FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ONCOLOGY SUBCOMMITTEE OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE (pedsODAC)

Wednesday, June 17, 2020

1:20 p.m. to 3:11 p.m.

Topic 2

Afternoon Session

Virtual Meeting

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(1:20 p.m.)

Call to Order

Introduction of Committee

DR. PAPPO: Good afternoon, and welcome back. For media and press, I would like to announce the FDA press contact is Nathan Arnold. His email is nathan.arnold@fda.hhs.gov, and his phone number is 301-796-6248.

My name is Alberto Pappo, and I will be chairing today's virtual meeting. I will now call the afternoon session of the Pediatric Oncology Subcommittee of the Oncology Drugs Advisory Committee to order. Like we did in the morning, we will use a call/respond method, where I will call the panel member's name to prompt the member to speak, and then the panel member will identify and introduce himself, or herself, and then we can put that into the record.

We will start with Alberto Pappo. I'm the chairperson of the Pediatric ODAC. I'm a pediatric oncologist at St. Jude Children's Research

Hospital.

Dr. Jonathan Cheng?

DR. CHENG: Good afternoon. Jonathan Cheng. I'm the industry rep, and I'm with Merck.

DR. PAPPO: Dr. Catherine Bollard?

DR. BOLLAR: Hi. It's Dr. Catherine Bollard. I'm from Children's National and the George Washington University in Washington, DC.

DR. PAPPO: Dr. Steven DuBois?

(No response.)

DR. PAPPO: Steve, if you can unmute your phone.

DR. DuBOIS: Hi. I'm here now. Steve DuBois, pediatric oncologist from Dana-Farber Boston Children's in Boston.

DR. PAPPO: Dr. Ira Dunkel?

DR. DUNKEL: Hi. This is Ira Dunkel, pediatric neuro-oncologist at the Memorial Sloan-Kettering Cancer Center in New York.

DR. PAPPO: Dr. Julia Glade Bender?

DR. GLADE BENDER: Hi. I'm Julia Glade Bender also from Memorial Sloan-Kettering in New

York City. I'm a pediatric oncologist and vice chair for clinical research in the Department of Pediatrics.

DR. PAPPO: Dr. Richard Gorlick?

DR. GORLICK: I'm Richard Gorlick. I'm the division head of pediatrics at MD Anderson Cancer Center in Houston, Texas.

DR. PAPPO: Dr. Theodore Laetsch?

DR. LAETSCH: Theodore Laetsch, a pediatric oncologist at UT Southwestern Medical Center in Dallas, Texas.

DR. PAPPO: Donna Ludwinski?

DR. LUDWINSKI: Donna Ludwinski, Solving Kids' Cancer in New York.

DR. PAPPO: Dr. Andy Kolb?

(No response.)

DR. PAPPO: Andy, are you on the line?

(No response.)

DR. PAPPO: We will come back to him.

Dr. Katie Janeway?

DR. JANEWAY: Dr. Katie Janeway, pediatric oncology and sarcoma specialist at Dana-Farber and

Boston Children's in Boston, Massachusetts.

DR. PAPPO: Dr. Naynesh Kamani?

DR. KAMANI: Good afternoon. This is Naynesh Kamani, pediatric immunologist, bone marrow transplanter at Children's National in Washington, DC.

DR. PAPPO: Dr. Tobey MacDonald?

DR. MacDONALD: Good afternoon. This is Tobey MacDonald, pediatric neuro-oncologist at Emory University and Children's Healthcare of Atlanta.

DR. PAPPO: Dr. Leo Mascarenhas?

DR. MASCARENHAS: Hi. This is Leo Mascarenhas. I'm the deputy director for the Children's Cancer and Blood Disease Institute at Children's Hospital, Los Angeles, and the head of oncology, and a pediatric oncologist.

DR. PAPPO: Dr. William Parsons?

(No response.)

DR. PAPPO: I will try to call their names at the end of this. Next slide?

Dr. Elizabeth Raetz?

DR. RAETZ: Hi. Elizabeth Raetz, pediatric oncologist and division director at New York University.

DR. PAPPO: Dr. Nita Seibel?

DR. SEIBEL: Hi. Nita Seibel, pediatric oncologist in the clinical investigation branch at CTEP at the National Cancer Institute.

DR. PAPPO: Dr. Malcolm Smith?

DR. SMITH: Hi. Malcolm Smith in the cancer therapy evaluation program at the National Cancer Institute.

DR. PAPPO: Dr. LaToya Bonner?

CDR BONNER: Hi. Good afternoon. This is LaToya Bonner, DFO for this meeting.

DR. PAPPO: Dr. Gregory Reaman?

(No response.)

DR. PAPPO: Dr. Denise Casey?

DR. CASEY: Hi. This is Denise Casey, pediatric oncologist, Division of Oncology 3, FDA.

DR. PAPPO: Do we have another slide? Dr. Leslie Doros?

(No response.)

DR. PAPPO: Dr. Megan Zimmerman?

DR. ZIMMERMAN: Hi. This is Megan Zimmerman. I'm a pediatric oncologist and a clinical reviewer in the clinical hematology branch at FDA.

DR. PAPPO: So before we go any further, I just want to call out a couple of names that were missing.

Dr. Kolb, are you on the line?

(No response.)

DR. PAPPO: Dr. Parsons?

DR. PARSONS: Yes, I'm here. Sorry about that, Alberto. Will Parsons from Texas Children's Hospital and Baylor College of Medicine in Houston, Texas.

DR. PAPPO: Thank you.

Dr. Doros?

(No response.)

DR. PAPPO: And Dr. Reaman, which I hear he's in the participant pod, but he'll be moved up to the presenter's pod.

(No response.)

DR. PAPPO: So we will get started.

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

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

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, the FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is

reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Dr. LaToya Bonner will read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

CDR BONNER: Thank you, sir.

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

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

Related to the discussions of today's meeting, members of the committee and temporary voting members of the subcommittee have been screened for potential financial conflict of interest of their own as well as those imputed to them, including those of their spouses or minor

children, and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

For today's agenda, information will be presented regarding pediatric development plans for two products that are in development for an oncology indication. The subcommittee will consider and discuss issues relating to the development of each product for pediatric use and provide guidance to facilitate the formulation of written requests for pediatric studies if appropriate.

The product under consideration for this session is marizomib, presentation by Celgene International II Sarl, a wholly owned subsidiary of Bristol-Myers Squibb. This is a particular matters meeting during which specific matters related to marizomib will be discussed.

Based on the agenda for today's meeting and

all financial interests related by the committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Drs. Ira Dunkel, Theodore Laetsch, and Leo Mascarenhas.

Dr. Dunkel's waiver involves consulting interests with four companies for which he receives remuneration between $0 and $5,000 per year from three companies and between $10,001 and $25,000 per year from a fourth company.

In addition, his employer has a contract for a study funded by Bristol-Myers Squibb. Lastly, Dr. Dunkel serves as chair of the Pediatric Brain Tumor Consortium, which funds studies and receives support for studies from Apexigen, Pfizer, Celgene, Novartis, Lyla Nsouli, and Novocure.

Dr. Laetsch's waiver involves two of his employer's research contracts. One is funded by the Children's Oncology Group and the second is funded by Novartis.

Dr. Mascarenhas' waiver involves his employer's contract for a study funded by

AstraZeneca.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver document, which are posted on FDA's website at www.fda.gov/advisorycommittees/committeesmeetingmaterials/drugs/default.htm. Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267.

For the record, Dr. David Mitchell has been recused from participating in this session of the meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they may have concerning the product at issue. With respect to FDA's invited industry representative, we would like to disclose that. Dr. Jonathan Cheng is participating in this meeting as a nonvoting

industry representative, acting on behalf of regulated industry. Dr. Cheng's role at this meeting is to represent industry in general and not any particular company. Dr. Cheng is employed by Merck & Company.

We would like to remind members and temporary voting members that if the discussion involves 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 participants to advise the subcommittee of any financial relationships that they may have with the firm at issue. Thank you.

DR. PAPPO: Thank you very much. I see that. Dr. Kolb just jointed.

Andy, do you mind just standing your name for the record, introduce yourself?

DR. KOLB: Yes. Hi. This is Andy Kolb. Sorry I was a little late getting back.

DR. PAPPO: Thank you.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency of the advisory committee meeting, the 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 firm at issue such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interests and those based upon the outcome of the meeting.

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

speaking.

We will now proceed with Celgene International II Sarl's presentation.

DR. TADY: Hello, Dr. Pappo? Can you hear me?

DR. PAPPO: Yes, we can hear you very well.

DR. TADY: Great. Thank you.

Industry Presentation - Deborah Tady

DR. TADY: Good afternoon. I'm Debbie Tady. I'm a global regulatory strategy lead for oncology at Celgene, a Bristol-Myers Squibb company. On behalf of BMS and the marizomib team, I would like to thank the FDA and Dr. Gregory Reaman and his team for the invitation to participate in today's pediatric ODAC meeting.

We are here today to present information and to gain feedback on marizomib, a proteosome inhibitor that we are developing for the potential treatment of children with high-grade gliomas, including glioblastoma and diffuse intrinsic pontine glioma.

During our presentation today, we will

present information on the topic shown on this slide. First, Sherry Leonard, our global regulatory lead for marizomib, will share our commitment to working collaboratively to advance pediatric research. She will provide a summary of the overview of the marizomib development strategy and the regulatory history and she will highlight key activities related to pediatric development.

Next, Dr. Mark Kieran, our clinical lead in pediatric oncology, will review the marizomib mechanism of action. He will provide a summary of the Phase 1/2 clinical trial experience in adults, and he will walk us through the ongoing and planned clinical trials for children.

For the Q&A session, I will serve as the moderator and will direct the questions from the advisory committee to one of our marizomib team subject matter experts to respond. I would now like to turn this presentation over to Sherry Leonard.

MS. LEONARD: Thank you, Debbie.

Before I get started, I just want to ask if

anyone can see the slides.

DR. PAPPO: We can see the slides.

DR. REAMAN: I cannot see the slides, and I think there are others that --

MS. LEONARD: Okay. I cannot see the slides as well, so I wanted to make sure before I start that they are visible to most people.

DR. REAMAN: They're not visible.

DR. PAPPO: While we do this, Greg, do you mind introducing yourself?

DR. REAMAN: Yes, sorry. I was waiting to be automatically connected as the instructions were, but unfortunately I had to sign off and get back on, so I apologize for being late. But I'm Gregory Reaman, associate director for pediatric oncology in the Oncology Center of Excellence, and I apologize for the technical snafu here and the inability to see the slides.

DR. PAPPO: Can everybody see the slides now or are we still working on it?

DR. REAMAN: All I see is a green circle twirling around.

MALE VOICE: Others of us can see them.

CAPT WAPLES: Good afternoon. This is Yvette Waples from the FDA. Can we please put a 5-minute pause why we try to figure out the connection?

DR. PAPPO: Absolutely.

CAPT WAPLES: Thank you.

(Pause.)

DR. PAPPO: Can everybody see the slides now?

MS. LEONARD: Yes.

DR. REAMAN: Yes, they're visible now.

FEMALE VOICE: Good afternoon. If you still cannot see the slides, you may consider to disconnect your VPN. What we realize is a lot of people, when they have VPN connected, it occupies some bandwidth and causes a delay in the internet.

DR. PAPPO: It looks like most people that were not able to see the slides are now able to see them.

Greg, can you see them, and everybody else can see them?

DR. REAMAN: Yes, I can see them, finally.

DR. PAPPO: Okay. Let's proceed with the presentation, then.

Industry Presentation - Sherry Leonard

MS. LEONARD: Thank you.

This is Sherry Leonard, global regulatory lead for marizomib. Celgene and BMS are committed to pediatric cancer research. This includes early evaluation of the oncology pipeline using the molecular target to identify potential pediatric tumor type as well as early discussions with FDA for alignment on the pediatric development plan. Our goal is to improve treatment options for children with cancer by decreasing the lag time between adult and pediatric studies and obtaining written requests earlier.

As covered in Dr. Reaman's introduction, we are here today to gain advice on the potential role of marizomib in the treatment of pediatric cancers and on the optimal line of studies that may serve as part of a written request. Today we will present an overview of the marizomib program,

including development plans for pediatric patients with high-grade glioma, including GBM and DIPG.

The adult marizomib development program is focused on newly diagnosed GBM based on two key findings from the phase 1/2 studies. First, marizomib is an irreversible proteosome inhibitor that crosses the blood-brain barrier. This is evident from findings in nonclinical studies and the observed dose-related CNS AEs in adult clinical studies. Second, these CNS AEs, while reversible, determine that the overall benefit-risk profile for marizomib was more favorable for the use in patients with CNS tumors.

The phase 1/2 clinical studies have led to a phase 3 study being conducted by the EORTC that is adding marizomib to the standard treatment of temozolomide and radiation therapy, followed by temozolomide. The pediatric development strategy for marizomib is based on the molecular target of proteosome inhibition and CNF penetration, and therefore is focused on high-grade glioma, including GBM and DIPG.

We are here today to gain advice for a potential written request focused on high-grade glioma, including GBM and DIPG. On slide 6, you will find a regulatory history and key activities for pediatric development.

In 2006, the first adult studies began in advance solid tumors lymphoma and multiple myeloma, then in 2015 development was refocused on GBM based on nonclinical data and the observance of CNS AEs that indicated brain penetration.

Beginning in 2017 and over the last three years, we have engaged pediatric advisors. An advisory board convened by Celgene gained regulatory scientific advice from three national health authorities in the EU and reached agreement on a pediatric investigation plan with the European Medicines Agency in an initial pediatric study plan with FDA. Both plans will be discussed further during this presentation.

Pediatric expert opinion and health authority advice was thought to guide the marizomib pediatric development plan. Based on activity

observed with marizomib and panobinostat in cell lines and models, a pediatric advisory board recommended a gated approach, starting first with DIPG, and as supported by nonclinical studies and the DIPG phase 1 study, proceeding with other pediatric high-grade glioma. This approach was encouraged in the scientific advice received from three national health authorities.

As described on the earlier slide, we have reached agreement with FDA and EMA on separate pediatric plans. The key difference between these two plans is that the FDA agreed iPSP only includes high-grade glioma, including GBM, which was based on the adult indication, while the EMA PIP includes these studies and studies for DIPG. Celgene was encouraged by FDA to seek a written request that could include the plan studies as well as any other pediatric indications for which marizomib could offer potential benefit.

Next, Dr. Mark Kieran will present the marizomib mechanism of action, a summary of the phase 1/2 clinical experience in adults, as well as

the ongoing and planned pediatric clinical trial.

Industry Presentation - Mark Kieran

DR. KIERAN: Thanks, Sherry.

I'm Mark Kieran, senior director of pediatric oncology at Celgene BMS, and as mentioned previously, marizomib is a potent irreversible proteosome inhibitor. Proteosomes are important cellular structures that degrade unwanted or aberrant proteins within the cell. Some of these proteins may function to maintain normal cellular homeostasis, while the TP53 protein and tumor cells benefit by removing protein such as this.

Proteosome inhibition can alter the relative contribution of proteins within a cell, including those deleterious to the tumor. In general, proteins targeted for destruction are ubiquitinated and pass through the proteosome central core. Three important proteolytic enzymes labeled beta 1, beta 2, and beta 5 within the inner core of the proteosome digest the protein into smaller peptides for recycling.

Marizomib has a lipophilic structure that

allows it to pass through the blood-brain barrier and covalently binds to these three enzymes within the proteosome core, resulting in the inhibition of protein degradation and preservation of key proteins that may reset normal cellular homeostasis.

Marizomib has been studied in five different non-GBM, phase 1/2 single-arm studies involving 280 adult patients with a variety of advanced solid tumors, lymphoma and multiple myeloma. While the drug had manageable toxicities, a number of dose-related and reversible CNF AE events were observed.

First, this suggest that the drug penetrates the brain, and it's supported by nonclinical data. Second, there are other proteosome inhibitors, three of which are approved for multiple myeloma or mantle cell lymphoma, as well as others that are in clinical trials in non-CNS diseases such as the treatment of solid tumors, lymphoma, and hematologic malignancies. For the blood-brain barrier penetrating qualities, marizomib has

focused its development on studies in adult patients with GBM.

There are two phase 1/2 studies of marizomib in adults with GBM, Study Marizomib 108, which has been completed, and Study Marizomib 112 that still has subjects on treatment. Study 108 had three parts looking at marizomib alone or in combination with bevacizumab, a VEGF inhibitor commonly used in adult GBM.

Study 112 had two treatment arms in an Optune cohort. Arm 1 evaluated marizomib in combination with radiation therapy and temozolomide, the standard of care for adult GBM, while arm 2 evaluated marizomib in combination with adjuvant temozolomide.

The Optune cohort evaluated marizomib in combination with temozolomide in tumor-treating fields, or TTFs, which are low-intensity electric fields. Whether it's a single agent or in combination, the recommended phase 2 dose of marizomib with 0.8 milligrams per meter squared typically administered once a week for 3 weeks of

each 4-week cycle.

Study 108 assessed the activity of both single-agent marizomib as well as marizomib in combination with bevacizumab in recurrent GBM as mentioned before. Some single-agent activity as defined by radiologic responses or prolonged stable disease was observed. See the middle column of the table. The column on the right shows the combination of marizomib with bevacizumab, which has an overall response rate of 34 percent and a duration of response of 5.2 months.

To help benchmark these results, a recent report of the GLOBE study of bevacizumab in recurrent GBM, which used the same renal criteria for disease response, demonstrated an objective response rate of only 21.9 percent and a duration of response of only 2.2 months. While this was of interest and recognizing the limitations of cross-study comparisons, there was no improvement in median PSF or OS, and the development of marizomib was refined to focus on newly diagnosed GBM.

As mentioned previously, the overall safety profile of marizomib in patients with GBM, both relapsed and newly diagnosed, was similar to that observed in patients with non-GBM tumors. The most common TEAEs are listed on this slide for patients receiving marizomib monotherapy shown in the purple bar, first marizomib in combination with bevacizumab shown in the gray bars and those receiving marizomib in combination with radiation and temozolomide shown in the black bars.

DR. PAPPO: Sorry to interrupt you, Mark, but we cannot see those bars in this slide.

DR. KIERAN: Do we want to -- is there a possibility -- can you go to the next slide?

(Pause.)

DR. KIERAN: Okay. No. So both of them are missing the material. I could kind of point it with my hands if we were sitting in front of each other, but unfortunately without the images here, it's going to be hard to show people the results.

Alberto, do you want me to just keep going to describe what they would look like or do you

want to wait and see if those slides can be fixed?

DR. PAPPO: Whatever you think. I mean, if you want to just describe the percentage of toxicities, that would be perfectly fine, Mark.

DR. KIERAN: Okay.

So what you should have seen on slide number 13 was that the majority of the toxicities observed for grade 1 and 2 events were frequent but not of significant grade. There were a small number of grade 3 and grade 4 adverse events that were presented there originally on the slide.

These occurred only in a smaller fraction of patients, obviously a little bit depending on whether it was monotherapy in combination with bevacizumab or in combination with radiation and temozolomide, but again, typically less than about 10 percent or so of patients.

The most common AES were manageable and the vast majority, as I said, were really grade 1 or grade 2. Slide 14 was meant to show you the CNS adverse events from marizomib, again, alone or in combination since, as was pointed out previously,

these are often the issues that led to the development of this drug in malignant gliomas.

The CNS AEs that you unfortunately can't see on this slide, again, certainly supports the concept that there's blood-brain barrier penetration clinically for marizomib, and this tended to occur early in the first dose, sometimes during cycle 1 or early in cycle 2.

Although you can't see the toxicities here, the two that were most problematic for patients were hallucinations, predominantly visual, as well as ataxia. Again, the CNS adverse events were reversible and resolved with dose delays, reductions, or discontinuation in medical management. Again, the majority of these toxicities were grade 1 and grade 2.

I also want to point out that in the GBM program, there were six grade 5 TEAEs reported by clinical investigators, including 3 intracranial hemorrhage, 2 progressive disease, and 1 sudden death. None of these events, however, were considered related to marizomib. So in summary,

the safety profile of marizomib is manageable, alone and in combination, with bevacizumab or radiation and temozolomide in adult GBM.

Let's go to the next slide and see. In summary, although you didn't see all of the specific data, the nonclinical data and clinical experience supports the penetration of marizomib across the blood-brain barrier.

The occurrence of dose-related reversible CNS adverse events due to the blood-barrier penetration has shown that the risk to benefit ratio is more favorable for use in patients with brain tumors where marizomib has a manageable safety profile, as well as with preliminary evidence of activity in GBM and further potential when used in combination.

Based on these results, the EORTC is conducting a randomized phase 3 trial of marizomib, radiation, and temozolomide versus radiation and temozolomide, assessing overall survival benefit in newly diagnosed adult GBM patient.

Based on the molecular target of marizomib,

it's blood-brain barrier penetration, safety, and tolerability from the adult phase 1/2 studies in the nonclinical findings, that I'll detail in a moment, further development was initiated in children with DIPG. A phase 1 study of marizomib and panobinostat in pediatric DIPG has been initiated, and additional studies in pediatric high-grade glioma are being planned. The initial pediatric clinical and nonclinical data will pave the way for future development.

On the next slide is the marizomib agreed PIP, which includes eight different elements, which are detailed in the table. In addition, four of these studies will also support the requirements of the FDA agreed to iPSP.

The QUALITY study is focused on the development of a lower dose vial for children and will be gated based on the clinical phase 1/2 study results. The nonclinical studies assess the activity of marizomib in combination with a number of different inhibitors in DIPG cell lines and patient-derived material, and similar work is

planned for the high-grade gliomas. Identifying more active combinations with marizomib continues to be an important initiative.

The last three are clinical studies, including the phase 1 safety and tolerability assessment of marizomib alone and in combination with panobinostat in children with DIPG. Based on these results of the initial trial of nonclinical study identifying optimal combination approaches as it becomes available, in conjunction with the safety and tolerability from the phase 1 DIPG study, a phase 1/2 trial of marizomib in combination with another drug or modality would be developed for pediatric high-grade glioma. Taken together, Celgene BMS is committed to assessing the quality, the nonclinical, and the clinical activity of marizomib in children with DIPG and other high-grade gliomas.

This slide, which fortunately you can see, the top half is labeled part A and shows the in vitro activity of marizomib, panobinostat, or both, in a series of pediatric DIPG cell lines as

measured by relative cell viability. The blue bars are for panobinostat activity, the red bars are for marizomib activity, and the purple bars are for the combination of panobinostat and marizomib.

In looking at the top graph on the far left, while marizomib, again shown as the red bars, had limited activity and panobinostat, the blue bars, had limited activity in the cell line second to the left, the two drugs together showed significant synergistic activity in all 60 DIPG cell lines shown as the purple bars. In the bottom half of the slide, part B, in vivo or the topic assessment demonstrated activity of both marizomib and panobinostat in a DIPG model.

I've mentioned previously the phase 1 trial of marizomib and marizomib plus panobinostat was developed based on the nonclinical studies just presented and was designed to assess the safety and tolerability, PK, and preliminary activity of marizomib and panobinostat in pediatric patients with DIPG.

The first cycle will assess the safety,

tolerability, and PK of marizomib alone. Beginning with cycle 2, panobinostat will be added, and ongoing safety, tolerability, PK, and preliminary response will continue to be evaluated. This study has just been activated.

In conclusion, based on the manageable safety profile in adults, the CNS penetration capacity of marizomib, preliminary evidence of activity in adult GBM, and nonclinical evidence of synergistic activity in DIPG cell lines, marizomib is now being evaluated in children with DIPG. Celgene and BMS would like guidance for a written request that would include both patient populations, high-grade glioma as well as DIPG, and we look forward to gaining your feedback.

This final slide, let me thank you on behalf of the marizomib team and now turn the presentation over to Debbie, who will serve as the moderator for the Q&A session.

MS. TADY: Thank you, Mark.

For the Q&A session, as Mark said, I will serve as the moderator and direct your questions to

one of our marizomib team subject matter experts to provide a response.

Clarifying Questions from Subcommittee

DR. PAPPO: Thank you very much for your presentation. We will now take clarifying questions for Celgene International. Please use the raised hand icon to indicate that you have questions. Please remember to put your hand down after you have asked your questions, and please remember to state your name for the record before you speak. It would also be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with that's all of my questions for now so we can move on to the next panel member.

So we will start with any questions. Nita?

DR. SEIBEL: Yes. Nita Seibel from the NTI. Thank you for that nice presentation. I have two main questions. First of all, can you expand more on the CNS adverse event management plan? You mentioned dose delays, interruptions, and you did mention a pattern somewhat, but how often do they

recur? Then the use of antipsychotics, you said they were mainly visual hallucinations, but perhaps you could go into more detail about that.

Then my second question is, particularly if you had looked in the preclinical setting at rhabdoid tumors or the SMARCB1 deficient cancers, I know with rhabdoid tumors I think there's been a report of association with those with mixed responding somewhat to proteosome inhibitors; so if you have any preclinical data about that as well.

MS. TADY: Thank you, Dr. Seibel. I want to just make sure that we understand. First your question is you'd like for us to expand and provide more information on the CNS management plan and how often the hallucinations recur such that you get a sense of the characterization of the events; and number two, whether we have preclinical data on rhabdoid tumors.

DR. SEIBEL: Yes --

MS. TADY: Go ahead.

DR. SEIBEL: Yes, that's correct, particularly to give us an idea how this would be

manifested in children or what we would expect in younger patients.

MS. TADY: Okay. To begin with, I'm going to ask our clinical development lead for the adult programs to provide some information on the CNS management plan and how often those hallucinations recurred. That would be Dr. Ileana Elias. Then I'll redirect the second question to another responder once we've answered your question.

Ileana, are you on mute?

DR. ELIAS: No, I'm here. I hope I'm not on mute. Can you hear me?

MS. TADY: We can hear you.

DR. ELIAS: I'm Ileana Elias. I'm the clinical development physician for the adult program. We have seen the CNS associated adverse events in about 40 percent of the patients, and as mentioned before, one of the hallmarks of the CNS adverse events were the visual hallucinations. In general, these occurred by cycle 2, but they could have occurred as early as after the first dose of cycle 1.

The management was mainly with dose delays and dose reduction. We did not introduce any prophylaxis for these hallucinations because it was not possible to determine which patients would be most likely to experience the hallucinations. In general, after a dose reduction, these hallucinations did not recur with reintroduction of treatment.

MS. TADY: Thank you, Dr. Elias.

Dr. Seibel, did we answer the first question completely?

DR. SEIBEL: Yes.

MS. TADY: Okay. And your second question was about whether we have any preclinical data on rhabdoid tumors. The short answer is we don't currently have any data on that. I can just open it up and ask if Dr. Suman Machinani or if Dr. Mark Kieran want to make any additional comments about that in terms of the thinking around obtaining additional data.

DR. KIERAN: Thanks, Debbie. This is Mark Kieran, the senior director for pediatric oncology.

With respect to the rhabdoid tumors or ATRTs for those in the brain, there has been a recent report. In fact, we're in discussions with academic centers who are specifically interested in those tumors.

One of the things we are interested in is identifying combination agents so that any clinical study could be gated not just on the development of this nonclinical and preclinical data, but it would also then give us a chance to incorporate the data that we obtained from the phase 1 DIPG study vis a vis the dosing, the PK, the tolerability, and early evidence of activity.

MS. TADY: Thank you, Dr. Kieran.

Dr. Seibel, did we fully answer all of your questions?

DR. SEIBEL: Yes. Thank you.

MS. TADY: You're welcome.

DR. PAPPO: Next is Ira Dunkel.

DR. DUNKEL: Thank you, Alberto.

Ira Dunkel, Memorial Sloan-Kettering. I have two or three questions. One question, kind of related to Dr. Seibel's question, is I believe that

I've heard at least one presentation from a non-Celgene BMS investigator suggesting that marizomib may have some potential for medulloblastoma, so I'd like to hear from Dr. Kieran or others if there are data about that and what the development plan might be for medulloblastoma.

My second question is maybe a two-part second question. I'm wondering if the phase 2 planned study described in the PIP depends, A, on the results of the phase 1 studies or whether it's committed to move ahead regardless of whether there's any suggestion of efficacy in phase 1, and similarly, is it dependent at all on the ongoing EORTC phase 3 study, and when will the results from that EORTC study be available? Thank you.

MS. TADY: Thank you, Dr. Dunkel. First of all, we'll address the first question, does marizomib have some potential for activity in medulloblastoma, do we have any data, and if so, what would be the development plan?

For this question, I'd like to direct to

Dr. Mark Kieran for a response.

DR. KIERAN: Yes. Thank you.

Ira, a great question. Yes, I think we've probably heard the same presentation vis a vis the potential for proteosome inhibition in medulloblastoma in early preclinical models, and we're actually in discussions with academic centers interested specifically in that disease and the role of marizomib.

Again, with regard to the ATRT or rhabdoid, it would be important, not just as a single agent but in combination, to get as much preclinical data as possible and then gate that along with what we learn both from that preclinical data, the preclinical data from our other tumor types, as well as the results, PK toxicity and evidence of activity, of the DIPG trial in terms of determining the optimal way to take that information forward.

MS. TADY: Dr. Dunkel, does that answer your question?

DR. DUNKEL: Yes, it did. Thank you.

MS. TADY: I do know you had additional --

DR. PAPPO: Steve?

MS. TADY: -- I'm sorry.

DR. PAPPO: I'm sorry. There are additional questions. I apologize. Go ahead, Ira.

DR. DUNKEL: Oh, I'm sorry. I thought I posed the second question already.

MS. TADY: You did, Dr. Dunkel. That was my mix-up.

Let me then direct. Your second question was in two parts. You were asking if the phase 2 study that was planned as part of the pediatric investigational plan would depend on the results of the phase 1 DIPG study or if it would proceed regardless. Then the second part of that second question was whether or not the phase 2 study would be dependent on the results of the EORTC phase 3 in adults with newly diagnosed GBM.

So at least for the first part of the question with regard to whether the phase 2 study would proceed, I'm going to ask Dr. Mark Kieran to begin that response.

DR. KIERAN: Great.

Ira, again, although the first study is a phase 1 study to determine the optimal dose and schedule of marizomib in this patient population, it includes an expansion cohort. So by the end of the phase 1, there should be a sufficient signal to give an indication to justify the phase 2. This is an important distinction from strictly a dose-finding study where there's very limited ability to interpret clinical activity; here, there would be an opportunity.

The trial includes both patients that are newly diagnosed after having received radiation as well as those with recurrent disease. So I think the opportunity to develop that signal, to guide the development of the phase 2, would be available at the time that decision is made. I'll let Debbie take over vis a vis the EORTC question.

MS. TADY: Thank you, Mark.

Dr. Dunkel, with regard to whether the phase 2 study would be dependent on EORTC, the phase 3 study in patients with newly diagnosed GBM, the answer is it is not gated to the phase 3 study. I

think you also were interested in maybe understanding a little bit of the timing around the EORTC phase 3 study.

Did I remember that correctly?

DR. DUNKEL: Yes.

MS. TADY: For the response to an update on the status of the EORTC phase 3 study, I'm going to ask our clinical lead, Dr. Ileana Elias, to give some information in terms of an update on where that study is.

DR. ELIAS: Yes. This is Ileana Elias. The EORTC study is currently accruing. This study has an overall survival as a primary analysis and we are looking at 488 events. Based on the current number of events and the projections on how these events occur, they are expecting that the final analysis will be available in the fourth quarter of 2022.

DR. DUNKEL: Thank you very much for answering my questions. I apologize to my colleagues if I've taken up too much of the time.

MS. TADY: No problem. Thank you,

Dr. Dunkel.

DR. PAPPO: Steve, you're next.

DR. DuBOIS: Steve DuBois from Dana-Farber Boston Children's; a few questions. With other proteosome inhibitors there has been a safety signal of peripheral neuropathy, but I didn't hear that mentioned, so I'm curious about rates of peripheral neuropathy, just thinking about potential combination partners. Then what is known about the role of the proteosome during CNS development, and in pediatric patients, might there be an issue, an impact, on neurodevelopment based on what is known about this pathway in CNS development?

The third question is just the lower age of eligibility for the EORTC trial.

MS. TADY: Dr. DuBois, thank you. Your first question about the observation with other proteosome inhibitors of peripheral neuropathy and whether that has been seen in the adult studies with marizomib, I'd like to ask Dr. Ileana Elias to please respond.

DR. ELIAS: The rate of peripheral neuropathy in our phase 1 studies was extremely low. We had just about 3 percent of grade 3 neuropathy in one of the studies, which was in the current GBM. In the newly diagnosed phase 2 GBM study, we didn't see a grade 3 of peripheral neuropathy.

DR. DuBOIS: Thank you.

MS. TADY: Thank you, Ileana.

Ilena, while you're speaking, could you please address Dr. DuBois' question about the lower age of eligibility for the EORTC phase 3 study?

DR. ELIAS: The EORTC study enrolls patients 18 years and older.

MS. TADY: Thank you very much.

DR. DuBOIS: Thank you.

DR. PAPPO: Then, Dr. DuBois, with your second question, you were really asking what we know about the role of the proteosome in terms of development, I think neurodevelopment, and how that might impact children.

DR. DuBOIS: That's exactly right.

MS. TADY: What I'd like to do is ask our translational medicine lead, Dr. Suman Machinani, if you could please address Dr. DuBois' question.

DR. MACHINANI: Excellent. With regard to a specific role of proteosome, there are no specific targets known, although there is speculation that there could be downregulation of cell cycle and tumor suppressor proteins.

With regard to what we know from a neurodevelopment standpoint as it relates to our nonclinical studies, what we can state is that from a 9-cycle or 9-month cynomolgus monkey study, marizomib-related microscopic findings in the brain were present in male and female monkeys at the high dose of 0.45-0.60 milligrams per meter squared and consisted of minimal to mild axonal myelin degeneration, which was restricted to the deep cerebellar white matter.

Following the recovery period of 3 months, there were no marizomib-related microscopic findings in the brains of recovery animals, suggesting reversibility. The clinical relevance

of the cerebellar findings is unknown, but may include reversible CNS AEs such as ataxia.

DR. DuBOIS: Thank you.

Alberto. I don't have further questions. Thank you.

DR. PAPPO: Thank you.

Malcolm. you're next.

DR. SMITH: Thank you. Malcolm Smith, NCI. Most of my questions have been answered already. I did have one question, another one about the CNS adverse event. The slide stated that they were generally reversible. Were there any CNS AEs that were not reversible or that reversed very slowly?

The second question related to the combination of HDAC inhibitors with proteosome inhibitors and has been studied preclinically in most adult cancers, and data very similar to what was presented for DIPG have been developed. Aside from the myeloma and the panobinostat-bortezomib combination, is there evidence for an HDAC inhibitor/proteosome inhibitor combination showing positive results in a kind of proof-of-concept

randomized study?

MS. TADY: Thank you, Dr. Smith. Your first question is around what we observed in the adult studies for CNS adverse events. We said they were generally reversible, and your question was, were any not reversible or did they reverse slowly?

To respond to that question, I'd like to turn this over to Dr. Ileana Elias.

DR. ELIAS: So we observed that the CNS, the toxicity did resolve upon dose reductions, and if they didn't resolve upon dose reductions once the drug was discontinued, then there were no lasting CNS toxicities.

Now, this is to say that all these studies -- of course the two studies that were conducted were nonrandomized studies, and having these patients with glioblastoma, at times it's not that easy to differentiate what is due to the disease and the drug. But we have not seen long-lasting CNS toxicities that were thought to be associated with the drug.

DR. SMITH: Thank you.

MS. TADY: I think your second question, Dr. Smith, had to do with the combination of HDAC inhibitors and proteosome inhibitors. I think your point was that even though it's been studied in most cancers, aside from maybe multiple myeloma, you were asking if there's any data from a randomized study with this combination. Is that --

DR. SMITH: Right, is there any proof of concept that an HDAC inhibitor or proteosome inhibitor combination actually works in the clinic the way the in vitro synergy would suggest it might.

MS. TADY: I think for the answer to that question, what I'd like to do is ask Dr. Kieran if you could respond to Dr. Smith's question.

DR. KIERAN: Malcolm, it's, I think for me at least, a hard question to answer, so I will call on some of my colleagues because I think the question was based on the adult data for the combination of HDAC and proteosomes, where similar in vitro and in vivo preclinical data showed

similar activity to what we showed in DIPG, and did any of those turn into activity in adult tumors. Obviously, there's no pediatric data yet, since the pediatric trial is just now beginning.

I'll let others with more expertise in the adult area answer that, but one of the things is, obviously, the biology of tumors we know is different, and although there are general overlapped mechanisms, understanding why it is that proteosome inhibitors, for example, work so well in a particular disease like multiple myeloma but not others means that we don't always, or can't always, in pediatrics rely on the adult data of different disease pathways as a perfect guide for activity in pediatrics.

I know that's not a complete answer because we don't have any pediatric data yet. I don't know. Debbie, that perhaps Suman has any knowledge of how to answer this question.

MS. TADY: Maybe so.

Suman, Dr. Machinani, is there any additional information that you can share to

respond?

DR. MACHINANI: Definitely. I am not aware of any proof-of-concept data generated in adults using HDAC inhibitor and proteosome inhibitor combination for the indications on the discussion.

MS. TADY: Thank you very much.

Dr. Smith, did we answer your questions to the best of our ability?

DR. SMITH: That's fine. Yes, that's fine. Thank you.

MS. TADY: Okay.

DR. PAPPO: We only have four minutes left for the questions, so we're going to try to get as many people as possible.

Tobey, you're next.

DR. MacDONALD: Tobey MacDonald, Emory University. Sorry. I had a series of questions, but I'll try to be quick if possible. I just want to know if there is, based on the mechanism, a biologic rationale for focus on DIPG versus other tumors, and in that setting, is there any dependency of activity on H3K27M that's on the

slide that was wild type versus K27M but didn't see clearly enough the difference there. And of course that's important since adult GBMs infrequently harbor that mutation.

Third, I just wanted to know the rationale for panobinostat in combination versus other drugs, or particularly radiation therapy, and whether there'd be consideration of an upfront DIPG with radiation in the drug if there were data to support that.

Finally, are there any biomarkers that are predictive of response or pharmacodynamic assays that could be used to track and follow whether there is a functional activity of the drug when given to the patients. Sorry for many questions.

MS. TADY: No, it's quite alright. I was just trying to make sure that I have all of what you'd like to know. First of all, I think you're asking that based on the mechanism of action. is there a biologic rationale for the use in pediatric GBM; is that correct?

(No response.)

MS. TADY: Dr. MacDonald?

(No response.)

MS. TADY: I think you're on mute.

DR. PAPPO: Tobey? Tobey, can you answer the question?

DR. MacDONALD: Sorry about that. Specifically, DIPG in relation to H3K27M and GBM, diffuse midline glioma versus non-diffuse midline glioma.

MS. TADY: For your first question, I think this might be a shared response, but I'm going to ask Dr. Suman Machinani if you can start based on the mechanism of action, and then perhaps, Mark, you can also contribute.

DR. MACHINANI: Thank you, Debbie.

What we know in terms of the mechanism of action, the role in terms of biological rationale, it's still largely unknown with regards to proteosome inhibition, in particular DIPG settings. I'd like to maybe defer to my colleague, Mark Kieran, if there's any additional data on this front. At least from the proteosome stand front,

we have not identified a clear biological rationale.

DR. KIERAN: Thanks, Suman. Thanks, Tobey.

As was pointed out, we don't know exactly which proteins are being inhibited of degradation that account for the effect, but as you noted in the figure, the cell line on the very right-hand side was an H3K27 wild type, and it had the same synergistic activity as the five cell lines with either H3.1 or H3.3 mutation, suggesting that this is not restricted to the H3 mutational status.

You're right that DIPG and diffuse midline glioma, the term is originally defined more on the classic historical definition of DIPG vis a vis short symptomatology and radiographic appearance as opposed to the new molecular one. But as we talked about, particularly in the context of thinking about the development of a high-grade glioma trial, which would be kind of high grades other than DIPG and diffuse midline, it is again -- because at least in the early preclinical experience, this does not seem to be restricted to H3K27.

Does that --

MS. TADY: Dr. MacDonald, does that answer your first question?

DR. MacDONALD: That does.

MS. TADY: Okay. Then I know you had asked for some information around the rationale for the combination with panobinostat versus other drugs or possibly radiation therapy. I'm also going to ask Dr. Kieran if he could speak to this question about how panobinostat was selected for that phase 1 DIPG study.

DR. KIERAN: Yes, thanks.

Tobey, in the paper that was published by the Stanford group, which was a large collaboration unto itself, they had screened literally thousands of combinations. In the six DIPG cell lines, panobinostat and marizomib was by and afar the strongest signal they detected and was, again, present in all 6 out of 6 cell lines, and it was based on that, that this kind of went forward.

There was some activity, for example, when they looked at panobinostat in combination with

some other pathway inhibitors, but not present in all of the cell lines and not to the same degree. And that's why this one has kind of taken precedence in terms of its clinical development.

So that's how we got there. Lynn Adele [ph] is the first author of that publication from Michelle Monje's lab where that data was provided.

DR. MacDONALD: That's helpful. Any preclinical data with radiation in suggesting upfront trial?

DR. KIERAN: Debbie, it is ok if I go ahead and --

MS. TADY: Yes, please do, Mark.

DR. KIERAN: Actually, as was already mentioned in terms of the adult EORTC trial, in which it will be upfront with their radiation and temozolomide versus radiation and temozolomide, some of that data will hopefully guide us in the future as we kind of see what happens there.

In addition, with the DIPG study, although we will not be combining it with radiation, as had been mentioned in the presentation, patients will

get one month of marizomib alone, then start the combination with marizomib and panobinostat. But patients eligible for the trial are those that are newly diagnosed with completed radiation, so they won't be on radiation when they start the drugs. They will have just completed their radiation, which I know isn't quite the same thing as synergism with radiation.

I'll ask Suman to comment if he knows better. I'm not aware that that was one of the combinations that they did at the Stanford study, but part of our goal is to see whether two drugs are tolerated in pediatric patients and whether there's any signal of activity with absolutely the idea that hopefully one could at some point, if there is activity and it's tolerable, move this more immediately up into the upfront situation. Particularly for a disease like DIPG where there really are no survivors, it would be an absolutely reasonable thing to do. But step 1 and 2 is single agent and combination tolerability and signals of activity.

Hopefully that answers the question.

DR. MacDONALD: Thank you.

DR. PAPPO: I'm sorry. We need to move on. I'm just going to let Dr. Reaman ask the last question.

MS. TADY: Sure. Absolutely.

DR. REAMAN: Just briefly -- and again to go back to the treatment-emergent neurotoxicity, the only intervention that I understand that was utilized was dose modification or discontinuation of marizomib. Was that a complete discontinuation of marizomib or were patients allowed to restart therapy? And if so, did they have recurrent hallucinations upon restarting?

MS. TADY: Thank you, Dr. Reaman. For your response, I'd like to ask Dr. Ileana Elias to please comment on whether there was complete resolution following discontinuation or if marizomib was restarted and the CNS AEs recurred.

DR. ELIAS: The recommendation was for the drug to be
first-dose reduced. Two dose reductions have been

allowed, and the majority of the patients, while they were dose reduced, the hallucinations did not recur. In fact, on the top of my head, I cannot recall any of the patients in our phase 1/2 studies who had had several episodes of hallucinations after they had dose reductions. Of course, for the ongoing phase 3 study, where the patient population will be much larger, we don't have that data available yet.

DR. REAMAN: Okay. Thank you.

DR. PAPPO: Does that answer your question, Greg?

DR. REAMAN: It does. Yes, thanks.

Questions to the Subcommittee and Discussion

DR. PAPPO: If you still have your hand up, please lower it. There is no open public hearing session, so we will now proceed with the charge and questions to the subcommittee and panel discussions. After each question is read, we will pause for any questions or comments concerning its wording; then we will open the questions for discussion. We will ask the FDA to read the first

question.

DR. CASEY: Hi. This is Denise Casey. Can you hear me?

DR. PAPPO: Yes, we can.

DR. CASEY: Hi. Good afternoon. Thank you, Celgene, for your presentation and for the thoughtful discussion during the clarifying questions. I think a lot of these topics have been at least partially addressed during that discussion, but we will just go through them.

The first question to the committee is to please discuss your thoughts on trial design and rational combination partners for marizomib investigation in pediatric patients with high-grade glioma.

DR. PAPPO: If there are no questions or comments concerning the wording of the question, we will now open the questions for discussion. I only see Steve.

DR. DuBOIS: Steve DuBois, Dana-Farber. I think during the presentation, I was a little bit worried that the first-in-child study would assign

children to marizomib monotherapy and keep them there. And understanding that the population of interest is rather ill, I was a little bit worried about that and was pleased to see that after the first cycle, children move on to the combination.

So it's not a question; it's really a comment and maybe praise. That was good to see.

Second, in terms of rational combination partners, I seem to recall that this panel discussed ONC201 in midline glioma in the past, and I wondered if that has been looked at preclinically since that appears to be another agent of interest in high-grade midline gliomas.

DR. PAPPO: Does anybody on the panel have any insights to that question? Tobey?

DR. MacDONALD: Sorry. I don't have any specific insights with regard to ONC201, but it relates back to another question of mine, which was trying to determine the biomarker that may be predictive of response.

I don't know if any sort of sequencing analyses have been done post-drug treatment of the

DIPG to understand what pathways are being affected most, which would obviously inform us better of what combinations from a functional standpoint may be the most relevant to look at as opposed to just blasting with drug screenings, which are also important, but the complementary approach would be helpful.

So as far as I know from the mechanism action of ONC201, which is both a DRD2 antagonist and a QUIP-P [ph] agonist and mitochondrial system, that there is not a specific overlap that I'm aware of, but I could be wrong.

DR. PAPPO: Any thoughts on some epigenetic modifiers combined with this, given the histone mutations, that you've seen some of these gliomas in children?

(No response.)

DR. PAPPO: Any thoughts from the panel, Tobey or Ira, or the experts in CNS tumors?

DR. MacDONALD: Again, not specifically that I can see the connection. I would need to see exactly the pathway that is being modified.

DR. PAPPO: Ira?

DR. DUNKEL: Thank you, Alberto.

Ira Dunkel, Memorial Sloan-Kettering. I wanted not to comment on that epigenetic question you just posed, but to reflect on Steve's comment about the strategy for sequentially adding the second drug after a brief window of single-agent drug; although I also agree that it's such a desperate population that this is attractive.

I am really playing devil's advocate more than disagreeing, but I wonder when you study it this way, when you then determine the tolerance of the combination, whether you can only conclude that a patient who can tolerate single-agent marizomib can then tolerate the combination at the dose rather than that combination data being relevant for a recommended phase 2 dose for a treatment-naive population.

DR. PAPPO: We have Malcolm.

DR. SMITH: Yes. Malcolm Smith, NCI. Thank you, Alberto. I think in staying with the combination discussion, obviously we all hope that

this study that's ongoing with the panobinostat and marizomib shows a good activity signal. I think it will be very important, though, to understand whether the activity is more related to marizomib and whether panobinostat actually has a contribution.

As per my question, the HDAC inhibitor/proteosome inhibitor combinations have been studied preclinically across many adult cancers, but as far as I know, this is not translated to the clinic aside from the panobinostat added to bortezomib and dexamethasone for myeloma. But outside of myeloma, I'm not aware of any translation.

Also, the CNS penetration is low for panobinostat, so I hope that if the study is a success, that we're not locked in necessarily to the combination without understanding whether marizomib might actually be the primary activity driver.

DR. PAPPO: Thank you. We have Julia.

DR. GLADE BENDER: Thank you for that really

interesting presentation. I was just wondering -- and I may know the answer myself. But there's been a precedent in the Children's Oncology Group, particularly for DIPG, to combine the new agent concurrently with radiotherapy in newly diagnosed patients.

I'm wondering if this was considered as a strategy and whether it was really the concern over interpreting the CNS toxicity that is the reason that you would initiate the drug after the radiotherapy or whether there's a biologic reason.

DR. PAPPO: Thank you. I have Greg.

DR. REAMAN: Thanks, Alberto. Greg Reaman. I just wanted to go back to what I thought was maybe a rhetorical question that Ira raised in response to Steve's statement about moving to a combination after single cycle of single agent. I think most patients who end up on investigational drug therapies are desperate, and irrespective of their desperation. I think we have a responsibility to learn from those patients.

I would be a little bit concerned about

moving too quickly to a combination that may result in toxicity, which is unacceptable, and then abandoning a strategy and potentially abandoning a single agent that hasn't been adequately evaluated that may take more than a single cycle before we see a signal of activity. So just a word of caution.

DR. PAPPO: I don't see any other additional comments to this question. If anybody else wants to add anything or I can try to summarize the comments for question number 1.

DR. MASCARENHAS: Alberto, this is Leo. Could I ask a question, recommend?

DR. PAPPO: Of course.

DR. MASCARENHAS: This is Leo Mascarenhas from Children's Hospital Los Angeles. I didn't get to ask this question earlier, but based on Greg's comment, I also would take a little bit of caution with combination therapy because the other class effect seems to be cardiac toxicity and also is the consideration in combination with panobinostat, and CNS tumor patients tend not to have cardiac

toxicity in general because of pre-exposure. That's something to keep in mind with combination therapy.

DR. PAPPO: Thank you very much.

The panel initially expressed some concerns just with monotherapy, but some of the panel members were very happy to see that after the first cycle, there was going to be a combination therapy. However, we strongly caution them to proceed with caution in this specific area because we do not want to abandon the potential strategy of a drug that could be potentially valuable for this disease and then stopping because of significant toxicity. Some other concerns of toxicity, for example, as Leo just raised, might be cardiac toxicity.

As far as which agents to combine this with, there were not a whole lot of ideas. Somebody mentioned ONC201, somebody mentioned epigenetic modifiers, but there were really not a lot of other ideas. There was a comment regarding the tolerance of the combination and whether this will be enough to give us enough information for a recommended

phase 2 dose. Another one of the comments was whether it has been at least contemplated to add radiotherapy with this drug like it has been done in other trials in DIPGs and COG.

I will be more than happy to add anything you want me to add or if I missed anything, please let me know before we proceed to the next question.

(No response.)

DR. PAPPO: Everybody seems to be happy, so we will now have the FDA read the second question to the committee.

DR. CASEY: Hi. This is Denise Casey again. Again, this question was alluded to in the prior discussion, but maybe we can ask the panel.

Considering the CNS toxicity profile associated with marizomib in the adult clinical experience to date, can you discuss possible risk mitigation provisions that could be included in pediatric clinical trials and comment on any developmental or age-related assessments and management guidelines that could potentially mitigate risk in younger children who may

experience CNS adverse reactions that have been relatively common and occasionally dose-limiting in the adult program.

DR. PAPPO: If there are no questions or comments concerning the wording of the question, we will now open this question for discussion. I see a hand with Tobey and a hand with Leo.

Tobey, do you want to start?

DR. MacDONALD: Sorry. I was raising early for discussion.

DR. PAPPO: Steve?

DR. DuBOIS: This is Steve DuBois from Dana-Farber. I think the struggle here is that the target patient population with advanced DIPG, unfortunately -- I mean, unless this is an active drug or an active combination, in the initial studies, it will be very challenging to follow these patients for long enough to understand at least the neurodevelopmental effects, if any, of the agent.

So I think certainly there will be a plan to manage acute toxicities, but I think any evaluation

of longer term neurodevelopment outcomes will likely need to come on follow-on trials.

DR. PAPPO: Thank you, Steve.

Tobey, do you have a comment about this question?

DR. MacDONALD: Yes. In my mind, I think this is really the most critical question, that there be very specific guidelines in place for how to mitigate with 40 to 50 percent hallucination/ataxia and other CNS side effects. Life is short for these patients. Quality of life is even shorter.

This is going to be in a particularly young age group. I'm concerned that reporting AEs may be challenging, if it's visual hallucinations, exactly what's going on with our patients who will probably be on steroids as well, so there's that effect in combination. Risk could be greater in the younger population.

I think this may slow accrual because if faced with other trials that have drugs, and there are trials with very little to no side effects, it

will be a little bit of a hard sell. And we know despite the very promising preclinical data, as Malcolm said, the translation to a clinical benefit has yet to be realized. So I think there needs to be thought into exactly what drugs would be used and how this will be addressed because I see this as a challenge. Thank you.

DR. PAPPO: To follow up on your comments, I've had the same concerns about the attribution. Given the toxicity profile of this drug and the type of disease that you are targeting, I think that sometimes it will be very challenging to assign an attribution as to where this was related to progression to the disease or to the drugs. So that's going to have to be very well specified in the guidelines of the protocol.

I think that Greg raised his hand again.

(No response.)

DR. PAPPO: Greg, do you have a comment about the question?

(No response.)

DR. PAPPO: I think you're on mute.

DR. REAMAN: Sorry. I think I'm off mute now. I just wanted to clarify, Alberto, that the point of this question was not about long-term neurodevelopmental toxicity, but really acute neurotoxicity risk mitigation or management. We're well aware that in at least the early phases of evaluation of this agent, if the signals of activity are compelling enough, we're not really focused on long-term, but it was really the acute neurotoxicity.

I would agree that particularly in this patient population, attribution of some of these neurotoxicities are going to be difficult to establish, and recognizing visual hallucinations in very young children I think will be difficult as well. But that's what we were trying to elucidate, were really discussions around that issue.

DR. PAPPO: Anybody else have any comments? I don't see any other hands.

(No response.)

DR. PAPPO: Okay. To summarize this, the purpose of this question was really not to talk

about, really, the long-term effects of these agents but acute toxicities and how to mitigate the occurrence of these toxicities. Some of the panel suggested that there will be very specific guidelines on how to mitigate the effect and how to make attributions of the drug to the side effects. The other important thing would also be how to identify side effects in a younger population.

I don't know if I've missed anything or if anybody wants to add anything, Tobey, or Greg, or anybody else.

DR. REAMAN: I think you covered it.

DR. MacDONALD: I think you covered it.

DR. PAPPO: So if everybody's happy, we will proceed to the third question. The FDA will read the third question.

DR. CASEY: Hi. This is Denise Casey. The third and final question is, are there non-CNS pediatric cancers that should be considered for evaluation in the marizomib development program?

DR. PAPPO: If there are no questions or comments concerning the wording of the question, we

will now open the questions for discussion.

Bill?

DR. PARSONS: Was that for me, Alberto? This is Will.

DR. PAPPO: Yes. You raised your hand, yes.

DR. PARSONS: Thank you. I've been trying to ask a question previously, and we didn't have time. I think this question gets to one challenge of several discussions we've had here, which is, based on the previous discussion, I'm actually not quite sure of the specific biologic rationale for which CNS tumors should be studied. People have asked specific questions about rhabdoid tumors, medulloblastomas, et cetera.

There's honestly, as far as I've perceived, not a very specific biologic rationale for why H3K27Ms, DIPGs, or midline gliomas would be the priority. I understand from practical reasons that those are patients who desperately need therapies that we might want to try there.

So that actually is what makes, I think, consideration of other types, both CNS and non-CNS

tumor types, a little bit difficult. It's also what I believe made discussion of rational combination therapies a little bit difficult because we could discuss other investigational agents that are relevant to DIPG and high-grade glioma, but trying to make the link to the specific biology of this agent was challenging.

So I think it's, I guess, more a comment than a question, but my comment is essentially that it's challenging for me to say what other tumor types specifically should be studied beyond other clinical needs or strategic concerns.

DR. PAPPO: Thank you. One of the comments I had is sort of related to what you said, Will, and that was when they presented the data, they said that the CNS tumors outweighed, because of the toxicity profile, some other tumors.

So I really cannot think of any other non-CNS pediatric cancers, at least at this stage, in which there would be a very strong rationale for testing this agent, especially with the toxicity profile that has been described under high CNS

penetration.

Catherine Bollard is next.

DR. BOLLARD: I was just interested, given that I'm a lymphoma doctor, what the data would be to support a lymphoma indication in a relapse setting for children, given that, obviously, this was evaluated in adults with lymphoma and myeloma.

DR. PAPPO: I don't have an answer for you. I don't know if anybody on the panel wants to comment.

DR. BOLLARD: I was just putting it out there for Celgene, too.

DR. PAPPO: Then we have Steve.

DR. DuBOIS: Steve DuBois from Dana-Farber. There is literature on bortezomib in combination with chemotherapy for children with relapsed ALL that I think showed nice activity, and that's not a primary CNS cancer but certainly a childhood cancer that can disseminate to the central nervous system. So I do wonder about that as an option and would welcome maybe Elizabeth or Andy's thoughts as bona fide leukemia doctors, which I can't claim to be.

DR. PAPPO: Any comments on the leukemia aspect?

DR. KOLB: Yes. Hi. It's Andy Kolb from --

DR. RAETZ: Yes --

DR. KOLB: -- oh, sorry, Elizabeth. Do you want to go first?

DR. RAETZ: No, no. Please go ahead, Andy.

DR. KOLB: Oh, sure. This is Andy Kolb, and I represent the COG Myeloid Disease Committee and a pediatric oncologist at duPont Hospital for Children.

I think from the AML perspective, we have invested quite a bit in studying proteosome inhibitors in pediatrics. I think it would be hard to conduct another trial in AML. There are signals. You could enrich a population looking at signals, first signal, but I don't think that that would be a primary development path.

I'll let Elizabeth comment about T-cell and T-cell ALL.

DR. RAETZ: Thanks. This is Elizabeth

Raetz. I think, Steve, just as you've mentioned, there have been some promising results. Bortezomib has been used in a salvage relapse regimen for a relapse B and T ALL, and the results from that trial were published and showed some favorable early response rates. Then the ALL 1231 Frontline TLL trial closed early, but had a randomization to bortezomib during induction and delayed intensification for T-cell ALL.

So I think we're still waiting for final definitive conclusions from that study, but I think because proteosome inhibitors have been studied, I would see that there may not be as much of a path forward there because they've been studied fairly extensively previously.

DR. PAPPO: Thank you very much.

Greg?

DR. REAMAN: Thanks, Alberto. Just to address Dr. Bollard's question about lymphomas, I think it's a very difficult space, fortunately, in that the number of children with relapsed and non-Hodgkin lymphoma is really very, very small.

I think in a recent international Accelerate the Strategy forum, proteosome inhibitors were not really high on the list of priority agents to evaluate given some of the other immune-directed therapies, antibodies, naked antibodies, as well as antibody drug conjugates, and even possibly engineered cell therapy, so it might be a little difficult.

I think evaluating another proteosome inhibitor in the lymphoid leukemia space, it is also crowded. There are a couple of proteosome inhibitors under evaluation, and the studies are fraught with great difficulty in accruing patients. The real role for proteosome inhibitors in either salvage therapy or upfront therapy, and anything other than T-cell ALL, I think is really a question that is of real interest.

DR. PAPPO: Thank you. Just a friendly reminder that if you've asked the question to lower your hand, and then we have Leo.

DR. MASCARENHAS: Sorry. I should have put down my hand because Steve asked my question.

DR. PAPPO: Thank you.

Are there any other comments on this third question? Will? We have Malcolm and Will.

Malcolm, would you like to comment on this question?

DR. SMITH: Yes, please. This is Malcolm Smith, NCI, a couple of points and some reiterating points made. I think there's a general question of is there really any place else left to study for proteosome inhibitors in childhood cancers? There's been a good discussion about AML and other cancers, but I think an agent that has substantial CNS toxicity really isn't going to rise to the top among the class of proteosome Inhibitors. So I think just from that reason alone, the answer is no.

I do want to emphasize Greg's point about especially the non-Hodgkin lymphoma and especially the B-cell non-Hodgkin lymphoma. Greg mentioned the ACCELERATE meeting. The publication in 2019, I think it listed that there were 13 PIPS already, and thankfully our treatment has gotten so

effective for most of these children that the number of children who would be eligible for these trials of novel agents has gotten quite small.

Then there are all the T-cell engagers that are exciting to the adult lymphoma docs, and ADC [ph] that's shown high-level activity and reported at ASCO looks exciting, AND the CAR T-cell. There are so many opportunities, so I think the bar is incredibly high for non-Hodgkin lymphoma, and I just think we need to acknowledge that whenever we talk about NHL and new drugs moving into the pediatric NHL area.

DR. PAPPO: Thank you, Malcolm.

Dr. Cheng?

DR. CHENG: Hi. I just want to make a comment, so thank you for recognizing me. Jon Cheng, industry rep. I think we all want to understand other pediatric tumors, but as everyone recognized, sometimes it's a little bit difficult. I do think it's helpful to distinguish studying other tumors in the context of investigate and

initiate hypothesis generating, and then also getting clarity on the context of a written request.

So I think studying it in the context just to understand biology is helpful, but studying in the context of a request I think should be pretty focused so that it allows the sponsor an opportunity to clarify things.

So as I understand it, Celgene the sponsor has studied a number of tumors, and they're focused on GBM appropriately. So I just want to make sure that that's maybe helpful to understand maybe from the committee or the FDA's perspective. Those are two different things. potentially, from a sponsor's perspective.

DR. PAPPO: Thank you very much for that comment.

Anybody else have any comments or I'll try to summarize this very brief discussion on question number 3?

(No response.)

DR. PAPPO: I think the overall consensus

was that this proteosome inhibitor space in that leukemia-lymphoma world is very crowded, and there was not a lot of interest in pursuing this agent in that patient population. There was some concern also about what is the optimal patient population with CNS tumors in which this specific compound needs to be studied.

The other thing that we talked about was what Dr. Cheng just said, that we need to be cognizant of the fact that we need to consider the written request versus investigator-initiated trials, and there's a specific biological rationale for this specific agent.

I don't know if I left anything out or if anybody wants to add anything to what I just mentioned.

(No response.)

DR. PAPPO: If not, Dr. Reaman will now provide our closing comments for the day.

Closing Remarks - Gregory Reaman

DR. REAMAN: Thanks, Alberto. My closing comments will actually be very brief. I'll start

again with a thank you to the members of the advisory committee and also to our sponsor, Celgene BMS. I think this was an interesting product. I think we had some very interesting insightful discussions. Again, I just want to thank everybody for their participation. I look forward to your participation tomorrow.

Again, I just want to apologize for the change in agenda since our second day was planned to discuss the relevant molecular target list and look at the specific targets that are the result of specific genetic aberrations and go over that. But given the fact that we had to do this meeting as a virtual meeting, we'll plan for some time in the future when things get back to normal, or when we all get used to the new normal, and hopefully plan a face-to-face open public workshop to discuss the target list.

So again, thank you very much for the discussions and presentations today. Thanks.

DR. PAPPO: Thank you very much, Greg. We will now adjourn the meeting for today and continue

to the next session tomorrow morning at 10 o'clock in the morning.

Dr. Bonner, anything we need to know about? We have the same link to join the meeting tomorrow, the same that you sent this morning, or any other things that we need to know about?

CDR BONNER: Hi. This is LaToya Bonner. It is the same length, so you'll use the same link for tomorrow morning's meeting starting at 10. Make sure, for those who are participating in the actual discussion to phone 30 minutes before the meeting starts.

Adjournment

DR. PAPPO: Thank you very much, and we will see you all tomorrow. Thank you so much.

CDR BONNER: Thank you.

(Whereupon, at 3:11 p.m., the afternoon session was adjourned.)