FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PEDIATRIC ONCOLOGY SUBCOMMITTEE OF THE ONCOLOGIC DRUG ADVISORY COMMITTEE

Session 1

Thursday, November 19, 2015

8:01 a.m. to 10:12 a.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31 Conference Center

The Great Room (Rm. 1503)

Silver Spring, Maryland

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C O N T E N T S

P R O C E E D I N G S

(8:01 a.m.)

(Call to Order

Introduction of Subcommittee

DR. PAPPO: Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Sarah Peddicord. If you are present, please stand.

I would like now to introduce the members of the panel, and we'll start with Dr. Morrow. We're going to start introducing ourselves. Can you introduce --

DR. MORROW: P.K. Morrow, industry representative from Amgen.

DR. KIM: AeRang Kim, pediatric oncologist from Children's National.

DR. DuBOIS: Steven DuBois, pediatric oncologist, Dana-Farber, Boston Children's.

DR. RAETZ: Elizabeth Raetz, pediatric oncologist, University of Utah.

MS. WEINER: I'm Susan Weiner. I'm the patient advocate from the Children's Cause for Cancer Advocacy and the Children's Brain Tumor Foundation in New York. I'm a veteran.

MS. HAYLOCK: I'm Pamela Haylock. I'm an oncology nurse, and I am the acting-consumer representative.

DR. ARMSTRONG: Deb Armstrong, medical oncologist and chair of ODAC.

DR. PAPPO: Alberto Pappo, pediatric oncologist and chair of the Pediatric ODAC.

DR. TESH: Lauren Tesh, designated federal officer for ODAC.

DR. KIERAN: Mark Kieran, pediatric neuro-oncology from the Dana-Farber Boston Children's Hospital.

DR. WEIGEL: Brenda Weigel, pediatric oncologist, University of Minnesota and chair of developmental therapeutics for the Children's Oncology Group.

DR. EHRLICH: Lori Ehrlich. I'm a medical officer at the FDA and a pediatric hematologist

oncologist.

DR. BARONE: Amy Barone, medical officer at FDA and also pediatric hematologist oncologist.

DR. REAMAN: Gregory Reaman, associate director of the Office of Hematology Oncology Products, FDA.

DR. PAPPO: Thank you.

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

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

meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings.

However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks. Thank you.

We will proceed with the opening remarks from Dr. Greg Reaman, followed by a presentation by Amy Barone.

Introductory Remarks

DR. REAMAN: Thank you, Dr. Pappo. I would just like to take the opportunity to welcome and to thank all of the members of the panel. We're here today to discuss two products, one approved, one not yet approved, and to discuss them within the context of their potential relevance for evaluation and assessment in children with cancer.

Dr. Barone, shortly, will provide a little bit of a background on the pediatric legislative initiatives, which provide a regulatory base for

the evaluation of new drugs, including new cancer drugs in the pediatric population.

You'll see from her presentation -- and we can discuss a bit after if necessary -- that the majority of what we can do in oncology is utilize to our maximum authority the Best Pharmaceuticals for Children Act and issue written requests, which are voluntary on the part of industry to accept and then to develop and conduct appropriate studies.

We're really here today to discuss two products to see if there is a feeling of a consensus among you that these products are worthy of investigation and how best they might be investigated.

It makes little sense for us at the agency, even though there are now a number of pediatric oncologists in our office to actually put into the written requests, which are pretty detailed pieces of information that actually go to sponsors, the details of studies and investigations that are actually going to be conducted by people outside of the FDA.

Having appropriate investigator input into this process makes the whole process much more rational, much more efficient, and really allows us to issue requests that are going to be followed up on.

So with that, again, thank you, and I think Dr. Barone is going to provide some details.

Presentation - Amy Barone

DR. BARONE: Good morning. As Dr. Reaman mentioned, my name is Amy Barone. I'm a medical officer in the Division of Oncology Products II. I'm very excited to be here this morning. I'm just going to give you a brief background on an outline of some of the pediatric legislation initiatives and cancer drug development. I have no financial disclosures.

The two pieces of legislation that we'll briefly talk about are the Pediatric Research Equity Act, or PREA, and the Best Pharmaceuticals for Children Act, or BPCA. Both of these acts were permanently authorized by the Federal Research and Innovation Safety Act, or FDASIA.

The Pediatric Research Equity Act, or PREA, was passed by Congress in 2003, and it's part of the Food, Drug, and Cosmetic Act. This is a requirement. This requires that companies assess the safety and effectiveness of certain products in pediatric patients.

These are typically any products that are being approved, we ask that the study also be studied in children for the same indication that is being approved for in adults. So this authorizes the FDA to require pediatric assessments for a new indication, a new dosage form, a new dosing regimen, new route of administration, or a new active ingredient.

Oftentimes in oncology, the products that are being studied in adult patients do not have the same indication in pediatric patients, so for oncology drugs, these are often waived.

As Dr. Reaman mentioned, what we're going to talk most about, or our best tool, is the Best Pharmaceuticals for Children Act, which is BPCA. And this is the incentive program that we can use.

This is a voluntary program, and it was passed by Congress in 2002 and also is part of the Food, Drug, and Cosmetic Act. This provides a financial incentive to companies to voluntarily conduct pediatric studies under a pediatric written request.

There are two ways that a written request can be developed. One is that a sponsor can request that the FDA issue a written request, and the way that this is done is through the submission of a proposed pediatric study request or a PPSR.

The PPSR contains rationale for studies and study design, a detailed study design, and appropriate formulations for each age group. If a company submits a PPSR, we will review this and can then issue a written request. And the FDA can also issue a written request without a PPSR.

Applicants who submit studies that fulfill a written request are eligible to receive pediatric exclusivity. And what that means is an additional six months of exclusivity attached to all existing marketing exclusivities and patents for the drug

moiety, so not just for the pediatric indication but for all moieties of that drug.

It doesn't necessarily mean that the study has to be a positive study to be given exclusivity. The goal of this legislation is to gather more information about pediatric patients so that even if the drug is not effective, we feel that that's useful to know for the community, especially when a lot of drugs are used off-label in pediatrics.

The written request is our primary regulatory mechanism for obtaining the pediatric data for pediatric cancer therapy and product labeling. OHOP is the Office of Hematology and Oncology Products.

We've issued over 50 written requests since the implementation of this law. Nineteen of these therapies were granted exclusivity, and there is new labeling information added for 15 of these therapies. Some of it was safety information, and three of the therapies are approved for pediatric indications.

The goal of this, and part of this meeting,

is to try to consider what relevant products can be discussed earlier in the developmental timeline and can a written request be part of that discussion to have early and frequent engagement between investigators, industry, and FDA to really prioritize which drugs should be used for investigation to really talk about research strategy and harmonizing goals and increasing efficiency.

With that, I think we can move on to our products. Thank you.

DR. PAPPO: Before we proceed, I would like to ask Dr. Angiolillo to introduce to herself so we can put that in the record.

DR. ANGIOLILLO: Good morning. My name is Anne Angiolillo. I'm pediatric oncologist at Children's National Medical Center in Washington, DC.

DR. PAPPO: Thank you.

We will now proceed with Session 1, ABT-414 from AbbVie. Dr. Tesh will read the conflict of interest statement for this session.

Conflict of Interest Statement

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

With the exception of the industry representative, all members and temporary voting members of the committee are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with the federal ethics and conflict of interest laws, covered by but not limited to those found in 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 particular individual's services outweighs his or her potential financial conflict of interest.

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

This session's agenda involves information to gauge investigators' interests in exploring potential pediatric development plans for two products in various stages of development for adult cancer indications. The subcommittee will consider

and discuss issues concerning diseases to be studied, patient populations to be included, and possible study designs in the development of these products for pediatric use.

The discussion will also provide information to the agency pertinent to the formulation of written requests for pediatric studies if appropriate. The product under consideration for this session is ABT-414 sponsored by AbbVie, Inc. This is a particular matters meeting which during specific matters related to AbbVie's product will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

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

With respect to FDA's invited industry

representative, we would like to disclose that Dr. Phuong Khanh Morrow is participating in this meeting as a non-voting industry representative and acting on behalf of regulated industry. Dr. Morrow's role at this meeting is to represent industry in general and not in any particular company. Dr. Morrow is employed Amgen.

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 special personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. PAPPO: Thank you, Dr. Tesh.

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

For this reason, FDA encourages all participants, including the sponsor's known employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue; that is consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interest 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 the sponsor's presentation.

Sponsor Presentation - Kyle Holen

DR. HOLEN: Thank you and good morning. My name is Kyle Holen. I'm a project leader of oncology at AbbVie and a medical oncologist by training. I'm responsible for the development of ABT-414.

We're here today to discuss our proposal for the development of ABT-414 in pediatric high-grade gliomas. We appreciate the opportunity to obtain your feedback, and we look forward to learning from you, our advisors, as well as from the FDA.

I'll start with a brief review of ABT-414, a first-in-class antibody drug conjugate. We'll discuss the mechanism of action, as well as some of the emerging clinical data in adults with glioblastoma.

It was these data that led us to first consider the assessment of ABT-414 for pediatric brain tumors, a condition that is as fatal in children as it is in adults and similarly in dire need of novel therapies. In our review today, you will begin to understand the difficulties of

conducting such a study in a rare condition. And therefore, we propose a novel way to approach this challenge, an approach that we believe is the best way to move forward for ABT-414.

Let me first describe how ABT-414 works. ABT-414 is an antibody drug conjugate. It's an antibody, also known as ABT-806, bond by covalent, non-cleavable linker to a powerful chemotherapy agent otherwise known as MMAF. This technology empowers an antibody with a warhead that is many times more powerful than standard chemotherapy.

The beauty of this technology is that by using the antibody's tumor-specific binding properties, this warhead is delivered to the tumor and most normal tissues are spared. ABT-414 binds preferentially to tumors by targeting a unique epitope on EGFR. This is an epitope that is only exposed when EGFR is amplified or has a V-3 mutation, conditions that only occur in cancer and not in normal tissue.

Here's a graphic depiction of the mechanism of action. Once ABT-414 binds to a tumor, it is

internalized. Lysosomes then release MMAF, thus causing microtubule inhibition and subsequent apoptosis.

Let me walk you through some of the preclinical data with early evidence of the potency of ABT-414 from some of the patient-derived xenograft models in both V-3-expressing tumors shown on the left and amplified wild-type tumors shown on the right.

In these models, we injected glioblastoma cells from patients into mice, and we treated them with either ABT-414 or a control as indicated by the green arrows. We then monitor the tumor growth in animals. The X-axis records the time in days and the Y-axis depicts the tumor volume.

The growth of both tumors increases dramatically when the control is administered as shown in black. However, upon treatment with ABT-414, there is a pronounced and prolonged tumor shrinkage, shrinkage that occurs out to 45 or 60 days as indicated by the blue line.

Many of these animals were cured with no

viable tumor present. It was these and other preclinical data that prompted us to aggressively pursue clinical trials in adult glioblastoma.

Here is a review of our clinical trial experience to-date. I'd like to start out with study M13-379. This is our first-in-human study, which enrolled patients with a variety of solid tumors and established our initial safety profile.

The next four studies are all studies in glioblastoma, phase 1, phase 2, phase 3, as well as our regional study in Japan. All of these studies were either ongoing or initiated in 2015. But there are two studies of particular importance that I'd like to highlight for you today.

Study M14-356 has the most mature data, and I'll walk you through these data on the next few slides. The Intellance 2 study is the study where we plan on including pediatric patients. More about the Intellance 2 study will be discussed later.

Let's move on to our phase 1 GBM study design, study M12-356. This study has three arms:

Arm A is an arm with radiation temozolomide and ABT-414 combination; Arm B is an arm with temozolomide and ABT-414; and Arm C is ABT-414 monotherapy. We have identified the recommended adult phase 2 doses of all these regimens. All arms also have expanded cohorts for a further assessment of safety and efficacy.

But because patients in Arm A were newly diagnosed and recently had surgery, changes from baseline measurements were not possible. Only Arms B and C allowed recurrent GBM enrollment where we could see if there was a direct effect on the tumor.

Within the first few patients enrolled, we started seeing dramatic changes in tumor size. This waterfall plot examines the changes in tumor size along the Y-axis with an individual patient depicted as a bar long the X-axis.

As you can see, more than half of our patients with recurrent disease had some amount of tumor shrinkage and a few had deep and pronounced responses that have lasted a year or more.

These responses have been observed for both the combination treatment as shown in gray, as well as for monotherapy patients as shown in blue. Of note, we observed RANO-confirmed responses, which requires at least a 50 percent reduction in tumor size, as denoted by the dash line, only in subjects with tumors that EGFR-amplified.

None of the 15 non-amplified patients had a RANO-confirmed response. And because of this, we have limited enrollment of this study and all future studies to only those patients who have tumors that are EGFR-amplified.

Now, let me show you an example of one of the most impressive responses on the study to-date. This is a 43-year-old man who was diagnosed with glioblastoma in 2012. He underwent a gross total resection, followed by radiation and temozolomide as per standard of care.

Soon after completing adjuvant temozolomide however, his tumor recurred as evidenced by the MRI on the left. He was then enrolled in Arm B of the ABT-414 study, and a 24-week MRI showed a near

complete response, and he continued on treatment for more than 12 months.

As you would expect, there are toxicities that accompany these responses. This is a listing of the most common adverse events reported in Arms B and C of study M12-356.

The majority of these toxicities are common in the disease and from temozolomide treatment. However, there is one clear exception, and this is a unique ocular toxicity that's related to the warhead, MMAF. These events are all manifestations resulting from the formation of microcysts in the cornea, which is called microcystic keratopathy.

Next, let me show you what we've learned regarding microcystic keratopathy. The cornea is like fingernails or skin. The cornea will regenerate and grow anew every three to four weeks. The new cornea is formed at first by the limbal stem cells. These cells give rise to cells called transient amplifying cells, which in turn give rise to the more differentiated cells of the cornea.

Our hypothesis is that it's the transient

amplifying cells that are most effected by ABT-414. When these cells are damaged, they form small deposits or microcysts that develop within the cornea. When you have many of these microcysts, it can cause blurry vision or irritation, and sometimes eye pain.

As the new cornea replaces the old cornea, the cysts go away and the vision is restored. This occurs about the time the patients are ready for their next dose of ABT-414, setting off a new cycle of events.

As you can see from a picture of one of the patients eyes, there's a small ring of cysts that have formed around the periphery of the cornea after ABT-414 dosing. Now, this toxicity is generally manageable and does not commonly lead to serious sequela, but I'd like to make a few important points.

This toxicity is not unique to ABT-414 as it is also observed with other antibody drug conjugates and in some cases with chemotherapy, particularly with high-dose cytarabine. It is

often manageable with dose interruptions and reductions. It is dose related and generally reversible. Lastly, we've observed that steroid eye drops administered around the time of the infusion appear to lessen some of these symptoms.

I've shown you some of the early promising clinical data that we've observed in adults with high-grade glioma. Now, let's turn our attention to how this is relevant to pediatric patients.

As you all know, children diagnosed with high-grade glioma share a similar fate as adults. There are few effective treatment options and a very high morbidity and mortality. Because of this, we thought it was critical to see whether or not ABT-414 could deliver comparable benefits to children as we've observed in adults.

But let me walk you through some of the challenges to this proposition. As you are keenly aware, pediatric high-grade glioma is not a common occurrence. As you can see from this slide, it's estimated that there are fewer than 300 cases diagnosed in the U.S. each year.

Similar to adults, we expect EGFR amplification to be necessary for tumor response in children. Further, ABT-414 is not without toxicities. In order to maximize the benefit-risk ratio, we believe it's important to limit enrollment to those children with EGFR-amplified tumors as we're doing in adults.

Unfortunately, EGFR amplification is quite uncommon in pediatric high-grade gliomas. In fact, pediatric high-grade gliomas are molecularly distinct from adult high-grade gliomas.

Here, you can see the overall landscape of genetic alterations in adult GBM. The most common recurrent generic abnormalities are listed on the left, and each colored bar represents one patient with a specific alteration.

Collectively, EGFR amplification or mutation occurs in approximately half of the cases. In fact, this happens to be one of the most common genetic alterations in adults. But in sharp contrast, here, you can see the overall landscape of genetic alterations in pediatric brain tumors

from DIPGs on the left to high-grade gliomas on the right.

I'll point out here that histone H3, CDK and 2AB, and P53 are the most common genes affected where you'll see many bars. But in contrast, EGFR, unlike in adults, is amplified or mutated in only a few rare cases. There are only two red bars of EGFR amplification on this plot. However, both of these bars originate from the same patient.

Consistent with the previous slide, EGFR amplification is not expected to occur in more than 5 percent of pediatric high-grade gliomas. Although the rates of amplification vary by the population assessed and the techniques used, there are two studies that use the same FISH assay that we're using for patient selection. These two studies demonstrated no more than 3 percent of the tissues were EGFR-amplified.

Currently, EGFR testing is not common practice because EGFR alterations in children are rare, and the results do not influence clinical decision-making. There are no treatments that

require testing, nor is there a clear prognostic or diagnostic relevance. Therefore, very, very few cases of EGFR-amplified pediatric high-grade gliomas are identified.

With these challenges in mind, here are some of the trial options that we considered. First, we considered a stand-alone pediatric study. But feedback from multiple pediatric brain tumor cooperative groups has suggested that there's a limited interest in opening up a stand-alone study given the high screen fail rate and the small population of patients at most medical centers.

We also considered collecting data from a more formal expanded access program or a compassionate-use program. However, as I mentioned, it would be highly unlikely that we'd be able to identify any eligible patients.

We also discussed some type of widespread EGFR screening program. However, high-grade glioma tissue is quite scarce, and there would be a low yield of EGFR amplification positive cases identified.

In the feedback from pediatric oncology advisors, we are proposing a pediatric nested study, a study that will be conducted within an ongoing adult study known as Intellance 2. By doing this, we leverage the resources of a preexisting study already open at multiple sites globally.

Let me walk you through this proposal. This is our global phase 2 study known as Intellance 2. This study is being run in the United States, as well as 26 other countries in collaboration with the Brain Tumor Group of the European Organization for the Research and Treatment of Cancer, also known as the EORTC.

I'll highlight here a few points. First, this is a study for adult recurrent EGFR-amplified GBM. Second, patients are randomized to three different treatment arms, including a temozolomide lomustine control arm. Third, the primary endpoint of this study is overall survival. Clearly, this is not a study that was designed for a pediatric population and thus, we will have to make

significant changes that are relevant for a pediatric evaluation.

Our pediatric plan is to create a nested study that is an appendix that exists within Intellance 2 that will have objectives, eligibility, and screening procedures that are designed specifically for pediatric evaluation. Within this appendix, we hope to capture any pediatric patient identified at any of our sites that have the adult study open, as well as perhaps at additional major pediatric oncology centers.

Further, there are few other important considerations. First, the sample size is going to be much smaller than the adult sample size, and therefore the objectives are going to have to be quite different. As opposed to the adult objective of overall survival, given the small pediatric numbers expected, our objectives for the pediatric patients will focus mainly on safety and PK with descriptive summaries of efficacy variables.

As I mentioned, Intellance 2 is a randomized study where some of the patients are randomized to

a temozolomide lomustine control. But for the pediatric participants, all of them must be on active treatment.

On the next slide, I'll review our plan for pediatric dosing. In order to determine an appropriate pediatric dose, a population pharmacokinetic model was developed using adult PK data from phase 1 studies. Body weight was found to have a significant effect on the PK parameters of ABT-414. Simulations for ABT-414 in pediatric patients were conducted by extrapolating the adult PK model down to lower body weight ranges.

As you can see in this figure, a 1-milligram per kilogram dose of ABT-414 is expected to produce a similar exposure across multiple age ranges. Therefore, we propose to use the same dose in children as what we're using in adults, and that is 1 milligram per kilogram.

This next slide depicts the Intellance 2 study schematic. Here, you see the typical flow for an adult patient, from registration to screening procedures, and then randomization,

followed by treatment. After treatment is ended, the patients will have a post-treatment visit, as well as ongoing survival follow-up.

In contrast, here is the flow we propose for the pediatric patients. First, they have EGFR testing. If a patient is identified to have an EGFR-amplified tumor, he or she will then be consented and then enrolled into the study, and all patients will be assigned to active therapy.

Based on the patient's clinical history, investigators will be permitted to add temozolomide as part of their care. Patients will continue to be followed during the course of treatment, as well as during the evaluation and survival periods.

I'd like to next focus on our screening methods that we're using in this study. In order to capture every pediatric patient who has EGFR-amplified high-grade glioma, we will encourage widespread molecular profiling for every case diagnosed worldwide.

In order to make the screening of patient tissue as attractive to investigators as possible,

we're providing two options: First, we have an established relationship with the EORTC, or an existing next-generation sequencing panel referred to as SPECTA will be used to analyze pediatric tissues.

SPECTA will not only sequence for common pediatric abnormalities but will also provide information regarding the EGFR copy number. These data will then be relayed back to the investigators, allowing them to learn more about their patient's tumor than just about EGFR amplification.

The second option is to accept local EGFR amplification testing. Given the urgency for treatment initiation in these children, we propose to allow enrollment based on the local or SPECTA assays, and then follow this up with confirmation using our EGFR ABT-414 FISH assay. However, we will need to collaborate with the FDA to confirm this proposal.

Now, let me walk you through some of the major eligibility criteria for this nested study.

Similar to adults, EGFR amplification will be required. But different from adults is that we will include grade 3 gliomas, and of course, the age will extend down to 6 years.

We've also eliminated eligibility criteria that may have been a barrier to enrollment for the pediatric population and are including only the eligibility criteria that are needed to ensure patient safety.

In summary, we've seen very encouraging activity in adults with GBM, and therefore it's critical to test ABT-414 in children where there's also a very high unmet need.

This will not be an easy task and requires some creative thinking to solve these challenges. But with our partners in pediatric oncology, at the EORTC, as well as the FDA, we hope to confront these challenges with a novel approach, a nested study within our ongoing adult study. This provides the opportunity to evaluate ABT-414 in a pediatric population while allowing access to a drug that could hopefully make a significant

difference in their lives. If this proves successful, it may also provide a roadmap for future oncology programs that face similar challenges.

The ABT-414 team would like to thank the patients and their families who have participated in the ABT-414 studies, as well as the FDA and the members of the advisory committee for the opportunity to share our ideas with you today. We look forward to your questions and discussions. Thank you.

Clarifying Questions from Subcommittee

DR. PAPPO: Thank you very much.

We will now take clarifying questions for the sponsor. Please remember to state your name for the record before you speak. And if you can, please direct questions to a specific presenter. We will open the questions.

DR. DuBOIS: Steve DuBois. What is the age spectrum for EGFR amplification in the pediatric population? Are they mainly older teens, for example?

DR. HOLEN: We believe so, yes, that the rates of EGFR amplification are higher in the adolescents than they are in the really young population.

DR. PAPPO: Yes, Dr. Armstrong?

DR. ARMSTRONG: You indicated that you expect about 6 patients per year in the United States, but this is a global study. How many do you expect per year -- I don't know what percentage of the trial is in the United States and which percent is out the U.S. How many patients total do you expect per year?

DR. HOLEN: Yes. We don't have data outside the EU and countries where the studies are open like Korea, Australia. But we have looked at the data in the EU, and there are multiple sites throughout the European Union that are open. There are about 300 cases diagnosed with high-grade glioma in the EU, about 200 in the U.S.

DR. ARMSTRONG: In the adult studies, did you see any interaction with temozolomide in terms of the pharmacokinetics of the investigational

drug?

DR. HOLEN: We did check the PK parameters with and without temozolomide, and it turns out that temozolomide did not affect the PK of ABT-414.

DR. PAPPO: Brenda?

DR. WEIGEL: I have two questions. The first, can you clarify the vision for the inclusion of the temozolomide? It's plus/minus. And is it up to the investigator, treating physician's discretion the timing of it, your vision for inclusion?

DR. HOLEN: Sure. Our vision is to try and be as inclusive as possible to allow the investigators to make that determination. We're leaving it completely up to the discretion of the investigator. If they believe that temozolomide would also benefit the patient, along with 414, we're allowing them to use at, whichever dose and schedule as their standard practice.

DR. WEIGEL: I'm Brenda Weigel. I apologize. I didn't say that at the start of my prior question. Do you have any data in -- you had

in the one study, you treated patients in combination with radiation therapy.

Do you have any data on the subsequent radiation effects in combination with ABT-414 in any of your patients for radiation recall type of phenomenon or any other secondary effects from radiation because most of these patients will have received radiation?

DR. HOLEN: Yes. We have looked at this fairly extensively in our phase 1 study. Interestingly, we were able to achieve a higher dose of ABT-414 in combination with radiation than without the radiation. Then we followed some of these patients for -- one patient has been on for 2 years after completing her radiation with ABT-414, and we haven't seen any long-term sequela such as radiation recall in any of these patients.

DR. KIERAN: Mark Kieran from the Dana-Farber. A couple of questions. The first is, the concept of amplification versus a new epitope for recognition by the antibody, typically when something is amplified, it's still the normal

sequence, which means it would have the same recognition as normal EGFR within the body.

I wasn't clear. I tried to understand from the documents what it is about the amplification that makes it recognizable by the drug that also recognizes the V-3 form that would make it different from the native EGFR.

DR. HOLEN: The epitope is hidden when EGFR is in a resting state. It's only when EGFR is in an active state where the confirmation of the receptor changes, and then it exposes the epitope so that the antibody can bind. We found that EGFR is more commonly in that active state when there is EGFR amplification present.

We also believe that there may be more receptor turnover when EGFR amplification is present. As you know, if the receptors are having a heightened turnover, it would bring in more antibody into the cell, also bringing in more toxin, which may lead to enhanced efficacy.

DR. KIERAN: So the amplification is really a surrogate for activated molecule, and obviously

the V-3 is constitutively activated.

When I was looking at some of the adult data, I was trying to separate out what percentage of the adults with amplification, which frequently have the V-3, have a differential response from those that just have amplification.

DR. HOLEN: We've looked at that as well, and the numbers are still pretty small. But we have seen responses in patients who are wild-type amplified, as well as patients who are amplified with the V-3 mutation. We believe that V-3 is not necessary for a response, but amplification is. And every patient who has the V-3 mutation is also amplified.

DR. KIERAN: Presumably, there will be patients that have constitutively active non-amplified that would also have responded, or you didn't see any?

DR. HOLEN: We did not see any -- I'll tell you that the assays that we've used to try and correlate with response have been a PCR looking at mRNA levels. We looked at overexpression with IHC,

and we've looked at amplification with our FISH probe. It looks like amplification is really the only one that can accurately predict whether or not someone may respond to treatment.

DR. KIERAN: Because there is a small percentage of the -- again, it's a small percentage in all of the cohorts. But for the pediatric group where we do see point mutations in activating EGFR, not the V-3, which is quite rare in pediatrics, but not amplification. And I just wondered if that group would also be appropriate, but I think you've answered that.

Is it okay to ask another -- you had shown the results from the M12-356, looking at the differential outcome in the adults of Arm 2 versus Arm 3, and it didn't really look like those that got temozolomide did any better than those who just got the drug.

I wondered, given that it complicates the analysis of determining or at least crediting what the response is due to by those two different groups, therefore, is temozolomide really an

important component for this?

DR. HOLEN: That's an excellent question. We have the same question ourselves about whether or not temozolomide is an important component. Because we have that question, that's how we've designed our next study as a randomized study of the temozolomide with 414 versus just 414 alone.

The results are similar as you pointed out on this waterfall plot. We've had more data that has accumulated since the time of this waterfall plot that we presented at ASCO this past June. There may be a slight preferential response rate in the combination over the monotherapy. However, the PFS-6 remains similar in both arms.

At this point, we really don't know which one may be better, and we'll have to wait and see what our randomized data show.

DR. KIERAN: Would you correlate that with MGMT expressions since I think for many places, both in the adult and pediatric world now, the only patients that get MGMT are those that are -- or that get temozolomide are those that are

non-MGMT-expressing, those that do not have the promoter methylated.

But of course, then that's also predictor of response, which means you may be selecting the patients that are likely to respond to temozolomide, at which point then your drug would also be getting credit for some of that.

DR. HOLEN: We have looked at that, and it turns out that the patients who had combination treatment who responded were patients who had recently recurred either during their adjuvant temozolomide therapy or within weeks after completing their adjuvant temozolomide therapy. That correlated also with their MGMT status where they were unlikely to have responded to temozolomide alone.

Now, there was one exception of a patient who responded to treatment and was likely to have responded to temozolomide, and we believe that to be true because of his methylation status. But he wasn't a confirmed responder.

RANO requires two scans to make sure that

the 50 percent reduction in tumor size is maintained, and this patient, although had a 50 percent reduction on the first scan, rapidly progressed right after the first scan.

So he wasn't a confirmed responder, and we think that might have been one example of a temozolomide response. That patient was also not amplified, so it wasn't on the waterfall plot.

DR. REAMAN: Can you just clarify -- the Intellance 2 study is the one in which you want to embed the pediatric study. The enrollment or the eligibility, are these newly diagnosed patients, recurrent patients, the adults?

I just question the randomization to the temozolomide lomustine-only arm if these are recurrent patients, all of whom have likely received temozolomide. I'm just not clear who the patient population is that's being studied here.

DR. HOLEN: Intellance 2, that study is a second-line recurrent population only. None of those patients receive radiation. They only receive ABT-414 or they receive ABT-414 with

temozolomide.

Lastly, the control arm is either lomustine or a temozolomide re-challenge because we have observed that some patients with recurrent disease, if it's been a long time since their last exposure to temozolomide and they happen to be MGMT methylated, that some investigators will decide to treat them with a temozolomide re-challenge. So the control arm is either a temozolomide re-challenge or lomustine.

DR. MORROW: PK Morrow. Amgen. I really liked slide 12, and I wanted you to perhaps give a little clarity that I noted in the briefing book related to your response rate, particularly complete response rates in arms that contained ABT-414.

DR. HOLEN: Sure. Just to clarify, you want me just to run through this again real quick?

DR. MORROW: The complete response.

DR. HOLEN: The complete response, yes. We did see patients with a complete response, not only the patients on the combination arm but also in the

monotherapy arm, which was really good to see. Complete response is something that's typically not reported in recurrent adult GBM.

If you look through the literature of treatment with bevacizumab, it's hardly ever reported with complete response, so we were really excited about these complete responses. These responses happen to be very durable as well.

Unlike the example that I showed you, I discussed with the temozolomide responder who progressed on the very next scan, these responders were RANO-confirmed; multiple scans continued to show that they had continued tumor shrinkage.

We have one patient now that's been on 414 with recurrent disease for over two years; so a very, very long period of time for a patient who was told by his doctor that he might only live 4 to 6 months at the time of recurrence.

So really great stories and stories that we'd hopefully like to see in the pediatric population as well.

DR. PAPPO: Elizabeth?

DR. RAETZ: Elizabeth Raetz, University of Utah. Just in terms of the testing, would you envision that the testing for EGFR would be done on diagnostic tissue or is there a requirement for testing at the time of recurrence and progression?

DR. HOLEN: A diagnostic tissue would be fine. In fact, we've done a study where we've looked at paired biopsies, tissue taken at the time of surgery compared to tissue that was done upon re-resection.

In turns out that amplification was consistent across that period of time, so it doesn't require fresh tissue at the time of enrollment in order to understand whether a patient may be amplified.

DR. DuBOIS: Steve DuBois. If the confirmatory test done centrally does not confirm the presence of amplification, what would be the status of the patient that you would propose in that situation?

DR. HOLEN: We have talked a little bit about that, the discordant results, and what we've

decided might be the best option -- but I'd like to hear from you all about this, too -- is that we would relay that information back to the investigator so the investigator is aware.

Then he or she can then talk to the family and the patient and make a determination whether or not they would like the patient to continue in the study or whether they want to look for something else. I think part of that will depend on whether or not the patient has been dosed or whether the patient may be benefiting from drug, what some of the toxicities may be.

We'll allow patients to stay on, but allow the investigator to make a determination of whether they would want to take the patient off study.

MS. WEINER: I'm Susan Weiner, patient advocate. First of all, I'd like to thank you for trying to think through a plan for pediatrics in a very difficult disease under difficult scientific circumstances as well. But of course, as the patient advocate, we're concerned about the toxicities and what that may mean if the drug is

successful and would be brought forward to phase 2, presumably not phase 3 testing.

The drug apparently attacks dividing cells; is that correct?

DR. HOLEN: Yes, the drug -- the warhead attacks dividing cells. However, the warhead is targeted to cells that have that epitope that's exposed on the receptor.

The warhead is like standard chemotherapy, but because the warhead is attached to the antibody, the antibody takes the chemo only to cells that would have the ability to bring that warhead into the cell.

MS. WEINER: Is the implication that developing brain cells, a healthy brain tissue, or even healthy stem cells would not be affected?

DR. HOLEN: Correct. We have not observed any EGFR expression on cells in the bone marrow, or stem cells, or normal brain tissue cells. Those cells should be spared.

Now, we do have tissue in our body that does express EGFR. Your skin, as an example, has EGFR

expression. There are EGFR antibodies, as we all know, that can cause pretty severe skin rashes. But the EGFR in the skin, that EGFR is in a normal quiescent state and not typically activated. And because of that, our antibody doesn't bind to that normal EGFR on skin.

So we haven't seen skin rashes with this antibody drug conjugate. It's been extraordinarily rare where we'll see a rash. Certainly, when we do see a rash, it's not the type of rash that you expect with an EGFR drug. It's not the acneiform rash that happens over your face and your chest.

We believe that the antibody is quite unique in that regard and hopefully then avoids some of those normal tissue toxicities.

MS. WEINER: My second toxicity question really, of course, has to do with the ocular toxicity and how that will affect scheduling if the corneal cells regenerate every 3 to 4 weeks as you said. First of all, is that true for kids, and second of all, how would that likely affect the scheduling for the pediatric patients?

DR. HOLEN: Great questions. We don't really know about children, how that would affect the cornea. We do know that the cornea is still developing in the real young population, from zero to 3, and there are neuronal pathways that are developed even after the age of 3 between the eye and the brain, and those are set down at a pretty early age.

We think at the age of 6 is about when we think that likely we wouldn't have to worry about the developing cornea. That's why we've set an age range from 6 to 18 for this study to try and avoid some of those toxicities that may occur in the developing cornea.

MS. WEINER: For the patient who's been on it for two years, how has that worked, the cycles and the regeneration work for that patient, and the visual function?

DR. HOLEN: Again, great questions. She's doing great, but she is annoyed at this constant eye problem. I have to admit that I'd prefer to have a drug that didn't have eye problems. She

deals with it. She figures out a way to manage her life, where she can have these eye problems and still do the things that she needs to do every day.

Now, her husband has to take her places and drive for her. She's got to read things much closer than she used to. And it's cycles, so she's gotten used to the cycles. She knows that her vision is going to be worse and the irritation is going to be worse at about day 7 or 10. And then it's going to get better before her next cycle and be good until that 7 or 10-day afterwards.

So it's challenging, yes, but it's something that our patients have learned to live with and can manage.

In terms of your question about dosing, our dose in adults is once every two weeks. That seems to be a reasonable dose for patients to tolerate. We don't plan on changing the schedule in children because that was also the schedule that showed efficacy. And once we start changing the schedule, we're worried that maybe we won't see the same efficacy in children that we would see in adults.

At this point, our plan is to use the same dose and schedule to achieve the same exposures that we're seeing in adults that we'll hopefully see in kids so that they have the highest chances of getting some benefit.

MS. WEINER: My final comment is that I hope that you have families review your consent forms before you give them to parents.

DR. HOLEN: That's a great idea, and we will certainly do so. Thank you.

DR. WEIGEL: Brenda Weigel. Following up on the toxicity questions that were just asked, you alluded to the use of dexamethasone eye drops. Is there a required regimen and do you have data -- I would imagine that really as a symptom-management decreasing inflammation. It doesn't change the cyst formation. It doesn't change the turnover time of the cell regeneration, but maybe it does, so if you could address that.

Is that now a required element, and has that changed what you're seeing with regards to ocular toxicity?

DR. HOLEN: Yes. Early on in the program when we started noticing these ocular symptoms, I quickly went to the literature and tried to find out everything I possibly could about the cornea and became an armchair ophthalmologist.

I found some literature about high-dose cytarabine, and this is where this all started. High-dose cytarabine causes almost the exact little microcysts in the eye. And that's where I found out that with high-dose cytarabine, you give steroids pre- and post. I remember doing that back in fellowship a long time ago, but I happen to not be more of a medical oncologist and hematologist, so I don't have a lot of experience with high-dose cytarabine.

But based on that experience, we tried it in our patients, and we were able to continue to escalate ABT-414. In fact, there were a couple of patients who received a dose without the steroid eye drops and then received the same dose with the eye drops, and we saw a decrease in their toxicity, the severity of their eye symptoms.

Once we started seeing this, we made it mandatory that every patient have the steroid eye drops before treatment administration. If a patient comes in and they haven't had their two days of eye drops before they get their dose, we ask them -- to send them home, start their eye drops, and then come back in a couple of days to get their 414 infusion.

The way we think this works -- and this is all speculation. But from what I've read about the way it works in cytarabine and what some of the expert ophthalmologists -- in fact, there's an expert that we call on frequently who happens to be an expert in oncologic manifestations of the eye, in particular the cornea. Any type of oncologic manifestations that happen in the cornea, she's an expert. She's the first person we called.

She told us that what she thinks is happening is these transient amplifying cells have a very high turnover rate, and there are some sort of nonspecific uptake into these cells that's causing them to become necrotic. But the steroid

eye drops reduces that turnover rate so that the transient amplifying cells are not quite as susceptible to that warhead.

So we think that we're preventing some of the microcysts from forming but not all of them. And that's why the symptoms -- although they're still there, they're not as severe as when we give the steroid eye drops.

DR. WEIGEL: You mentioned you give it for two days following it. Do you continue it after --

DR. HOLEN: Yes.

DR. WEIGEL: -- and does that make a difference, and for how long do you need to continue it?

DR. HOLEN: Our current schedule is to start 2 days before the infusion of ABT-414 and continue for a total of 7 days; so 2 days before and 5 days after, that first or the fifth day is the day of the infusion.

DR. REAMAN: Actually, you addressed many of the questions I was going to have about the

toxicity. The ocular toxicity you assume is associated with the midostaurin, not with the antibody, correct? I know it's both because it's bound and is taken up by these corneal cells that are transiently amplified. But is the same kind of toxicity seen with this agent alone?

DR. HOLEN: Yes. We do believe it's the auristatin that is the main component of this toxicity. There is EGFR expression on these transient amplifying cells. However, there are a few other agents, antibody drug conjugates, that use this same toxin, monomethyl auristatin F. Those have almost exactly the same ocular toxicities that we've observed, and those antibodies have absolutely no target to identify on these transient amplifying cells.

Specifically what I'm talking about is a drug that's being developed by Seattle Genetics, and they published on their drug, SGN-75. SGN-75 is another monomethyl auristatin F conjugate, which has the ocular toxicities.

They looked backwards and forwards all

throughout the eye for CD70 expression, and they couldn't find it anywhere in the eye. We really believe this is more of a nonspecific uptake of the antibody drug conjugate, and then the MMAF is what causes this problem.

Now, interestingly, the linker toxin is not cell membrane permeable. The only way it can get into the cell is when it's bound to the antibody and the antibody is internalized.

So just giving the monomethyl auristatin F IV to patients doesn't do anything, not to the tumor, not to the bone marrow, nothing else because it's not cell membrane permeable. There's some degree of cell membrane permeability but not in significant quantities to cause side effects.

DR. REAMAN: Thanks. I have some follow-up questions about the testing. Can you just comment on your FISH test and its availability and correlation between that and what institutions might do with IHC testing for EGFR amplification?

DR. HOLEN: Sure. As I mentioned, we have performed IHC in our studies, and protein

expression did not seem to correlate with response. So that's what led us to the FISH test. We have an open IDE for our FISH assay, so that allows us to use it for screening purposes and enrollment into our studies. It's available worldwide because we're using it for our global studies.

We have samples being shipped to three different sites around the world in order to perform that FISH assay to determine whether or not a patient is amplified or not amplified. And we plan on using this as a companion diagnostic for potential submission along with ABT-414 should we be in it.

DR. REAMAN: Okay. Thanks. So the requirement then would be for this to have a centralized testing?

DR. HOLEN: For the pediatric patients, we don't want pediatric oncologists to use tissue solely for the purposes of understanding whether their patient is EGFR-amplified because it's so rare. Only 3 percent are amplified.

We think a better use of the tissue is to

send it out for next-generation sequencing so that you can get tons of information on that tissue. For that, that's why we set up that SPECTA test, where any pediatric oncologist anywhere in the world can talk to their patient and their families and say, hey, we have this SPECTA test that we can do for free; would you be interested in sending it out?

If so, they can have the next-generation sequencing performed. They can find out lots of information about the tumor. And if by chance the patient happens to be amplified, then they can start the process of thinking about whether the study with 414 might make sense for that patient.

DR. REAMAN: Can you just elaborate again where is the test being done?

DR. HOLEN: The SPECTA test?

DR. REAMAN: The SPECTA, yes.

DR. HOLEN: That's a good question.

DR. REAMAN: Outside the U.S., is that right?

DR. HOLEN: Currently, it's being done

outside the U.S.

DR. REAMAN: And are there problems with the shipment of specimens internationally and then getting results back? How does that work?

DR. HOLEN: Good question.

DR. REAMAN: Is it something that you're requiring for your adult study, and are those logistics worked out? Because I would foresee some potential problems here.

DR. HOLEN: We've worked this out for our adult study, and it hasn't been an issue. I don't think it'll be an issue for the pediatric population.

The only places we're sending specimens across international boundaries that's been a big issue for us is China and Brazil. And currently, those countries aren't participating in this Intellance 2 study where we'd have pediatric patients enrolled.

So I think we'll be okay. But maybe Dr. Ansell, did you want to say a little bit more about the SPECTA perhaps? Pete Ansell here from

our biomarkers group.

DR. ANSELL: Hello. Pete Ansell AbbVie, biomarkers. In terms of the logistics, as Dr. Holen alluded to, we do have three testing labs right across the world for adult studies: one in Australia, one is Belgium, and one in the United States; although we have sites from many different other countries.

They all ship to those respective testing labs. Customs and shipping delays and things like that have been ironed out, so we don't anticipate any issues like that.

In terms of your other questions regarding concordance between our FISH assay and next-generation sequencing, we have done some comparisons there, so we do not expect a high discordant rate.

DR. KIERAN: Mark Kieran, Dana-Farber, a couple of questions. Is the development of the eye toxicity a potential biomarker itself in terms of who responds?

DR. HOLEN: We have looked at that, and

because the eye toxicity is so common, about 80 percent or so of patients have some degree of eye toxicity, we haven't been able to assess that. It is the case that all of our responding patients have had eye toxicity. But I think until we have more numbers and given the high rate of the eye toxicity, it's impossible for us to say right now.

DR. KIERAN: You didn't talk a lot about the blood-brain barrier penetration of the drug, and one would wonder how a big antibody gets across in the first place. The radiographic response, for example, you showed us look like a patient who had a tumor that went all the way out to the meninges and along the surface, so it may not have been as much of a blood-brain barrier issue. I suspect you've got some data that way?

DR. HOLEN: We do, yes. The first thing that we did was we looked at an orthotopic model to see whether or not we would have efficacy in an orthotopic model and look at binding to the tumor in the orthotopic mouse. And those studies showed that there was binding to the tumor as well as a

tumor shrinkage.

But we also have another program where we bind the antibody to indium. We label it with indium, and then we administer the antibody indium-labeled product to patients, and we performed spec scans, similar to bone scans.

In those studies, in patients with brain tumors, we see fairly intense uptake of the antibody with the indium labeling on the scans for patients with glioblastoma and almost every patient with GBM.

Now, I think the bigger question is, is that antibody truly crossing the blood-brain barrier or is it just that the blood-brain barrier is completely broken down because of the brain tumor? That's a question that we really don't know.

We are trying to explore this further by looking into whether or not it might make sense to administer a dose of drug prior to surgery, and then after surgery seeing what the binding properties may look like along the tumor. It's something that we're exploring.

DR. KIERAN: I notice in some of the preclinical stuff, it wasn't clear whether the tumors that you're using are enhancing tumors, which presumably do break down the blood-brain barrier. And obviously much of the problem in malignant glioma isn't so much the large enhancing nodule that the surgeon can often cut out; it's the infiltrative, non-enhancing kind of flared T2 signal that results in death. And the question was, is the drug getting to those places?

DR. HOLEN: We share a similar concern. It may be that we're affecting the enhancing areas. But oftentimes, that's a major component of a patient's tumor. And if you can at least get that to go away, that's one step in the process.

But I think that we might be also getting to some of the non-enhancing areas as well. And the reason why I say that is because if we look at our complete responders, patients who have had complete responses for -- one patient for over a year -- they had enhancing and non-enhancing areas in their MRI. And we believe that those both went

away with a complete response to drugs.

I speculate that maybe we're getting to both areas of the brain tumors, but we have not done formal studies where we, like I mentioned, take tumors out after a dose, and then look at binding across the entirety of the tumor to see how much binding there is across the tumor.

DR. KIERAN: Yes, because it's hard to understand how a big drug gets across a non-enhancing, intact blood-brain barrier.

I just had two other questions. One of them in figure 2 of the proposal -- or the graph, not figure 2, what you showed -- it was interesting that you actually had dramatic responses for the control antibody as well.

DR. HOLEN: That's true, and I can bring that up for people that don't have it handy. I think this is from the briefing book.

Yes, what we've noticed is that when you take the -- some of these models have some nonspecific uptake of just routine antibodies without targeting. That was the case for this

model. This is a U-87 model. U-87 models will internalize EGFR quite rapidly, but they'll also internalize other antibodies that aren't targeted necessarily to a receptor on the surface of the cell.

That's why we saw some degree of efficacy, and you can see that in the open circles with the red dash marks. You can see some degree of efficacy even with the control antibody. However, that was a pretty hefty dose of 10 mg per kg.

DR. KIERAN: The half-life of the drug you reported was, I think, about 8 days. I know you're going to redo the PKs and stuff in pediatrics because there is some evidence that they may have a slightly higher turnover rate of proteins, particularly in some of the younger age groups, at least based on some of the other antibody studies. But it will raise some questions about exactly whether the dose per kilo may be the same, but the duration of the timing of therapy may change as you do some of those studies just based on the fact that you've already got half-life.

There was no indication of whether you get accumulation of the drug?

DR. HOLEN: There is some accumulation of the drug. Because of the long half-life and because we're dosing every two weeks, that there is some drug accumulation. And we expect to see this also in children hopefully. As you mentioned, I think it'll be critically important to assess all the PK parameters in children, and then on an ongoing basis reassess are we at the right dose based on PK.

We're doing this based on modeling experiments, and sometimes you don't know if the model is going to accurately predict what your exposures are going to be in children. We'll be doing real-time PK in these patients who are enrolled so that we can better understand the PK parameters that are specific to the pediatric population.

DR. ANGIOLILLO: Anne Angiolillo. Thank you for your very fine presentation. I had four areas of thoughts. One you just addressed was the PK,

the clearance, because I imagine it would be different in pediatrics than adults. So you've already addressed the first concern.

Second, you mentioned this EGFR amplification is very, very rare in this tumor type in pediatrics. I was wondering if the team was looking at a whole panel or host of pediatric cancers, if you could comment, maybe you can't.

Next, I was wondering if you can comment on the convulsion rate. Next, I had concerns about vision. I think a journey for pediatric patients is different than adults with cancer, and then informing that child there will be a period where their vision is altered might make this extra scary.

Lastly, you mentioned this would be nested study. You didn't specifically say it had to be done where the adult study is open. But is that mandatory? Because I could also see issues having the pediatric patient cared for by an adult provider. They're very different. Thank you.

DR. HOLEN: Let me make sure I answer all

those. The first question, I think, was about other pediatric tumors. We've looked across a variety of different pediatric tumors, and EGFR amplification is rare in all pediatric tumors.

For this assessment, we thought it would be good to start to focus in on the pediatric high-grade gliomas and see what we can find out. But there's no reason why we couldn't study other pediatric tumors if we find that maybe there is other tumors with some degree of EGFR amplification.

The second question was about convulsions. I do have a slide here about the common adverse events. We were concerned about some of these adverse events -- headache, hemiparesis, aphasia, convulsions -- and what we did was we looked at these side effects compared to our solid tumor study, where patients did not have brain tumors, to see whether or not this was unique to our brain tumor studies or whether we'd see this across both studies.

As you can see here on this slide, in our

solid tumor studies where patients did not have brain tumors, we did not see the same degree of headache, or fatigue, or seizures, insomnia. Those all seem to be pretty unique to the patients with brain tumors.

In fact, we've talked to our investigators who are participating in the study, and I've asked them, are these rates unusual, or is this something you'd expect in the population? And they said, yes, this is something that you just see in patients who've had surgery and growing brain tumors.

The next question, I think, you had was about the vision. We're concerned as well about the vision and the visual impacts in children. I think that's a call that needs to be made not by us in industry; by the parents and the children and the investigators who are seeing these kids with brain tumors and decide.

This is a risk-benefit ratio. If these kids have visual problems, but they also have growing brain tumors, what choice do we make? I think

that's a difficult choice that maybe we as a sponsor aren't at liberty to make. I think that decision has to rest in the arms of the parents and the children. They need to take that risk and assess the risk-benefit and what makes sense for them. That's how we feel about that.

Lastly, nested study in adults. The Intellance 2 study is open at most of our sites. We have 85 sites globally. We've enrolled some patients. We have about 30 patients in that study already, and we hope to have the study complete by the end of next year, maybe mid-2017.

What we've done is we've set up a completely separate database for the children. We had to do that because they had to be outside of the randomization process because we didn't want them randomized to a control if there's only a few patients.

So we set up this separate database mainly because we didn't want them randomized. But it turns out that that's a good thing for us because we can close the adult database, and analyze the

data, and understand how it works in adults, but keep the pediatric database open as long as we need to, to make sure we have that assessment of PK and safety in children.

The two databases end up being a good thing, not only to prevent the randomization but to allow us to keep the study open as long as we need to.

I think that was your question, right?

DR. ANGIOLILLO: Part of it. It was also, these pediatric patients, are they cared for, the adults with the experience, or do you envision it's in the hands of a pediatric oncologist who doesn't have any experience with this?

DR. HOLEN: Yes, I can't see the adult neuro-oncologist treating the children. What we've asked our investigators that have the adult study open is to talk to their colleagues in pediatric oncology and ask them if they'd be willing to be sub-investigators so that they can participate fully in the study and enroll their patients as investigators into the study. I think that's what will work out best.

We also hope -- although we've been told that some centers wouldn't be interested in this -- but we'd hope that major oncology centers like St. Jude's or NCI would be interested in maybe opening up the study just at their institution even though they wouldn't see adult patients. That way we'd be able to capture not only the sites that have the adult study open but a few other sites that may have a really high volume of cases.

So if anyone is interested here, let us know. We're looking for sites.

DR. KIM: A couple of few questions on the -- I'm sorry, AeRang Kim from Children's National in DC -- on the screening test for EGFR. For the sequencing platform, can you comment briefly a little bit on the turnaround time of the results that you've seen in the adult population?

Also, you commented that the information on other sequencing will also be provided for the children. Would this be a separate consent form process or would they have to enroll in the trial in order to receive this information?

DR. HOLEN: The turnaround time for the FISH assay is pretty quick, about 5 to 7 business days. We believe the turnaround time for the SPECTA assay is about two weeks.

In terms of consent, we had envisioned -- and I'd like to get comments from the advisors if possible. But we envisioned that any oncologist, pediatric oncologist anywhere, could talk to their patients about doing some next-generation sequencing on their tumor. And we would offer this as a free service where you could get the next-generation sequencing done.

Therefore, the consent process would be between the pediatric oncologist and the patient and the patient's family about trying to learn more about their tumor and do the next-generation sequencing.

They wouldn't necessarily have to have the study open to send out tissue for next-generation sequencing. They could just do that as part of standard of care. Oftentimes, a lot of oncologists, pediatric oncologists, medical

oncologists, a lot of hospitals are just doing next-gen sequencing on their tumors at baseline.

So we're offering this more as a service, where if you aren't doing routine next-generation sequencing in all your tumors, that you'd have a place to send it. But you wouldn't necessarily have to consent for an ABT-414 study to enable tissue to be sent for next-generation sequencing.

Then the information would come back to the pediatric oncologist, and then she would look at the data, and then she would see whether or not the patient is amplified. And that's when the process of consenting for the ABT-414 study would occur.

DR. KIM: This would be done at no cost to the center?

DR. HOLEN: At no cost. We have a relationship with the people who are creating the assay called 14MG, where we would have a contract with them to pay for any samples that are sent to them. They bill us for that. But the results would not come to us, and that's why we wouldn't necessarily have to have an AbbVie consent. The

results would remain between the testing center and the pediatric oncologist.

DR. REAMAN: A couple more logistical questions. The eligibility criteria, patients over the age of 6 are reason for why children under the age of 6 are excluded. The DIPG patients, would they have to have been biopsied or resected and proven to have high-grade glioma and EGFR amplification?

DR. HOLEN: We have considered that population, zero to 6. As we talked about a little bit before, we're concerned about the safety in that population because of the developing cornea, because of what ABT-414 might be doing to a developing cornea. We just don't have that information. We thought that the population between 6 and 18 would be the best place to start.

The other question you had was about DIPGs. DIPGs, we still believe that EGFR amplification is necessary for benefit. There's no way, at this point, that we can determine EGFR amplification without some tissue. Although it's not common

practice in DIPGs, we thought we'd allow them enrollment in the study just in case there is tissue available and they're able to assess whether or not the patient is EGFR-amplified.

DR. REAMAN: I think it is probably a little bit more common practice now than it used to be, but I just want to make sure that it would just be the EGFR-amplified tumor, that those patients would be eligible for enrollment.

DR. HOLEN: Yes, only the EGFR-amplified patients.

DR. REAMAN: Then going back to the sort of logistical issue about opening the study at multiple sites, I think the concern was that your initial plan was to open the embedded pediatric study primarily at those sites where you have the study open for adult enrollment.

Many institutions have separate pediatric oncology and medical oncology programs. They're at separate institutions, a free-standing children's hospital that may be academically affiliated with a university medical center.

Is your concern about opening this at multiple places because of IRB issues? I'm sure you want to do this as easily as possible, but I think you really have to look at -- particularly given the low incidence of the EGFR amplification in these tumors -- to really spreading as wide a net as possible to enroll patients.

DR. HOLEN: Yes. We have looked into all these logistics, and we'd be happy to open the study at specialized pediatric oncology centers. But we have talked with two cooperative groups, the PBTC here in the U.S., as well as the ITCC in the EU. And what they've told us is many centers may not want to participate in this study because odds are that they would screen 20 patients and never identify a single patient who would be able to participate in the study.

There's a lot of work to open up a study, to go through the scientific review process, to go through the IRB process, to get your budgets and get your contracts all in place. And then to maintain the study open, you have to process all

the adverse events. I mean, you guys better than I know what it's like.

They said there probably wouldn't be much interest in opening a stand-alone study given the rarity of the disease, and that's what led us to this nested study. Now, if there is interest, as I mentioned, we're happy to get them engaged.

In our discussions with the PBTC and the ITCC, they told us that this has been done before through the EORTC. They've worked with the EORTC, and they've been able to coordinate the communication between the pediatric oncologist and the adult oncologist such that they could collaborate jointly on these efforts.

What they did before wasn't exactly a nested study. What they did is they just lowered the age limit of the study, but it required collaboration between the pediatric and the adult oncologist. So I think at some centers, it would work. But other centers, there just may not be that coordination between the pediatric group and the adult group to be able to make that happen.

One of the steps that we put in place is we've sent a list of all our open studies, our open sites, to the ITCC. And they're taking our list of where it's open and their list of their highest participating centers and trying to figure out if there's overlap between the two. And where there isn't overlap, they're going to get back to us and make some recommendations about sites.

The same is going to be true in the U.S. We've talked to the PBTC, and we're planning on sending them a list of where the study is open in the U.S. and see if they can give us some recommendations about who to approach.

DR. PAPPO: I would like to ask Dr. Leigh Marcus to introduce herself for the record. She just joined us.

DR. MARCUS: Hi. This is Leigh Marcus, one of the FDA medical officers. Thanks.

DR. PAPPO: We only have time for three more questions. It's going to be Ms. Haylock, Dr. Armstrong, and Dr. DuBois, and then we're going to move to the next part of the meeting. So

Dr. Haylock?

MS. HAYLOCK: I have some very specific logistical questions with regard to patient care and the expectations of family while the child is participating in the study.

First of all, I don't see how long -- I mean, do patients stay on this for the remainder of their lives until there's progression or what's that plan? But I mostly am interested in any kind of supportive care that happens between doses. Are there other medications or other supportive care measures that should be put in place along with the trial process itself?

DR. HOLEN: Yes. We envision treating children similar to how the adults are treated. They would stay on treatment for as long as the patient may be benefiting. If there aren't severe toxicities and it seems like the tumor is under control, then they can stay on treatment until the point when either the patient, or the family, or the investigator decides that it's no longer a benefit. And hopefully, that would be a long time

that they'd stay on treatment.

In terms of the supportive care, I agree with you. And this is not something that we've spent enough time on, but I think we need to develop educational and support materials specifically for families who might not be able -- the adult materials may not be so relevant.

So information about how to administer the eye drops in children, things like that, because oftentimes, it will be the parents that will be administering these eye drops in the younger population. I think that's very relevant and something that we should do, certainly.

Just to mention, we have a couple of ophthalmologists that we talk to. In fact, one pediatric ophthalmologist, I think they may be of help in creating those education materials.

MS. HAYLOCK: In terms of all these other possible symptoms, there's really no prophylactic measures used throughout the treatment process?

DR. HOLEN: The only thing that we do that has prophylactic measures is the steroid eye drops.

We had not recommended routine antiemetics because nausea, although it's reported in our studies, it hasn't been a significant problem. It's mainly been grade 1. And oftentimes, it's hard to tease out if that's from the disease or that's from the drug. It really won't be until we do the randomized studies against control where we can start understanding that a little bit better.

MS. HAYLOCK: Thank you.

DR. HOLEN: You're welcome.

DR. ARMSTRONG: Deb Armstrong. A couple of my questions have been answered. I'd just like to clarify, on slide 32, you indicate that central or local testing of EGFR, patients would be eligible. So if there's local testing of EGFR, that would be sufficient?

DR. HOLEN: Yes.

DR. ARMSTRONG: Okay. They wouldn't have to have the SPECTA testing eligibility?

DR. HOLEN: Correct.

DR. ARMSTRONG: Okay. I would encourage having major centers such as you mentioned, the NIH

and St. Jude, that might be able to access patients from around the country for this.

Two questions. You had zero responses in 15 patients in the adult population who were negative. Do you think there's any reason to consider having a cohort of negative patients in the pediatric population in case there are some responses? Negative doesn't mean zero; it just means not amplified so the potential for a response in that group of patients.

DR. HOLEN: Yes, we haven't considered that at this point, and it may be something that we would want to consider in the adults, too. But we've looked fairly extensively at some other biomarker that might be related to response.

The mRNA expression of EGFR and V-3 and IHC, they just haven't been reliable measures. We've had some patients who are amplified but have lower EGFR IHC, and those responded. And then patients who are not amplified with really high levels of EGFR expression did not respond at all.

It really doesn't seem like the protein

expression or the mRNA expression is a reliable way to segregate patients. And because of that, I don't think that the non-amplified patients really make sense for this drug.

DR. ARMSTRONG: Finally, I guess would sort of support one of Dr. Kieran's initial statements, which is about allowing the concomitant use of temozolomide.

Potentially, this might be an easier study for you with easier accrual if you had a little more lax eligibility criteria potentially allowing -- I think for the adult population, you allow one prior chemotherapy, but maybe allowing two prior chemotherapies and making it just an ABT-414 arm, which would probably simplify things. People might feel they wanted to give another course of temozolomide; or I don't know if they use bevacizumab in pediatrics like they do in adults, but, you know, some other treatment, and maybe have a more stringent performance status criteria because the patients might be more heavily treated.

But to make it a little bit cleaner study, I think, to me, would be -- and particularly since you're going to have a very small number of these patients, if you have a little more liberal pretreatment criteria but a higher performance status criteria, you might capture more patients.

Particularly when you start the study, there's going to be some people who might have the amplification but don't meet your more stringent eligibility criteria. And I just think it would be a cleaner study. You clearly had responses in the adult population and in patients with the drug alone.

DR. HOLEN: Yes. I agree with you. We want to be as flexible and open as possible with our eligibility criteria because of the rarity of this diagnosis, with EGFR amplification. We don't want to lose patients just because they happen to have only one prior therapy or three prior or more.

We've eliminated any mention of prior therapies from our eligibility. We've, in fact, even eliminated performance status. Yes, we may

get more variety in terms of the population that's under study, but I think we can adequately assess 414 toxicities, particularly because the toxicity is so unique, that ocular toxicity was our only dose-limiting toxicity that we observed.

There are many other chemotherapies that will give you that specific ocular toxicity. So I think that we'll be able to tease out what effects 414 is having on the eyes regardless of what the performance status may be or how many prior therapies they might've had.

DR. ARMSTRONG: I guess I just sort of would advocate for the cleaner study with the drug alone as opposed to allowing the addition of temozolomide if somebody is treating -- a physician really wants to give them temozolomide, they can give it to them and then put them on the study after that. I just think that that seems to be a cleaner study.

DR. HOLEN: That's a balance that we've grappled with a bit. If an investigator really wants to use temozolomide, would we lose the patient from entering the study because they gave

the patient temozolomide first, and then at the time they progressed on temozolomide, may not be able to participate in the study.

I think we'll have to speak more with experts like the people in this room to understand, okay, is temozolomide important? If it's not important, then I'm happy to get rid of it. But if it is important -- and I'm seeing some heads saying, no, it's not important.

If it's not important, we get rid of it. If it is important, then we'll keep it in as an option.

DR. PAPPO: We're going to discuss this a little bit further in the questions. Last question, Steve?

DR. DuBOIS: Following your ASCO presentation earlier this year, have you had requests for compassionate access from the pediatric population, and might that be a gauge of the potential pool of patients for a formal trial?

DR. HOLEN: Yes, we had one request from a 17-year-old who wasn't eligible for the study

because our age limit is 18. There was a request, and we approved the request, but the investigator -- and I'm not exactly sure why -- decided not to follow through. So he never received a dose of 414.

DR. PAPPO: Thank you very much, and thank you for the very lively discussion.

DR. HOLEN: Thank you.

DR. PAPPO: We do not have any registrants for the open public hearing portion of the session, so we will proceed directly to the questions to the committee.

Questions to Subcommittee and Discussion

We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. Dr. Lori Ehrlich will start reading the first question.

DR. EHRLICH: Thank you. Please consider whether ABT-414 is a viable drug candidate for

study in the pediatric population. Comment on the feasibility of a trial of ABT-414 in pediatric patients with high-grade glioma given both the rarity of the disease and the low frequency of pediatric HGG with EGFR.

DR. PAPPO: Let's start the discussion.

DR. KIERAN: Mark Kieran. Yes.

DR. PAPPO: I'm sorry. If there are no questions or comments concerning the wording or the question, we will now proceed to the discussion. Sorry about that.

DR. ARMSTRONG: I guess I would ask the people here who treat these kids what you feel about having the ABT-414 alone or adding in the temozolomide, what people's thoughts are about that, particularly since they have a very liberal eligibility criteria, which actually it sounds like it's just EGFR mutation; it's not a PS or a prior therapy limitation.

DR. KIERAN: Mark Kieran. I think on this side of the table, we probably agree that this is not really going to be much of an issue.

Virtually, all the kids get temozolomide up front. We're not even clear that it's really got a lot of activity. Pediatric high-grade gliomas have a much higher incidence of MGMT expression, which makes them resistant.

So if they haven't gotten it first -- so we don't put patients on temozolomide if they're expressing the resistance enzyme. Many of the patients will be temozolomide naïve, but they still wouldn't be appropriate candidates for the drug. And for centers that are not testing, it's almost always used in first line, which means any patient eligible for this study would already have it, so I don't think it's going to be as much of an issue.

DR. WEIGEL: Brenda Weigel. I agree completely with Mark. I think that temozolomide, in my mind, is sort of a non-issue and clouds both the interpretation of the study, both from a PK point of view as well as from an efficacy point of view.

I think these patients, most will have seen the drug; most will have progressed through it. I

think it would not inhibit enrollment because I think most pediatric oncologists would be very comfortable not giving it if their patient had progressed.

So I actually don't think it would be an issue, and I actually think the study would be stronger without it.

DR. PAPPO: We're already sort of answering question number 2. But if I'm hearing this correctly from the two experts, you do not believe that combining ABT-414 with temozolomide in this phase 1 study would be a reasonable or good idea, that we should just test the antibody alone; is that correct?

DR. WEIGEL: I would be in favor of just looking at the antibody alone, antibody conjugate alone.

DR. KIERAN: Yes. Mike Kieran. I agree. It complicates things unnecessarily. I think it would restrict on almost no entry into the trial, so you won't lose any patients because of it. Again, if you want to accredit in response to your

drug, then I think your drug ought to be the one that sits first and foremost.

Even the data you showed was kind of underwhelming for the addition of temozolomide, making -- I mean, if that curve had looked significantly better in Arm 2, that might have changed my mind. But certainly, based on what we saw, I would recommend a just single-treatment cohort.

DR. PAPPO: Greg?

DR. REAMAN: And I think that's amplified by the fact that there are multiple published observations of the lack of efficacy or activity of temozolomide in children with high-grade glioma.

DR. PAPPO: What about going back to the original question, whether to consider this drug as a viable candidate for development in pediatric patients with recurring high-grade gliomas? Any comments, suggestions?

DR. DuBOIS: I may support the comment of one of the other panelists. I can't remember who suggested evaluating other published data or

perhaps unpublished data from commercial entities who are doing next-generation sequencing in pediatric and adult tumors to see if there might be other relevant pediatric tumors for this agent, in which case the dose confirmation in PK evaluation perhaps could include a slightly wider net of patients in addition to those very rare patients with high-grade glioma and an EGFR amplification.

DR. PAPPO: Any other comments?

DR. KIERAN: Mark Kieran. To answer this specific question, I think really they've done a wonderful job of coming up with what is a methodology that would actually allow patients that will otherwise just be ignored. The one thing that we try to remind people on the clinical side is a child dying of a malignant glioma is just as dead as an adult. And the idea that they wouldn't get this opportunity -- and I think as all of us in this room begin to struggle with how to analyze rare diseases or sub-populations of rare diseases, which obviously all of pediatrics are, I think what you've put together here, in many ways, is

encouraging because it figures out a way to do something that I think otherwise really wouldn't be doable.

The number of the studies, we, the members, run that don't actually end up accruing because they're too rare and people haven't figured out a way to do them, I think I would certainly support the rarity of the disease, the approach that's been proposed.

DR. PAPPO: Greg?

DR. REAMAN: We would just want to echo that. And part of the reason -- or the major reason that AbbVie is here is because of this proposal. I would also commend the sponsor for doing exactly as they have done. We would love to see this paradigm repeated in other rare pediatric tumors. So I think our aim here is to facilitate the development of potentially relevant agents, and I think this is a great way to actually accomplish that.

DR. PAPPO: Any comments from the panel members on how to perhaps increase accrual, the

study design, where the studies are being conducted? Any suggestions?

DR. REAMAN: There are subsequent questions.

DR. PAPPO: Well, I was getting there. I was so excited.

(Laughter.)

DR. REAMAN: You're jumping ahead.

DR. PAPPO: Sorry. Any other comments about question number 1?

(No response.)

DR. PAPPO: I would like to summarize this. The first point was that preliminarily, although this was part of question number 2, there's not an overwhelming enthusiasm about adding temozolomide to this phase 1 pediatric study.

Number 2, we would suggest that the company also evaluates other published data on next-generation sequencing to determine where there are other potential avenues for this antibody in EGFR expressing pediatric tumors.

The third one is that we are very supportive of your novel idea of doing a nested study using

this antibody in a pediatric population with a very rare and devastating pediatric cancer, which is high-grade glioma. Based on what we've discussed today, we're highly supportive of your initiative.

Does anybody agree with the comments?

DR. ARMSTRONG: I would agree. I would just also add to the last one that sites that potentially don't have the adult population but would have the pediatric population be allowed to open the study. So although it's still a nested study, they would only be doing the pediatric arm.

I just will say, at our institution, some diseases, for example, germ cell tumors, we have adult trials that pediatric oncologists participate in and their patients. That's not outside the realm of doable or reasonable or even historically done. That can be done.

So I think it's sites where there's both pediatric and adult brain tumor treatments, this is not hard to do. You just add on some investigators from the pediatrics arm.

DR. PAPPO: Thank you. I guess we can

proceed to the next question.

DR. EHRLICH: I think we've already discussed this in part --

DR. PAPPO: Just a reminder to please say your names when you are having discussion.

DR. EHRLICH: I can read this question and perhaps we can move on. Question 2 is, please address the plans for administering ABT-414 in combination with temozolomide.

DR. PAPPO: Any discussion? We sort of addressed this but we can re-address it. Anybody wants to be the spokesman for this?

DR. KIERAN: I've changed my -- no.

(Laughter.)

DR. PAPPO: I think based at least on the discussions, not only on our direct discussions with AbbVie Pharmaceuticals but also on our first question, that we are not particularly supportive of adding temozolomide to the antibody, at least in the phase 1 portion of the trial. If anybody disagrees or anybody has additional comments, we'll be more than happy to hear that.

DR. KIERAN: Can I just -- this isn't really a phase 1 trial, right? This is really like a little pilot phase 2, I guess. Just to clarify that -- because there is no dose escalation here. Everybody gets the same dose.

DR. PAPPO: They sort of were as a phase -- but it's okay.

DR. REAMAN: 1B.

DR. PAPPO: 1B. Okay. We will now proceed to the next question.

DR. EHRLICH: Please comment on the proposal for a pediatric trial embedded in the adult trial and other components of the study design, including expected number of pediatric patients, age range and dose escalation. Consider the need for and/or the extent of a statistical analysis plan for evaluation of the response and pharmacokinetic endpoints.

DR. PAPPO: This is open for discussion. Brenda?

DR. WEIGEL: I have a couple comments. I think as we stated, I'm very supportive of the

nested design. I think that's really unique, and I applaud AbbVie for that. I think that's terrific.

A couple suggestions, and I think Mark Kieran alluded to this and others. With regards to the dose, I think we have enough experience with antibodies now in children to know that the clearance of antibodies, particularly in the younger children and smaller children, tends to be more robust than adults. The risk here is underdosing the children not overdosing the children. I think it's the balance between toxicity and efficacy.

I think the real key here is to have -- and you alluded to real time PK to assess are we underdosing particularly the smallest children? And your modeling suggests, and most of the studies done thus far with antibodies in adolescents suggest, that we're going to have the same as in adults.

So I don't know that you need to spend a lot of time doing a lot of work. I would encourage the consideration within the design to saying you want

to enroll potentially six patients in the 6 to 12 ballpark. And I'll get to the second part of my comment in a second. You run the risk of having all six of your patients be 16, 17, 15, and not answering the pediatric question unless you build that into the study.

So I would very strongly consider having a requirement for a younger-age PK so that we can get the toxicity and the PK data in the younger-age population.

That brings me to the less-than-6 comment. I think Dr. Reaman alluded to this, is that I think we have very little data that you've presented with regards to specific toxicity concerns in the younger patient population. I think the same argument holds that if you have a patient with an EGFR-altered tumor in that age group, it may behoove us to take that opportunity to enroll that patient on to a study.

So I would say we would need to really consider what is the hard evidence of the toxicity in that younger-age group, how are we going to

monitor that, and do we want to consider the opportunity, even though that patient will be very rare, to learn both from a toxicity point of view and an efficacy point of view. From a design perspective, those are my main comments, I think, with regards to age and dose.

DR. PAPPO: Let me briefly summarize your comment. If I understand this correctly, there is some evidence to suggest that the clearance of the antibody, actually, we might be underdosing some of the younger patients and that we suggest that there would be a requirement to enroll at least 6 patients in the 6 to 12-year age group to better define the PK of this antibody.

The other suggestion also is in the event that there is a younger patient, less than 6 years of age, with an EGFR-mutated or amplified high-grade glioma, to give consideration to enrolling those patients in the trial.

Does that reflect pretty much?

DR. WEIGEL: Yes. And I think very carefully consider what the age restriction should

be on this trial and consider pushing that limit down.

DR. PAPPO: Okay. Any other comments? Susan?

MS. WEINER: My comment has to do with the follow-up of patients -- I'm Susan Weiner -- the follow-up of patients who seem to respond -- where the evidence is clear that they're responding well to 414.

The fact that you're keeping the patients on drug for as long as they're responding hopefully is terrific, but I guess I would also want there to be some documentation of their functioning in the follow-up.

DR. ARMSTRONG: Deb Armstrong. It would seem to me that the antibody issue here is going to be one of how much the tumor takes up the antibody drug conjugate, so sort of the density of the binding sites and maybe the avidity of the binding sites.

We've talked about the fact that the metabolism and the clearance might be different in

these younger folks. But is the blood-brain barrier different? I know it's broken down into patients who have these tumors, but is there a difference in the blood-brain barrier between pediatric and adult?

DR. KIERAN: Mark Kieran. Actually, it's not crystal clear because we talk about the blood-brain barrier as if it is a single thing. In fact, the blood-brain barrier differs between different parts of the brain even in an otherwise healthy person, which means drug that easily gets into one area wouldn't get into another one anyway.

Unfortunately, I think the reality for blood-brain barrier right now is that if you have a drug that crosses, you want to test it because it crosses. If it doesn't cross, you argue the barrier is broken down, so it doesn't matter. I think we both -- every grant kind of plays both sides of that field simultaneously.

We had some questions today about the exact mechanism by which it penetrates and whether it penetrates all parts of the tumor, the enhancing

and the non-enhancing parts. I don't think we fully understand.

I agree that the target validation or phase zero component, that could certainly be done in the adults and is, in fact, now even being done in pediatrics, would be a great way to answer some of those questions.

DR. PAPPO: Are there any additional studies that should be considered to better define the PK of this product in pediatrics, some pharmacodynamic or imaging things that are not being considered for the clinical trial?

DR. KIERAN: Mark Kieran. Again, I think the patient population we're talking about is so rare and so spread out that to try and do an imaging component will certainly be part of it because you'll be looking at response anyway.

You've referred to the RANO criteria, and I will remind people in the room that in pediatrics, there is RAPNO. They're radiologic assessment in pediatric neuro-oncology, which for things like DIBG will be different than RANO. But for

malignant gliomas, it's going to be the same, which is why I was okay with the wording.

It's a very kind of complicated analysis. Again, I don't want us to get so bogged down in trying to put so many things in for what is going to be a minuscule number of patients that somehow we don't get all of this stuff done. It would be great if you could do some of those things, but I wouldn't make them a requirement.

I think the real question here is -- I think they're going to be real questions about the PK. And one of the things I think you're going to need in your study is this may not just be a standard dosing in pediatrics. You may need a dose escalation component in pediatrics, either dose escalation in terms of an increase in the actual dose, a loading dose, and/or a contraction of the time period like q10-day or 7-day administration, not q14.

I noticed in your data, you actually had 3-week dosing, 2-week dosing, and 2 milligrams and 1.25 and 1 milligram per kilo. So you've clearly

already done some of those in the adults, and I think those are going to be the big issues in pediatrics.

DR. DuBOIS: Steve DuBois. I'll just pick up on a couple of things that Dr. Weigel raised, one related to the age criteria. I agree completely that re-evaluating an age cut point perhaps below age 6 would be important. At the same time, I would encourage the sponsor to think about the key toxicity of this agent and thinking about an age at which a pediatric patient could reliably report that they're experiencing blurry vision or eye pain I think would be important. Certainly, somewhere below 6, I think would be reasonable, but not all the way to zero.

I'll also echo Dr. Weigel's thoughts about the dose. In particular on one of the background slides, the recommended adult phase 2 dose was anywhere from 1.25 to 2 milligrams per kilogram. So a flat dose of a milligram per kilogram I think would certainly have a risk of underdosing given what we know about antibody clearance in

pediatrics.

Finally, a point just about site selection, I would encourage the sponsor to think about institutions that, as a routine standard, provide next-generation sequencing to all of their pediatric patients as potential centers to consider given that they will already be potentially screening their patients as a matter of course.

DR. PAPPO: Any other questions? Greg?

DR. REAMAN: Just to clarify Ms. Weiner's comment about functioning, you're talking about visual functioning? I just want to be sure that --

MS. WEINER: (Nods in affirmative)

DR. REAMAN: Okay.

MS. WEINER: This is Susan Weiner. I'm not recommending a neuropsychological function.

DR. PAPPO: Okay. To summarize the second part of the discussion, because patients are going to be exposed to this antibody for a prolonged period of time if they respond, we suggest that the company includes functional observation of these

patients, particularly the ocular toxicity.

There were some discussions about the blood-brain barrier in younger patients and also to consider a dose escalation component, or either a dose compression component on this part of the study, given the fact that some of these patients might have increased clearance of the antibody.

The other question that was brought up again was to consider again the population of patients less than 6 years of age and also take into consideration the ability to self-report any ocular toxicities by younger populations.

The final comment was about site selection and to include sites that also routinely perform next-gen sequencing on some of their patients and tumors.

Any other clarifications or anything I did not include, or anything that I misquoted?

(No response.)

DR. PAPPO: We will go to the next question then.

DR. EHRLICH: Given the incidence of HGG in

children, please discuss how accrual to the pediatric sub-study might be increased and accelerated by opening this amended protocol in a broader group of institutions or clinical trial networks.

DR. PAPPO: It's open for discussion. Steve?

DR. DuBOIS: Perhaps I should have held my last comment for this.

(Laughter.)

DR. DuBOIS: I'll just say that that would be my suggestion.

DR. REAMAN: I would just suggest that even though you've gotten some -- "pushback" probably isn't a correct word -- from the PBTC and the ITCC, as a former cooperative group chair, I can tell you that most institutions don't open every protocol that a group is sponsoring or conducting.

But I think even though this is a rare disease, and a very, very rare disease, it's a disease that's associated with a tremendous unmet need. I think there may be more interest in this

than the usual protocols where we're concerned about not seeing a patient. I would continue to explore -- suggest you continue to explore every possibility of expanding the pediatric centers who might be interested in enrolling patients.

DR. PAPPO: Brenda?

DR. WEIGEL: This is Brenda Weigel. To echo what Dr. Reaman said, I think I would support sort of that double-pronged approach to optimize your centers. Talking to the cooperative groups, national and international, the difference is being that's a single contract with multiple sites, and then you can also add additional sites depending which groups you talk to.

You could really leverage almost every pediatric institution. And in a rare study, tumor study like this, I think it would be really important to continue to explore all those avenues.

DR. PAPPO: If I understood this correctly, I think that we recommend that you continue to explore other potential avenues for expanding enrollment into this study, whether it's through

the PBTC or other potential avenues, and also to consider one contract with multiple sites in order to leverage your ability to increase numbers of patients.

Any other suggestions? Mark?

DR. KIERAN: I think I would specifically include that because there are multiple groups around the country now, referral sites that basically already provide the molecular sequencing for all of the patients.

That's a way in which it would speed things up since time will be an essence for patients with malignant gliomas that have relapsed. They often can't wait very long for you send stuff off, get all of the stuff done, get the answer. I would kind of make sure that the wording that Steve had mentioned regarding -- particularly thinking about centers that are already doing this on a routine basis because the timing here is going to be critical.

DR. PAPPO: That's something that Steve had mentioned. Yes?

MS. WEINER: This is Susan Weiner. I would like to echo what Dr. Armstrong said earlier, which is concentration or a filter for institutions that have adult pediatric trials already started, a history of that in their own institutions is probably a good bet.

DR. PAPPO: Any other additional comments?

(No response.)

DR. PAPPO: We will proceed to the last question.

DR. EHRLICH: Please comment on any concerns relating to the use of ABT-414 in pediatric patients. Specifically, address any considerations for monitoring and/or preventing the known ocular toxicity.

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

Dr. Armstrong?

DR. ARMSTRONG: I think this is a particular concern for these kids, school issues and things like that. I suspect that many of these kids don't

meet their developmental milestones because of their disease and their treatment and having to be -- et cetera. But I think especially, for the kids that are on this for a longer period of time, looking at those in terms of toxicities and whether or not there are developmental delays or developmental milestones that aren't being met would be particularly of concern.

The ocular toxicity, I think, obviously in this school-age child is a big concern in making sure that these kids are hooked up with vision specialists. Maybe some of these kids may transiently need eyeglasses to help read and other things that adults could kind of deal with, but kids may not be able to deal with quite so well.

DR. ANGIOLILLO: Anne Angiolillo. Yes, I want to second that recommendation. I think official ophthalmology exams by an ophthalmologist would be very prudent since we're in unchartered territory and so much of our exam is subjective when it comes to neuro and ocular and talking to children, how is your vision. So I think a formal

session should be a required observation, just a recommendation. Thank you.

DR. PAPPO: Any other comments?

DR. RAETZ: I would just agree -- Elizabeth Raetz. Probably baseline, knowing the status, you don't want to make this any more cumbersome for entry, but I think it would be important probably to know their baseline status prior to receiving the agent as well.

DR. PAPPO: So the panel appears to have appropriate concern about the ocular toxicity of this product, and we would recommend that this is studied very, very carefully in the study and that also patients are routinely seen by a specialist, hopefully an ophthalmologist, and they have a baseline exam and routine follow-up to better define the toxicities of that antibody in this pediatric population.

Anything else?

(No response.)

Adjournment

DR. PAPPO: Well, we will now take a

15-minute break. Maybe a little bit longer, right? A little bit longer, until 10:50, so about 40 minutes or so.

Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any members of the audience, and we will resume at 10:50. Thank you.

(Whereupon, at 10:12 a.m., Session 1 of the meeting was adjourned.)