group and the experimental group. I think one area that we did not really delve into is the likely significant difference in the upfront treatment that these patients received as well, really highlighting the importance of the era of treatment. In addition, the importance of the era of treatment really enhanced the aggressiveness for which the neuroblastoma community approached relapse neuroblastoma and has changed greatly over time with the advent of newer therapies.

So I think all of those are extremely important confounding effects and really highlight the importance or limitations of the statistical analyses.

DR. LIEU: Thank you, Dr. Park.

Dr. Harrington?

DR. HARRINGTON: Thank you.

I think what I would like to acknowledge up front is that it's very rare, when using uncontrolled studies against observational

controls, that you can isolate a treatment effect. So I think at first blush, according to the statement, did the applicant isolate treatment effect? I would say no, but I would say it's very, very hard to do that in this setting.

For me, when I look at the comparison of a study with historical controls, what I look for is a certain robustness in the analysis, and by that I mean if you go at it several different ways, do the results hold up. And I think that what we're seeing here, what I'm seeing, is that approaches taken by the sponsor and approaches taken by the FDA can lead to very different conclusions here, and those are how you adjust for initial treatment, as been stated by Dr. Park, the era of treatment, immortal time bias, and coming down to very small sample sizes.

For me, of course, I have to balance against using this in a rare disease, which would preclude having a large observational database for a control. But for me, there are just too many differences in the way one looks at the study to be

comfortable that there's a -- not to say isolates the treatment effect but a plausible establishment of an important association with the administration of the drug. Thank you.

DR. LIEU: Thank you, Dr. Harrington.

Dr. MacDonald?

DR. MacDONALD: Toby MacDonald, Emory University. I think as a pediatric neuro-oncologist, what concerns me the most, and what I just can't get past, is the comparator group not using craniospinal irradiation versus a group that has craniospinal irradiation. We know from other malignant diseases, primary the brain -- medulloblastoma, ependymoma -- that in metastatic disease, craniospinal irradiation is much more effective at controlling the disease and improving survival than focal radiation.

Secondly, we don't even know the dose of the focal radiation given in the other group, so to really make any comparison, to me, is impossible from that standpoint alone. Second, the tumor responses, we know that radiation can have a

long-term effect and that responses may be delayed on imaging, and months later -- 3 months, 6 months later -- you can actually see responses occurring with radiation alone. So to me, that is the absolute obstacle point in trying to effect response data, as well as survival data. Thank you.

DR. LIEU: Thank you, Dr. MacDonald.

I want to open up for any additional comments or questions from the panel.

Dr. Hudgens?

DR. HUDGENS: [Indiscernible]?

DR. LIEU: Yes.

DR. HUDGENS: Sorry.

I agree with comments that have been made by others on the panel that there's some concern here about -- there's a lot of uncertainty in these data and the way it's analyzed.

I see two major concerns. Whenever we do these observational data analyses, we worry about adjustment for confounding, and I think we worry about unmeasured confounders, but I think here even

we're worried about measured confounders. Calendar time is a confounder here; it looks like the amount of treatment that the control and the treated have received; concomitant therapy is different; and there's a lack of overlap or a lack of positivity related to some of these measured confounders. So no amount of inverse probability weighting by propensity scores is going to help resolve. That to me seems like a major issue.

Then there's the immortal time bias that folks have talked about. And I don't want to harp on that, but I do want to address the second part of the discussion, which is this question about what additional data is needed. One thing that I think might be helpful is an analysis that emulates a target trial.

There have been many papers written about this idea, but to say what's the randomized trial we'd like to do but we couldn't do, and that would articulate very carefully what the eligibility criteria would be for that trial: what the different regimens would be that would be compared;

what would be the control arm; what would be the treatment arm; and what would be times zero; and to spell all those things out, and then use the 03-133 data, the German registry data, and what other data we have available as best we can to analyze those data in a way that's consistent with this trial emulation idea. That's all. Thank you.

DR. LIEU: Thank you, Dr. Hudgens.

Any other comment from the panel?

DR. PARK: This is Julie Park. I'd like to just follow with that as far as the additional data needed, again, harping on what the upfront treatment was for these patients. I think, in particular, the use of total body irradiation as part of a conditioning regimen for transplant or prior radiolabeled MIBG [indiscernible] in patient populations because that really could set you up for a differential response to radiation later at the time of recurrence, and I think that would be very important data.

DR. LIEU: Thank you, Dr. Park.

Dr. Widemann?

DR. WIDEMANN: Hi. Brigette Widemann, NCI. I just wanted to say I second Dr. MacDonald's concerns. It almost seems like the craniospinal radiation plus omburtamab would have to go together in a package because I don't think they can be separated, and I would not be able to tell which one is more important because I think the majority of the patients received the craniospinal radiation in comparison to the German group. It's very difficult.

DR. LIEU: Thank you, Dr. Widemann.

Any other comments from the panel?

Dr. Jonsson Funk?

DR. JONSSON FUNK: I just wanted to share Dr. Hudgens' perspective that I agree that confounding is front and center, and we have thought a lot about that. I think selection bias is often much more challenging to think clearly about, and the target trial emulation approach that he has mentioned I think is a tool that can help us think very clearly about the selection bias that may be introduced at different phases of when we

identify participants and how we follow them. So I would just like to second that suggestion for going forward. Thank you.

DR. LIEU: Thank you, Dr. Jonsson Funk.

Other comments?

(No response.)

DR. LIEU: Wonderful. Thank you for that discussion. I'd like to summarize what we just discussed over the last 10 minutes, and that is a fairly consistent theme across the discussion regarding measured and unmeasured confounders. Regarding overall survival data, there's concern from the panel regarding the era of treatment and how treatment has changed over the course of a more modern approach, also significant concern regarding cerebrospinal irradiation and how that may impact data.

There's also expressed concern regarding response rate data and confounders to potential responses, as well as a desire from the panel to see more robust data in an analysis that would be slightly more consistent but would certainly

include additional patients. And there was comment in regards to possible pathways forward in regards to what additional data could be helpful, and comments made from Dr. Hudgens and others in regard to a more clinical trial-like data set to be able to compare a control arm, even utilizing real-world data compared to the treatment arm.

Any additional comment before we move to the voting question?

(No response.)

DR. LIEU: Alright. We will now move on to the next question, which is a voting question. Dr. Phil Bautista will provide the instructions for the voting.

DR. BAUTISTA: Hi. This is Phil Bautista, the DFO. Question number 2 is a voting question. Voting members will use the Adobe Connect platform to submit their votes for this meeting.

(Audio feedback.)

DR. BAUTISTA: I would ask somebody to go ahead and mute their microphone.

Thank you so much.

After the chairperson has read the voting question into the record and all questions regarding the wording of the vote question have been answered, the chairperson will announce that the voting will begin. If you are a voting member, you'll be moved to a breakout room. A new display will appear where you will submit your vote. There will be no discussion in the breakout room. Again, there will be no discussion in the breakout room.

When voting, you should select the radio button that is a round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected. Please note that you do not need to submit or send your vote. You need only to select the radio button that corresponds to your vote. You'll have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, I will announce that the vote is closed.

Next, the vote results will display on the screen. I will read the vote results from the

screen into the record. Afterwards, the chairperson will go down the list, and each voting member will state their name and how they voted into the record. You can also state the reason why you voted as you did, if you'd like to, however, you should address any subparts of the voting question, if any.

Are there any questions about the voting process before begin? I see some hands raised here. If you do not have any questions, I'll ask you to lower them, please.

Dr. Harrington and Dr. Nieva, do you have any questions about the voting process?

DR. HARRINGTON: I do not. I'm trying to lower my hand right now. Thank you.

DR. BAUTISTA: Alright. Thank you so much.

Dr. Lieu, I'll go ahead and hand it back to you to read the question.

DR. LIEU: Great. I'll read the question for a vote.

The applicant has provided a comparison of omburtamab following multimodality treatment in a

single-arm Study 03-133 to an external control derived from a German registry. The voting question is, has the applicant provided sufficient evidence to conclude that omburtamab improves overall survival?

Are there any questions regarding the wording of the voting question?

(No response.)

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

DR. BAUTISTA: Thank you. We will now be moving only voting members to the voting breakout room. Within the voting breakout room, there will be no discussion of the question.

(Voting.)

DR. BAUTISTA: Hi, all. This is Phil Bautista, the DFO. The votes are now displayed. I'll read the vote total into the record, and then the chairperson is going to go down the list, and each voting member will state their name and how they voted into the record.

We have zero yeses, 16 noes, and zero abstentions.

Dr. Lieu?

DR. LIEU: Thank you.

We will now go down the list and have everyone who voted state their name and their vote into the record. You may also provide justification of your vote if you wish to. We'll start with Dr. Widemann.

DR. WIDEMANN: Brigette Widemann. I voted no.

DR. LIEU: Thank you, Dr. Widemann.

I'm next. I'm Christopher Lieu. I also voted no. I think this is a tough situation because I think we're all motivated to provide more of these therapeutics to these patients that desperately need them. I think the key issue here is whether or not there's clear overall survival benefit, and this bar has not been met. And I think that this is due to significant discrepancies between the external control and the treatment group.

I think the contemporary data from the external control arm showing similar survival is compelling, but these numbers are unbelievably small as well. It would also be nice if we saw a very significant clear response rate, but this is also confounded due to the multiple therapies being received by these patients.

I would just say, in terms of next steps, I hope and I believe that there may be a pathway forward. I appreciate Dr. Hudgens' and others comments in regards to a more robust and comparable contemporary external control group, and if there is a significant survival difference there, I think that would be helpful for this particular therapeutic. I think that this potentially could be done with some type of academic collaboration, but at this time the data do not support the continued approval.

Dr. Harrington?

DR. HARRINGTON: This is Dave Harrington. I voted no for all the reasons that have come up in the discussion and have been stated very eloquently

by Dr. Lieu.

DR. LIEU: Thank you, Dr. Harrington.

Mr. Mitchell?

MR. MITCHELL: I'm David Mitchell. Especially with a rare disease affecting children with a serious unmet need, I really believe in using the best available data versus insisting on a theoretical ideal. But using the best available data plausibly presented to us today, I can only conclude that the applicant has not provided sufficient evidence that allows us to conclude that omburtamab improves overall survival, so I voted no.

DR. LIEU: Thank you, Mr. Mitchell.

Dr. Parsons?

DR. PARSONS: This is Will Parsons. I voted no, as well; no further comments.

DR. LIEU: Thank you, Dr. Parsons.

Dr. Kolb?

DR. KOLB: Yes. Hi. This is Andy Kolb, Nemours Children's Health. I voted no. I'd just like to add commendation to Y-mAbs for continuing

to try to develop novel therapies and rare subsets in children. This is very hard to do, and I think this work highlights a lot of the difficulties that we face, and appreciate the agency's consideration in this matter, as well.

DR. LIEU: Thank you, Dr. Kolb.

Dr. McMillan?

DR. McMILLAN: This is Dr. McMillan, and I voted no.

DR. LIEU: Thank you, Dr. McMillan.

Dr. Nieva?

DR. NIEVA: This is Jorge Nieva. This is a trial that, if positive, would have affected a handful of children in the United States each year, and I really want to salute the company and the investigators for the work they did to try to bring this forward. But I'm not convinced that the drug is doing something more than the effects of selection bias of special applied center treatment.

From the standpoint of additional data, I'd like to see evidence of single-agent responses that are reliable and not contaminated by concurrent

therapy. It also may be possible to build a registry from similar large-volume centers that engage in clinical trials so that we're not simply seeing the effect of treatment at a specialized center versus treatment in a general population. Thank you.

DR. LIEU: Thank you, Dr. Nieva.

Dr. Park?

DR. PARK: This is Julie Park. I'd like to also recognize the considerable efforts that Y-mAbs and these investigators have provided for this very high unmet need in pediatric oncology, however, my vote is no because of all the reasons that were eloquently outlined by Dr. Lieu. I do also hope that there is a way forward for us to try to get more data to further investigate whether there is a benefit, but at this time I cannot prove that.

DR. LIEU: Thank you, Dr. Park.

Dr. Hudgens?

DR. HUDGENS: This is Michael Hudgens. I voted no. I have no additional comments for me. Thank you.

DR. LIEU: Thank you, Dr. Hudgens.

Dr. Jonsson Funk?

DR. JONSSON FUNK: This is Michele Jonsson Funk. I voted no, and I just want to recognize the pioneering nature of the work that is going on at both Y-mAbs and FDA to use external control arms to try to identify and understand the potential benefit of this therapy, and recognize that this is groundbreaking work, and it's not a straightforward or clear path forward. So I really look forward to seeing additional data and analyses, and hope that we can [inaudible - audio gap] what that treatment benefit is. Thank you.

DR. LIEU: Thank you, Dr. Jonsson Funk.

Dr. Esiashvili?

DR. ESIASHVILI: This is Dr. Natia Esiashvili. I voted no on the basis of all the points and discussions we've heard earlier, and again want to echo others' comments to really give credit to the company and investigators for this remarkable work, and hopefully find a better path forward to answer this very challenging -- and

clinically fill a big need for children suffering from this very high-risk patient population. So again, I hope there will be lessons learned and some better pathways and methodology to implement from this discussion.

DR. LIEU: Thank you, Dr. Esiashvili.

Dr. Vasan?

DR. VASAN: Hi. Neil Vasan. I voted no. In addition to what everyone else has just said, I just really wanted to acknowledge the heroic efforts by Y-mAbs, the investigators, and also the patients and their families who testified today. In addition to the comments that everyone else raised about trying to move forward, I would also encourage the company to perform more preclinical experiments to define the mechanism of action that this is on target, and perhaps that could also influence these trials. Thank you.

DR. LIEU: Thank you, Dr. Vasan.

Dr. Seibel?

DR. SEIBEL: Yes. I voted no, as well, particularly based on the discrepancy with external

controls, as well as the response documentation, and really hope that they could tighten up the disease evaluation at study entry so you could have accurate response assessment and not being confused with additional therapy that's given.

I do have to commend both the company, as well as the FDA for trying to use real-world data for this. There's no question this is an unmet need, and I just hope and encourage the company to alter their future plans so something like this could be available for patients with CNS and leptomeningeal neuroblastoma.

DR. LIEU: Thank you, Dr. Seibel.

Dr. Bagatell?

DR. BAGATELL: Hi. This is Ro Bagatell. Like everybody else, I appreciate the efforts of the folks from Y-mAbs and also the FDA for their very thoughtful analyses and efforts to try to understand the data as best we can, but I had to vote no just based on the difficulties in interpreting the data that exist.

But I do think that as a community of

investigators, and clinicians, and regulators, and applicants, we are going to have to use historical or real-world data for these rare subsets of patients and understand how to best use them. So I really appreciate everyone involved on the call today in carefully thinking about these things.

DR. LIEU: Thank you, Dr. Bagatell.

And Dr. MacDonald?

DR. MacDONALD: This is Toby MacDonald, and sadly I, too, vote no, but applaud Y-mAbs and Dr. Kramer for their efforts, and encourage them to continue to do so to bring forward in the future more compelling evidence that meets the bar to show a true survival advantage, and I would welcome that. Thank you.

DR. LIEU: Thank you, Dr. MacDonald, and my sincere appreciation to the panel for their discussion and their votes today.

To summarize, I won't belabor any of these points, as I feel like it's been very consistent, but the panel does not feel that the applicant has met the criteria needed to prove overall survival

benefit. The panel would like the increased response, obviously; if possible, an improved comparator; and potentially even more robust preclinical data.

There's sincere appreciation from the panel to both Y-mAbs and the FDA for their efforts, and obviously need to say thank you to our patients, and their providers, and their families for being involved in this research; and then significant appreciation that the FDA is considering external controls and real-world data to hopefully move forward therapeutics in rare diseases that obviously need better therapeutics.

Before we adjourn, are there any last comments from the FDA?

DR. DONOGHUE: This is Martha Donoghue. I just want to thank everybody for their service and coming together today to consider this application and the issues at hand, so thank you all very much.

Adjournment

DR. LIEU: Thank you, Dr. Donoghue.

With that, we will now adjourn the meeting,

and I want to say thank you to everybody involved. Have a great weekend.

(Whereupon, at 2:35 p.m., the meeting was adjourned.)