FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUTAION AND RESEARCH

PEDIATRIC SUBCOMMITTEE OF THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

Topic 1

Wednesday, June 21, 2017

7:58 a.m. to 9:41 a.m.

FDA White Oak Campus

The Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Lauren Tesh, PharmD, BCPS

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Alberto S. Pappo, MD

(Chairperson, pedsODAC)

Member and Head, Division of Solid Malignancies

St Jude Children's Research Hospital

Professor of Pediatrics

University of Tennessee Health Science Center

Memphis, Tennessee

Courtney J. Preusse, MA

(Consumer Representative)

Senior Research Administrator and CLIA Operations Director

Fred Hutchinson Cancer Research Center

Seattle, Washington

Bruce J. Roth, MD

Department of Internal Medicine

Division of Medical Oncology

St. Louis, Missouri

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS

(Non-Voting)

Phuong Khanh (P.K.) Morrow, MD, FACP

(Industry Representative)

Executive Medical Director, Amgen Oncology

Therapeutic Area Head, US Medical Organization

One Amgen Center Drive

Thousand Oaks, California

TEMPORARY MEMBERS (Voting)

Carola A. S. Arndt, MD

Professor of Pediatrics and Consultant

Division of Pediatric Hematology/Oncology

Department of Pediatric and Adolescent Medicine

Mayo Clinic College of Medicine and Science

Rochester, Minnesota

Steven G. DuBois, MD

(Participation in Day 1)

Director, Experimental Therapeutics

Dana-Farber/Boston Children's Hospital

Associate Professor of Pediatrics

Harvard Medical School

Boston, Massachusetts

Lia Gore, MD

(Participation in Day 1, Topics 1 and 3)

Professor of Pediatrics, Medical Oncology, and Hematology

Chief, Pediatric Hematology/Oncology/Bone Marrow Transplant

The Robert J. and Kathleen A. Clark Endowed Chair in Pediatric Cancer Therapeutics and the Ergen Chair in Pediatric Oncology

Children's Hospital Colorado, Center for Cancer and Blood Disorders

Aurora, Colorado

Richard G. Gorlick, MD

Division Head and Chair, Pediatrics

Robert A. Mosbacher

Chair of Pediatrics

The University of Texas MD Anderson

Children's Cancer Hospital

Houston, Texas

Leo Mascarenhas, MD, MS

Deputy Director

Children's Center for Cancer and Blood Diseases

Section Head – Oncology, Associate Professor of

Pediatrics

Division of Hematology, Oncology, and Blood and

Marrow Transplantation

Children's Hospital Los Angeles

Keck School of Medicine, University of Southern

California

Los Angeles, California

Elizabeth A. Raetz, MD

Professor of Pediatrics

Medical Director, Leukemia and Lymphoma Program

Pediatric Hematology/Oncology

University of Utah

Huntsman Cancer Institute

Primary Children's Hospital

Salt Lake City, Utah

Brenda J. Weigel, MD, MSc

Professor

Division Director, Pediatric Hematology/Oncology

University of Minnesota

Developmental Therapeutics Chair

Children's Oncology Group

Minneapolis, Minnesota

FDA PARTICIPANTS (Non-Voting)

Gregory Reaman, MD

Associate Office Director

Associate Director for Pediatric Oncology

Oncology Center of Excellence

Office of Hematology and Oncology

Products (OHOP)

Office of New Drugs (OND), CDER, FDA

Nicole Drezner, MD

(Participation in Day 1, Topic 1)

Medical Officer

Division of Oncology Products 2 (DOP2)

OHOP, OND, CDER, FDA'

C O N T E N T S

P R O C E E D I N G S

(7:58 a.m.)

Call to Order

Introduction of Committee

DR. PAPPO: Good morning. We're going to get started. We have a pretty full agenda. 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, Angela Stark. If you are present, please stand.

I would now like to ask all of the members, consultants, panel, and DFO to go around the table and state their name into the record, please.

DR. MORROW: P.K. Morrow. I'm the medical oncologist employed by Amgen.

DR. GORE: Lia Gore, pediatric oncology, University of Colorado and Children's Hospital, Colorado.

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

DR. MacDONALD: Tobey MacDonald, pediatric neurooncology at Children's Healthcare of Atlanta and Emory University.

MS. LUDWINSKI: Donna Ludwinski, research program advisor for Solving Kids' Cancer.

MS. PREUSSE: Courtney Preusse, Fred Hutch, Seattle and consumer rep.

DR. ROTH: Bruce Roth, a medical oncologist from Washington University St. Louis and chair of the parent committee.

DR. PAPPO: Alberto Pappo, pediatric oncology, St. Jude Children's Research Hospital and chairperson of the ODAC or the pediatric ODAC meeting.

DR. TESH: Lauren Tesh, designated federal officer.

DR. MASCARENHAS: Leo Mascarenhas, pediatric oncologist, Children's Hospital, Los Angeles, and the University of Southern California.

DR. ARNDT: Carola Arndt, pediatric oncologist, Mayo Clinic.

DR. RAETZ: Elizabeth Raetz, pediatric

oncologist, University of Utah.

DR. WEIGEL: Brenda Weigel, pediatric oncologist, University of Minnesota.

DR. GORLICK: Richard Gorlick, pediatric oncologist, M.D. Anderson Cancer Center.

DR. DREZNER: Nicole Drezner, medical officer at the FDA.

DR. REAMAN: Gregory Reaman, FDA.

DR. PAPPO: Thank you very much. We will now proceed with opening remarks from Dr. Greg Reaman.

FDA Introductory Remarks

DR. REAMAN: Good morning and welcome to this meeting of the pediatric subcommittee of the Oncologic Drugs Advisory Committee. We obviously appreciate your time and efforts and the personal sacrifice to participate in this meeting, which we're holding, as we have in the past five or six years, to engage in meaningful discussions with industry, academic pediatric cancer investigators, and advocates about the potential for pediatric development of new cancer drugs and biologic

products, either recently approved or not yet approved, and in various stages of development, as a proactive initiative to facilitate, and more importantly, expedite the evaluation and possible development of new drugs for the management of cancer in children, which has traditionally highly leveraged adult cancer discovery and development.

As you're well aware, these are important times in cancer drug development with the increasing appreciation of the genomic basis and heterogeneity of human cancer, which has resulted in many molecularly targeted drugs, which have demonstrated large treatment effects in small biomarker-defined subsets of patients, leading to precision medicine in cancer.

To date, the impact of precision medicine has been most apparent in adult cancers based on their molecular mechanism of action. However, many of these agents can be assumed to have potential activity against one or more types of pediatric tumors. And I would think that the adoption of histology or tissue agnostic cancer drug

development approaches portend increased opportunities for early evaluation of molecularly targeted drugs in rare pediatric cancers or rare subsets of more common pediatric tumors.

There is, as outlined in the briefing document, specific legislation which governs drug development in children, the two laws, the Pediatric Research Equity Act or PREA, and the Best Pharmaceuticals for Children or BPCA, which differ substantially, but to some extent actually complement each other and their impact on pediatric drug development programs.

PREA authorizes the FDA to require pediatric assessments when a new drug application or a biologic licensing application, either original or supplemental, submission includes a new indication, a new active ingredient, a new dosage form, dose regimen, or route of administration. However, that mandate pertains only to the indication or indications submitted in the application.

As well, products for indications, which have received orphan designation, which is

increasingly common for targeted therapy and rare cancer subsets, are exempted from PREA requirements. And therefore, PREA has very little, if any, relevance to pediatric cancer, which is why we now attempt to maximize FDA's authority under BPCA by evaluating whether the issuance of a written request early in a product's development timeline, rather than years after a drug's approval for the adult indication, may actually expedite pediatric development of potentially active drugs.

So BPCA provides a financial incentive to companies to voluntarily conduct pediatric studies under a written request, which can either be requested by the sponsor through the submission of a proposed pediatric study request, or they can be issued directly by the FDA.

PPSR should include a biologic rationale for the proposed study and some detail regarding study design and plans for formulation development. Obvious considerations -- and that's what we really ask you to think about today -- for deeming a drug or biologic product potentially relevant for early

evaluation in children include the molecular mechanism of action of the drug; the scientific rationale, and the evidence base for evaluation in pediatric tumors; the safety profile; activity in pre-clinical models if there are any, and specifically pediatric pre-clinical models and plans for formulation; and some suggestion or evidence that the drug has the potential to improve clinical outcomes for children.

Since 2000, nearly 60 written requests have been issued by the FDA for cancer products, resulting in the granting of exclusivity for some 22 products and pediatric labeling information being added for 17 drugs. Five drugs studied under a written request have actually been approved for a specific pediatric cancer indication, and there are approximately 30 drugs which continue to be actively investigated. So this program does have real elements of pediatric oncology.

For the next two days, we'll be discussing five unique products, only one of which has recently been approved. And I'd like to

acknowledge the sponsors who have agreed to present their product's background, non-clinical data, as well as early adult experience, and in some cases their proposed pediatric development plan.

We do look forward to a rich discussion, which will help us at the agency in our decision-making with respect to the issuance of written requests. So thank you very much.

DR. PAPPO: Thank you very much, Dr. Reaman.

For topics such as those being discussed at today's meetings, 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, as a general 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 topics during breaks or lunch. Thank you.

We will now proceed with topic 1, APX-005M from Apexigen, Incorporated. Dr. Lauren 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 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 at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

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

is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meetings, 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 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 investigator interest in exploring potential pediatric development plans for three 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 of the development of these

products for pediatric use. The discussion will also provide information to the agency pertinent to the formulation of written request for pediatric studies for the program.

The product under consideration for this session is APX-005M, presentation by Apexigen, Inc. This is a particular matters meeting for which specific matters related to Apexigen'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. P.K. Morrow is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Morrow's role at

this meeting is to represent industry in general and not any particular company. Dr. Morrow is employed by Amgen.

We would like to remind members and temporary voting members that if the discussion involves any other products or firms not already on the agenda for which the FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with a 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, the FDA encourages all participants, including the applicant's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interests and those based upon the outcome of the meeting. Likewise, the FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking. We will now proceed with Apexigen's presentation.

Industry Presentation - Ovidiu Trifan

DR. TRIFAN: Good morning. My name is Ovi Trifan. I'm the chief medical officer of Apexigen, Incorporated, which is a small biotech in California. One of our main products is APX-005M,

which is a monoclonal CD40 targeting agonistic antibody and will be the subject of the presentation, today's presentation.

I would like to over the next couple of slides work through the role of CD40 in the immune system. We think it's a very important target in immunotherapy because CD40 plays a central role in activating the innate and adaptive immunity. It is a receptor that sits on macrophages, dendritic cells, and also on B-cells, in general, known as antigen-presenting cells.

Then its activation can trigger macrophage, neutrophil, and NK activation, but mostly can trigger T cell activation via dendritic cells. And it is, regardless, a very important target because of its ability to compliment direct T cell targeting with receptors such as PD-1, or OX40, or GITR.

As a brief reminder, once the CD40 is activating on the dendritic cells, it triggers antigen presentation and also activates the expression and enhances the expression of all the

costimulatory molecules such as CD70, CD80, CD86, for 1BB ligand or OX40 ligand, and also triggers the productions of interleukins, in particular IL-12, that all of those result into CD8 T-cell positive activation and targeting of a specific antigen.

It has been demonstrated for many years now that targeting CD40 with agonistic antibodies, monoclonal antibodies, results in very effective tumor control in animal models. Over the next few slides, I will walk you through some of the data available in the public domain.

I'd like to point out from the very beginning that most of this data was generated with few antibodies that are rat/anti-mouse antibodies. And we have to use such antibodies as surrogates for the human antibodies because they don't cross-react. The extracellular domain of human CD40 is very different from the rodent CD40.

For instance, in this paper published in 2014 by Sandin and coworkers, they looked at the effect of targeting CD40 with monoclonal antibody

called FGK45, And they looked at the effect of this antibody, whether it's administered peritumorally or IV.

They've seen a high concentration of antibody at the 100-microgram. They've seen fairly equivalent effects, as you can see in this figure, the upper two lines. So animals, they have very good tumor control, and they survive for up to 90 days for the duration of the experiment, while the isotype control, the rat IgG2a didn't have any effect.

This data that's in this panel, it's in the bladder MB49 tumor model, but similar data is available in the public domain for other tumor models such as melanoma, pancreatic, and lung cancer. So again, CD40 targeting single-agent monoclonal antibodies can actually elicit the direct anti-tumor effect, and that has been demonstrated to be T-cell mediated.

When CD40 agonistic antibodies are combined with other immunoactivating agents or checkpoint inhibitors, the effect seems to be even better. I

know this is a very busy slide, but I would like to point out that in this MC38 model, a mouse carcinoma model, the group from Switzerland demonstrated that single-agent anti-CD40, anti-CTLA-4, anti-PD-1, or anti-PD-L1 have some effect, definitely better than isotype control antibodies, but very few animals survive for a very long period of time. So this is the group of lines on the lower part of the panel.

However, when anti-CD40 antibodies are combined with CTLA-4, or PD-1, or PD-L1, the long-term survival jumps from about 5 to 10 percent to about 50 to 60 percent, and that effect seems to be enhanced by triple combinations; so for instance, if you see the two lines up on the figure, once CD40 is combined with CTLA-4 and/or PD-1 or PD-L1.

This data suggests that, again, CD40 could have single-agent activity, but best activity would result, at least in this particular model, from combining anti-CD40 agents with other checkpoint inhibitors targeting CTLA-4 or PD-1 and PD-L1.

In a paper published very recently in cancer

research, a group from Australia showed that, actually, single-agent CD40 can trigger good tumor control; and this in the Renca tumor model on the right side of the figure. But also, singular injection of anti-CD40 antibodies can reverse resistance to PD-1 treatment. The AT3 tumor model is very resistant, very refractory to PD-1 treatment. However, one single injection actually reversed that effect.

The last example, I'd like to provide a bit of data from the public domain. A group from the University of Pennsylvania developed a spontaneous pancreatic cancer model and showed that single-agent checkpoint inhibitors do control tumors, but they are not very successful for very long-term tumor control.

However, when chemotherapy is combined with checkpoint inhibitors, and in particular with CD40, that results in very good tumor control and prolonged survival. So if you can see in this example, the best effect was obtained with chemotherapy combined with CD40, PD-1, and CTLA-4.

That's the purple line both in tumor and the survival graphs on the lower part of this here.

All those slides that we presented for the data was generated with an antibody called FGK45, as I mentioned in the beginning of the presentation. There are two additional antibodies that are used as surrogates. One of them is called 1C10 and the other one is 3/23.

We believe those three antibodies are actually very good surrogates for the APX-005M based on two characteristics. First of all, all those three antibodies block the binding of CD40 to the CD40 ligand. And APX-005M, to our knowledge, is the only antibody that has this property. And also, those antibodies are rat IgG2A, which is equivalent to human IgG1, and they do depend on Fc cross-linking.

So the molecular mechanisms of action of those antibodies are very similar to APX-005M, and it's quite different from the other CD40 targeting antibodies that are currently in clinical development.

So APX-005M, one of its main characteristics is that it binds to the CD40 ligand-binding site. Earlier on in the development of this antibody, we did epitope mapping, and we were able to show that our antibody binds to two peptides, so this is peptide mapping.

We show that it binds to two peptides. You see the panel in the middle, the blue and the red areas. And there is a very good overlap with the CD40 ligand-binding site on CD40, so the yellow color represents the area of overlap. We also know that APX-005M can actually block the CD40 ligand, CD40 interaction.

We believe that's an important property because what we're trying to achieve with this antibody is to mimic the actual physiological CD40, CD40 ligand interaction, so binding to the right area of the CD40 molecule could have physiological relevance.

When we're looking at the activity of the antibody in vitro, we do see a very potent agonistic activity. For instance, in this example,

we were looking at CD86 expression on dendritic cells as a marker of activation of dendritic cells. In CD54, APX-005M is very low. It's 89 picomolar. Also as a reference, we compare it to analogs of the antibodies, which are currently in clinical development or were in clinical development. Those are ADC-1013, CP-870, 893, and SGN-40. And as you can see, the APX-005M seems to be the most potent antibody in terms of CD86 expression on the dendritic cells.

We also looked at the mechanism by which APX-005M activates CD40. I mentioned a few minutes ago that the Fc portion of the antibody is very important. There is a lot of data in the literature showing that, for CD40 or for other TNF receptors, antibodies, they have to have a cross-linking ability. They need to be able to cluster the target molecule.

Our antibody actually has -- all of its activity is dependent on binding to ligand, but also binding to an Fc receptor. As you can see in the panel on the left, if we stimulate the B cells

with APX-005M, we see a very potent CD86 expression. In this particular experiment, the EC50 was 9 picomolar. However, when the Fc portion of the antibody is detached, it's clipped. The agonist activity disappears completely. That's the red line. So it's going back to isotype control, basically no activity whatsoever.

As a comparator on the lower panel, you see a figure that's coming up from a paper published by Dr. Vondeheide a few years back, where they look at the effect of clipping the Fc portion of the antibody for the CP-870, 893 antibody. And that antibody retains the agonistic activity independent of whether it has or not the Fc portion antibody.

We think this is relevant because the requirement to have both competent CD40 and Fc in the same system for the antibody to work will result in an activation of CD40 only in the cell environment when cells touch each other, so both components are present. As you will see in the next few slides, we were able to escalate in adult patients the dose to a much higher concentration

than any other CD40 agonistic antibody.

We also looked in in vitro system, the ability of our antibody to stimulate the T-cell response in a mixed lymphocyte reaction. The experiment is quite simple. We take isolated dendritic cells, human dendritic cells, and we incubate them with the antibody. And then we add allogenic T cells that also function as the antigen. And then we measure the T-cell proliferation on the interfering gamma production as the surrogate for T-cell proliferation. And as you can see in this example, the APX-005M is very potent. It can trigger very high levels of interferon gamma.

To date, APX-005M has been administered to 30 adult subjects with solid tumors in a phase 1 dose escalation clinical study, and we start the clinical exploration by looking at an every-3-week schedule. The majority of adverse events have been mild to moderate in severity and were considered to be unrelated to APX-005M.

The dominant toxicity is the infusion

related to reaction or cytokine releasing. We know that some of those patients that were having infusion reactions had cytokine production, increased level of cytokines in their blood. Within 10 out of 30 patients had infusion-related reaction or cytokine release syndrome at different rates.

There was one rate for event and 3 grade cytokine release syndromes during the study, but all of them happened at concentrations, very high concentrations above 0.6 milligrams per kilo.

The most common adverse events observed with our drug happened within the first 48 hours and include rigor, chills, fever, flushing, itching, nausea or vomiting, headache, and rush. And they are suggestive of a cytokine release.

A majority of those symptoms were mild, grade 1 or 2, and they do respond promptly to treatment with antihistamine, antiemetics, and antipyretic drugs. We did see from a pharmacodynamic point view reversible decrease in peripheral blood, lymphocyte counts in general, and

B cell counts in particular. It is considered to be a pharmacodynamic effect and has been described in the animal models, but also in humans with CD40 agonistic antibodies.

We do also see dose-dependent activation of antigen-presenting cells as demonstrated by increased expression of markers such as CD54, 70, CD80, 86, HLA-DR on B cells and dendritic cells. Also, we do see the markers of T cell activation being upregulated. And probably the most important thing is IL-12 is also upregulated, and it's going from undetectable levels to detectable levels in a dose-response manner.

For the adult population, we decided that the recommended phase 2 dose is 0.3 milligrams per kilo for an every-3-week administration. As I mentioned, we were able to escalate the dose up to 1 milligram per kilogram. However, if we look at antigen-presenting cell activation, the PK effects seem to be around 0.1, 0.3, or 0.6 milligrams while the toxicity goes up with the dose.

So again, the recommended phase 2 dose for

APX-005M on an every-3-week schedule is 0.3 milligram per kilo, and this is the dose we are currently using for a couple of combination studies.

So we have two company-sponsored studies in adults with cancer. One is an extension of the ongoing phase 1 study, where we're looking at APX-005M single agent in an every-2-week and an every-week schedule in patients with urothelial carcinoma, melanoma, squamous cell carcinoma, head and neck, non-small-cell lung cancer, and any solid tumor with MSI-high status.

We also initiated last month a study in combination with nivolumab. The study is looking at fixed dose of nivolumab given every 3 weeks with the increasing doses of APX-005M. And the target population is second-line immunotherapy-naïve non-small-cell lung cancer in patients with metastatic melanoma that failed PD-1 or PD-L1 treatment.

We also have two investigator-sponsored studies that were initiated. One of them is APX-005M administered intratumorally in combination

with systemic pembrolizumab in subjects with metastatic melanoma.

There is another study from the University of California in San Francisco looking at the effect of APX-005M on the tumor-immune microenvironment and the safety of APX-005M given in combination with chemoradiation in an adjuvant setting for esophageal and gastroesophageal junctions.

There are additional studies in adult subjects with solid tumors that are currently under consideration.

In summary, APX-005M is a humanized IgG1 monoclonal antibody, which has a very high affinity for CD40 and binds to CD40 ligand-binding domain on CD40. It is a IgG1, but we did perform a mutation in the Fc portion of the receptor that resulted in two desired effects.

One is increasing the ability to bind to Fc gamma receptor IIb, and that results in a very effective cross-linking. Also, this mutation decreases the binding affinity to Fc gamma receptor

IIIa, so by that way abolishes the ADCC activity. It was intentional because we didn't want to deplete the dendritic cells and the B cells by ADCC.

In vitro, we've seen increased T-cell response. We've seen very effective antigen-presenting cell activation. And the surrogate rat/anti-mouse CD40 antibodies demonstrated very effective anti-tumor efficacy in pre-clinical models.

We had probably better than the expected safety profile at the doses explored to date. Again, we were able to escalate to 1 milligram per kilo. It was expected that probably the maximum dose we would be able to go to would be 0.3 milligrams per kilo, maybe even lower based on very effective, very high potency in vitro, and also the experience with other CD40 antibodies, which were ahead of us in development. As I mentioned, we did see very convincing dose-dependent immune activation in cancer patients.

What we'd like to -- so during our process

of establishing what the indications for this agent should be, we very early on considered pediatric development. We partnered with PBTC to perform a phase 1/2 study in pediatric subjects with brain tumors.

This study is designed as a dose-escalation study with 3 dose levels in patients with recurrent or refractory malignant brain tumors. Once we established an MTD-recommended phase 2, we plan to expand that stratum to look for very early signs of efficacy.

An extension, a second stratum, is also planned to look at subjects with patients with diffuse intrinsic pontine gliomas, but we would like to re-escalate APX-005M single-agent in that population, and that's based primarily on the experience with other immune-activating or immune-targeting agents that showed a little bit more toxicity in this patient population versus other brain malignancies. The drug we plan to administer with APX-005M has an IV infusion every 3 weeks.

So the primary objective would be to

evaluate the safety of APX-005M and administer IV every 3 weeks to children with brain tumors. Also, we would like to determine the maximum tolerated dose and the recommended phase 2 dose of single-agent APX-005M.

Secondary objectives include pharmacokinetics of APX-005M pediatric subjects. We'd like to assess the incidence of anti-drug antibodies and to establish preliminary signs of efficacy via overall response rate, duration of response, progression-free survival, and overall survival for subjects with DIPG.

Some of the key eligibility criteria include, for inclusion, patients should be age 1 to 21 at the time of enrollment. They have to have bi-dimensionally measurable disease, adequate time from last dose of known myelosuppressive anti-cancer therapy, and adequate time from last dose of radiation therapy. They have to have stable neurological status, a Karnofsky performance status or Lansky performance status greater than 60 and adequate organ function.

Some of the key exclusion criteria include any clinically significant unrelated systemic illness such as serious infection, or cardiac pulmonary, or other organ dysfunction, history of any other malignancy except a secondary brain tumor and if the first malignancy occurred in the distant past.

Also, we would like to exclude patients that receive any other anti-cancer or investigational therapy, patients with presence of bulky multi-focal tumor on imaging, and non-coagulopathy, or bleeding diathesis, or treatment, so a requirement to use systemic anticoagulant medication.

This study will show that APX-005M is safe to be administered in pediatric patients, and if we see any preliminary evidence of efficacy, we'd like to follow up with an additional study. And obviously, we will reach out to the appropriate health authority and potential academic collaborators to design proper studies.

We believe also that the results of this study will inform the possible development of

APX-005M in other pediatric populations with solid tumors and/or in combination with other treatment modalities, including immunotherapy or chemotherapy.

So in conclusion, we believe that CD40 is a very promising immuno-oncology target. We think that APX-005M is a quite unique molecule and has this ability to bind to the CD40 ligand-binding site with very high affinity. Its activity is highly dependent on Fc receptor cross-linking, which, as I mentioned earlier, will actually make it more safe than other CD40 agonistic antibodies.

Also, in the pre-clinical setting, APX-005M outperforms other antibodies that are currently in development or were developed in the past, targeting the same target.

APX-005M has a good safety profile at doses explored to date, and it's a very good safety profile, particularly at the dose that we planned to take forward, at least the adult population, and also will be the highest dose probably to be explored in the pediatric brain tumor study. In

the clinical setting, we know that APX-005M triggers robust immune activation.

As you've seen in previous slides, we're teaming with PBTC to investigate the safety and efficacy of APX-005M in pediatric subjects with brain tumors, and we plan to perform additional confirmatory or combination study should the data be positive and supports further development of APX-005M. Thank you very much.

Clarifying Questions from Subcommittee

DR. PAPPO: Thank you very much for the presentation. We will now take clarifying questions for Apexigen. Please remember to state your name for the record before you speak, and if you can, please direct questions to a specific presenter. And I hate to say this, but I already put my name on there, so I'm going.

So the obvious question is why did you target -- my name is Alberto Pappo. Why did you target brain tumors and not other solid tumors, particularly since most of the pre-clinical data that you have was on solid tumors and most of the

ongoing studies in adults are in tumors that are non-CNS tumors?

DR. TRIFAN: For the first study, we're targeting pediatric brain tumors for a couple of reasons. One is that, in general, immune activation has been shown indirectly to be a valid mechanism of action for brain tumors.

Secondly, we also know that pediatric brain tumors are the main -- very large population of the solid tumors in adults -- in children. Also, we have to start somewhere, so it's also a practical question, a feasibility issue.

We were able to work with PBTC to actually establish this first trial. But we also -- as I said, we would be open to other indications should we determine that the drug is safe in the pediatric population.

DR. DuBOIS: Steve DuBois, Dana-Farber, Boston Children's. Thank you for the very clear presentation. Have you observed any anti-tumor activity in the clinic with monotherapy? And along the lines of Dr. Pappo's question, do you have a

responder hypothesis that might help us to inform the pediatric indications perhaps most likely to benefit from this agent?

DR. TRIFAN: To your first question, we've seen stable disease, but the phase 1 study was heavily oriented toward GI tumors. It was not by design, but that population turned out to be available to enroll at the time we were doing the phase 1 dose escalation.

We've seen prolonged stable disease in a couple of patients, but that's the reason we are now looking to some potentially more tumor -- immuno-responsive tumor such as non-small-cell lung cancer, melanoma, head and neck, and so on.

Another potential reason why we haven't seen single-agent activities so far is that the every-3-week administration schedule might be not intense enough to cause reduction in antigen-presenting cell activation, and anti-cell activation with the drug, with our particular drug.

We started with that every-3-week schedule

based on the history of other agents. There was no particular reason why we chose an every-3-week schedule.

For the pediatric population, again, looking at the mechanism of action of this molecule, it should be tumor agnostic more or less. What we're achieving with APX-005M, we're turning on CD40. We're activating antigen-presenting cells. Some of the data that I showed you and the data in the public domain showed that, sometimes, that's enough to cause a very strong immune response, to retrain basically T cells to go after the tumor.

Unfortunately, there's not a lot of data in the public domain with CD40 in pediatric tumors or pediatric population. There's actually nothing to my knowledge. There's no data in humans.

So again, the reason we decided to do this partnership with PBTC is because we have to start somewhere, and it is a good population to target with an immune-targeting agent in general.

Ira, do you have anything that you'd like to add? I invite Dr. Dunkel to the podium for a

second.

DR. DUNKEL: Ira Dunkel, Memorial Sloan-Kettering and PBTC. So from the PBTC perspective, before we had contact with Apexigen, our internal immunotherapy committee had already identified CD40 agonist antibodies as an agent that we were interested in investigating. So of course, we were happy when Apexigen approached us and we had this opportunity.

When we were developing this, we were aware of preliminary signs of efficacy in recurrent GPM adult studies, getting checkpoint inhibitors. And since we've been developing this study, we've become aware of the Toronto data that nivolumab appears to be effective for hypermutated pediatric brain tumors.

So I think those were all reasons that we are interested in pursuing this for pediatric brain tumors from the PBTC perspective.

DR. GORE: I have a series of questions that I hope will have some logical order to them. And I don't want to dominate this, but one question is

really whether or not you have data. Can I assume that in your adults treated to date, none of them have had brain mets?

DR. TRIFAN: I think we had two patients brain metastases, if I remember correctly.

DR. GORE: Do we know what happened to them in terms of CNS reactions or altered cytokine release?

DR. TRIFAN: No. There was no safety signal or we haven't seen any efficacy in those particular patients.

DR. GORE: Do you have any data in radiation models? Is there either an immunosuppressive or an abscopal effect with immunostimulation post-radiation?

DR. TRIFAN: It has been described as, actually, a very good synergistic combination.

DR. GORE: In this drug particularly?

DR. TRIFAN: No, but with a surrogate rat anti-mouse antibody, with FGK45. And that's actually the hypothesis behind one of the investigator-sponsored studies I had mentioned in

the presentation, the study from UCSF. That's looking for cognition of APX-005M with chemoradiation in an adjuvant setting.

DR. GORE: What data do you have for either efficacy or lack of efficacy in patients who have been treated with corticosteroids in proximity to steroid treatment relative to lympho-depletion and immunosuppressive effect of that?

DR. TRIFAN: So again, the group is very small, but we know from pre-clinical models and also from our hands-on experience that steroids don't go very well together with APX-005M. Actually, steroids are high doses of steroids that can wipe off the immune activation. So during our studies, we recommend there is a window of at least 2 weeks to 4 weeks between a high dose of steroids and APX-005M.

DR. GORE: I asked because I did not see lympho-depletive therapy in your exclusion criteria, only myelosuppressive therapy. Is that something that you plan to include?

DR. TRIFAN: We haven't had any experience

with that, so we plan just to exclude the previous exposure to steroids or recent exposure to steroids.

DR. GORE: One final question, can you talk a little bit more about the depth of the B cell suppression and how you plan to mitigate that in these patients or monitor that?

DR. TRIFAN: In the phase 1 study, we did look at very frequent time points. So in the first 48 hours, we had like 6 blood draws, and then another one a week later, and another one 2 weeks later, and another one at the beginning of the next cycle.

This B cell depletion is considered to be a pharmacodynamic effect. Actually, we know that we're not killing the cells. They just migrate the lymphoid organs. And we've seen in humans that, actually, the B cells come back to normal within a week. So it's a transient effect, and it matches reverse -- it's a reverse correlation on all the other markers.

So the APC activation, for instance, it's

very high, up to one week. I don't know how to explain this. As I said, it's a reverse effect, so cells tend to be activated, and once they're activated, we believe that they go to lymphoid organs. And then when that state of activation fades away, then they start migrating back into circulation.

DR. GORE: Thank you.

DR. WEIGEL: Thank you very much. I have a couple of questions. The first one I'll start with is you have treated a cohort of patients at the Q3-weekly dosing, but you're exploring every-2-week and a weekly dosing.

What are your endpoints to determine the optimal dose and schedule? Is it a biologic endpoint or is it an efficacy endpoint? And how are you going to choose which regimen you feel is optimal to take forward? And then I'll move to my second question.

DR. TRIFAN: So for the second part of this phase 1 dose escalation study, we would obviously look at safety. As I mentioned earlier, we started

with an every-3-week schedule because we looked at experience with CP-870, 893. That's an antibody which was originally developed by Pfizer, and I think right now is developed by Roche.

There was data in the literature that an every-3-week schedule, it was as effective as an every-week schedule, but the weekly schedule was more toxic. So that's the reason we started there. However, our data is suggestive that APX-005M, it's more safe. It's safe at least at the same concentrations. It's safer than other CD40 agonistic antibodies.

So we plan to continue to look at tolerability in an every-week and every-2-week schedule. And we also will obviously look at efficacy.

One of the reasons we also try to -- we also narrow down the patient population to some potential immunogenic tumors. But in order to decide what the best regimen is, obviously we would look at the totality of the data: safety, look at the PD effect, and also efficacy if we see any in

the second part of the study.

DR. WEIGEL: Assuming the toxicity is similar across the different dosing regimen, which I think you're alluding to, you expect, and assuming it marries your pre-clinical data that there is really limited single-agent activity, are there particular biomarkers that you will leverage your decision-making on to pick your dose to take forward?

DR. TRIFAN: Right. So as I had in one of the slides, we do monitor the antigen-presenting cells in circulation. And also, we plan to collect some tumor biopsies to look for what happens in the actual tumor. But we will make a decision based on the PD data.

DR. WEIGEL: That wasn't my second question. I just did a follow-up. My next question is towards the design of the pediatric trial. We have a fair bit of experience now in pediatric oncology of dosing antibodies as well as checkpoint inhibitors. And our experience thus far has suggested that the dosing is equivalent in

children, generally as it is in adults, or if anything, they tolerate higher doses to get similar effects.

So one of the potential ways to expedite the development in children would be to essentially start at the recommended phase 2 dose that you determine in adults once you've determined what that optimal dosing is. And then it's unclear to me why we would expect patients with DIPG to require a lower dose. If anything, it's a higher area of need.

So I would like some thought given to the dose escalation and why we would start at a lower dose. Most of our studies in pediatric oncology suggest that we can start at an equivalent dose to the adults to maximize benefit for children.

DR. TRIFAN: Yes, that's an excellent point. We did discuss this, discuss with the team about what would be the ideal starting dose. We have a little bit of a concern that maybe patients, kids would respond -- will be more sensitive to immune activation.

So at least for the stratum one, we might consider maybe two dose levels. However, the dose schedule that we plan to use is similar to the adult population. That's a semi-log scale, so we're going to start at let's say.0330 micrograms per kilo, and then go very quick to what we think is the optimal dose for single agent, at least for the every-3-week schedule.

For the DIPG population, if I recall correctly, there was more toxicity at the same dose. There was some immune infiltrate that caused -- I don't know. Maybe, Ira I can make sure answers that.

DR. DUNKEL: To just very briefly go back to the first question, I think we agree with you, but the initial CTEP review suggested that we start slightly lower than the adult-recommended phase 2 dose. So that was the basis for not starting at the adult-recommended phase 2 dose.

For the DIPG question, it's really an issue of safety toxicity. So on the PBTC, a currently open pembrolizumab study, which initially was

enrolling, in separate strata, patients with recurrent DIPG and recurrent high-grade astrocytomas, on the DIPG stratum, we did see patients have neurological AEs. And at the time and even now, it really was not clear whether those were early progression or tumor-flare immune-mediated reaction that was causing harm.

But because of that, we decided to exclude patients with recurrent DIPG from the initial dose escalation in the planned PBTC study, and then dose escalate separately once we had the pediatric recommended phase 2 dose and start one dose lower.

DR. MASCARENHAS: Leo Mascarenhas from Children's Hospital Los Angeles. So my questions are very similar to what Dr. Weigel had just asked. I was wondering, in the adult patients whom you've treated thus far, particularly those who had stable disease and were able to receive the drug on more than one occasion, most of the toxicity which you described appeared to be acute and infusion related.

Did you see any later toxicities which

occurred, particularly immune-related toxicities?

DR. TRIFAN: No. The short answer is no. We do see infusion reactions right during the infusion or shortly following the infusion. There were 3 patients that developed a cytokine release syndrome. That reaction was delayed. It was 24 hours after the infusion. The main symptom was the hypotension, prolonged hypotension that actually required intervention.

The other toxicity we've seen in very few patients that have liver metastases was a transient transaminase and bilirubin elevation, but it's very short-lived. It's less than 48 hours, and it just goes up and comes back to grade 1 or grade 2 within 48 hours.

A majority of the toxicity that we think is related, what we believe is related to the drug, it happens within the first week. And that's actually the reason why we decided to go for an every-2-week and every-week schedule.

DR. MASCARENHAS: So the liver toxicity which you mentioned, what's the relation to the

study drug? Is it early or is it late?

DR. TRIFAN: Within 24 to 48 hours.

DR. MASCARENHAS: But were they very similar?

DR. TRIFAN: Yes, very similar. So follows -- trace down all the immune activation.

DR. MASCARENHAS: So the follow-up question to that is, have you done any PK modeling based on your data in the adults so far to suggest that the drug exposure in those with lower body weight may be different from those at higher body weight to suggest that you may have different drug exposure in the pediatric age group?

DR. TRIFAN: No, we have not done that yet. However, very early, this is very preliminary data we have so far. The half-life is very short, and we don't think we saturate all the receptors in the body. So even at 1 milligram per kilo, probably we're not giving enough drug to saturate completely the receptors.

DR. MASCARENHAS: So that goes back to some of the questions I have about the study design

really in an attempt to minimize the number of patients and get the most amount of information, and move forward potentially rapidly, we've done, as Dr. Weigel suggested, so money studies with monoclonal antibodies.

Really, the recommended phase 2 dose is very similar to the adult dose or rather higher. And if it's really infusion concerns of toxicity, consideration potentially for a dose de-escalation study rather than an escalation study might be something to consider, where you start at the adult-recommended phase 2 dose, and then potentially, based on PK, either elevate or decrease the dose based on toxicity.

The second thing is it's very compelling data which you presented on combination therapy, particularly with immune therapy. In your study design, would you consider a rapid movement to combination therapy within the same study to potentially look at a signal?

I think since most of your toxicity appears to be early rather than late, and potentially after

a particular cycle and an evaluation of PK and early toxicity, to consider adding on other immune therapy or other agents within the same study.

DR. TRIFAN: So yes, we would be open to combination studies. But first of all, we'd like to gain a bit of experience with a combination of checkpoint inhibitors from the adult studies. So that's number one.

Number two, it also becomes a bit complicated when it comes to access to various drugs and how to combine in pediatric studies, but in principle we're open to that. As I think we mentioned early in the presentation that, following this study, we would consider additional combination studies in pediatric populations.

DR. MASCARENHAS: Thank you.

DR. ARNDT: That was my question, to combine them early.

DR. ROTH: Bruce Roth, St. Louis. I had just a quick design question about stratum 2. You're essentially giving this agent adjuvantly after radiation therapy, so I'm trying to figure

out what information you're going to get about response rate and duration of response, which is one of the secondary endpoints.

DR. DUNKEL: So you are correct that we are giving it post-radiation, and we don't consider response really to be an adequate sign of efficacy for that stratum. So we're really looking at overall survival as the efficacy for that stratum specifically.

DR. ROTH: Because the secondary objective listed here for DIPG patients is assessment of efficacy via overall response rate, duration of response, progression-free survival, and overall survival specifically for the DIPG patients. So that's not correct?

DR. DUNKEL: So we're looking of course at all the parameters, but I think the primary efficacy endpoint, specifically for the DIPG stratum in the protocol itself, is overall survival.

DR. REAMAN: So a lot of my questions have already been asked also, but I do have one. I know

your combination studies, which you showed, have been in the murine system with surrogate antibodies. Do you have any plans to actually do any comparative studies in the human setting with the CD40 agonist compared to other immune oncology drugs?

Is your ultimate development plan for this product as monotherapy? Or given the data that you've provided, that is pretty compelling with respect to its synergy with other immunomodulators, is that your ultimate development plan, to use it in combination with either other checkpoint inhibitors or other immune oncology drugs?

DR. TRIFAN: The short answer is we're looking for both. And again, if you look at the pre-clinical data, there is, again, very strong support for single-agent activity, particularly in tumor models that are refractory to checkpoint inhibitors.

There is also very good and very strong data suggesting that CD40 should be combined with a checkpoint inhibitor or could be combined with some

way of presenting an antigen such as radiation or chemotherapy. And we are looking at all those options at this moment.

So as I mentioned, there are four studies that already INDs are approved for them or they're part of R&D. So they're two company-sponsored studies. One of them is looking for single-agent activity in a different schedule. The other study is looking at a combination with nivolumab with the IV administration as looking at efficacy as a primary endpoint in the phase 2 portion of the study. We are targeting the approved patient population for nivolumab, so we have the reference to compare it to.

We also have two investigator-sponsored trials that look at other combinations. One is with chemoradiation and the other one with pembrolizumab with a different drug of administration.

Fortunately or unfortunately, the pre-clinical data is very good in a variety of models. So unfortunately, that's a little bit of a problem

for us because we don't have one or two trials that will be a clear yes or no answer. And that's the reason we're trying to do a variety of studies at this moment.

DR. REAMAN: Then in your adult studies to date, what's the longest exposure that any single patient has had to this product?

DR. TRIFAN: We had 10 cycles.

DR. REAMAN: Ten cycles. You said that you haven't seen any immune-related toxicities, but have you actually looked for them, or screened for them, or monitored patients that have been out any length of time for endocrine problems, pulmonary, GI?

DR. TRIFAN: No. None of the adverse events that were described in patients that stayed more than 3 cycles were suggestive of immune-related adverse reactions. However, that's --

DR. REAMAN: But were you specifically monitoring for it?

DR. TRIFAN: No, we're not specifically monitoring for anything except liver function tests

and adverse event collecting, the standard laboratory screening.

DR. REAMAN: Thanks. And then just to follow up with the 3-week schedule, do I understand that that was really selected just because of the experience with other immune-modulating drugs, specifically checkpoint inhibitors? I mean, you didn't have any other pre-clinical evidence to suggest that every 3 weeks versus every 2, or weekly, or daily had any difference in CD40 activation?

DR. TRIFAN: That is correct. So again, the antibody which was developed by Roche -- it is currently developed by Roche, but it was originally developed by Pfizer, called CP-870, 893, was studied both in every-3-week and weekly schedule. That was about 7 years ago, maybe 10 years ago.

DR. REAMAN: In humans or animals?

DR. TRIFAN: In humans. So there was data in the public domain. At the time, we decided to do the first human study, there was data available for that particular antibody that showed that an

every-3-week schedule is equivalent in terms of efficacy with a weekly schedule, however, the weekly schedule is more toxic.

So that first human study -- I mean both studies, the weekly and every-3-week schedule, looked at patients that were immunotherapy naïve at the time, and they were able to assess efficacy in that population.

So they concluded that efficacy is equivalent, but the weekly schedule is more toxic. And that was also corroborated with the fact that in pre-clinical models, our antibody is much more effective, more potent than the CP-870, 893 analog that we made.

So we were expecting at the time that an every-3-week schedule with a molecule that's potentially more potent will be probably as toxic. It turns out that the Fc engineering that we have gives different in vivo, in-human characteristics. So we do see a different safety profile. We do see the activation of the right antigen-presenting cells -- I mean, the right markers, and we also see

the cytokine production that is sort of favorable. So again, right now, we're looking at more frequent administration.

DR. REAMAN: So I guess that brings me to the pediatric study because, generally, we have a paucity of patients in which to evaluate novel and potentially relevant drugs. So knowing optimum dose and schedule I think is generally a pretty standard requirement before embarking on pediatric development.

So I'm a little unclear, if your plan is to look at different schedules and dosing, how that's going to relate to your current and future pediatric development plans.

DR. TRIFAN: So it is a very valid concern. But it might turn out very well that the every-2-week and every-week schedule is not any better or it doesn't lead to single-agent activity at least in the adult population.

So we discussed potentially adapting down the road to the pediatric trial. If we do see very good efficacy or a very good signal, then let's say

the every-2-week schedule is a better schedule than every-3-week, to amend the protocol and to look for that more frequent administration in the pediatric population. But in the absence of an efficacy signal for a single agent so far, it's very hard to make a decision of what is the right schedule.

As I mentioned earlier, we've seen in the adult population a very nice dose-response effect in terms of immune activation. Whether that is sufficient to trigger single-agent activity in pediatric brain tumor patients remains to be established.

DR. PAPPO: Last question, Tobey?

DR. MacDONALD: Tobey MacDonald, Emory University. Is it known or expected that the molecule will cross the blood-brain barrier and/or do you consider that relevant? For example, what effect might it have on brain microglia? We know that the microglia can initiate tumor-associated macrophage populations, which can be tumor promoting and/or tumor suppressive.

So is there any information in that regard?

DR. TRIFAN: Not to my knowledge. We would expect this antibody to behave as any other antibody, so it will have the same brain access issues. But from an efficacy standpoint, the training of the T cells doesn't necessarily have to happen in the organ where the tumor is. So we'd expect that if we trigger -- if we are able to -- sorry. The antibody can actually activate the antigen-presenting cells, and they can retrain a T cell response that should be sufficient.

DR. MacDONALD: Sorry. One quick follow-up on the other side of the coin. We know that CD40 is expressed on some cancer cells.

DR. TRIFAN: Correct.

DR. MacDONALD: Is there information whether this molecule can stimulate cancer cells or inhibit those as well, and is it correlated with the expression of CD40 on the cells?

DR. TRIFAN: It has been described that, for subtumor models for B cell lymphomas and for bladder cancer, if I remember correctly, CD40 actually has a pro-apoptotic effect. So if you

target with an agonist antibody, you can trigger direct apoptotic effect.

Actually, we were able to show a direct anti-tumor effect with our antibody in a lymphoma model, but we think that's sort of a secondary mechanism of action for CD40 agonistic antibody. The primary mechanism of action should be the activation of the antigen-presenting cells.

DR. PAPPO: Thank you very much.

DR. TRIFAN: Thank you.

Open Public Hearing

DR. PAPPO: We will now move to the open public hearing session of the meeting. 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 open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of

your written or oral statement, to advise the committee of any financial relationship that you may have with the applicant, its product, and if known, its direct competitors. For example, this financial information may include the applicant's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

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

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

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

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

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. POLANIN: Thank you for the opportunity to speak today. My name is Dr. Megan Polanin. I am a senior fellow at the National Center for Health Research, and I previously trained at Johns Hopkins University School of Medicine.

Our research center analyzes scientific and medical data and provides objective health information to patients, providers, and policymakers. We do not accept funding from pharmaceutical companies, and therefore, I have no conflicts of interest.

We realize that the goal of all five of the drugs discussed during this meeting are for

treating rare pediatric cancers and that these patients desperately need new treatments.

In some recent approval decisions, the FDA has been criticized for approving treatments for rare diseases based on inadequate data and wishful thinking. As a result, most insurance companies were not willing to pay for those approved drugs.

Instead of getting free drugs in clinical trials, those patients are left with no affordable options. So it is essential that the studies conducted are designed to be able to prove whether or not any of these five drugs have benefits that outweigh the risks.

We strongly support FDA advisory committee meetings like this one to garner input from experts on how best to design and conduct clinical trials for pediatric patients.

This committee has been and will continue to be thorough in asking specific questions of the drug sponsors on their trial design while also offering helpful critiques and suggestions when needed.

Despite the challenge of studying these drugs for extraordinarily rare populations of patients, it is critical to uphold the scientific integrity of the proposed trials. For example, when possible, researchers should use randomized or well-matched control group with comparison samples for new drugs because it is the most methodologically sound design in order to demonstrate whether a drug is safe and effective.

When a proper control group is not available, researchers should observe a robust single-agent response rate in order to support a drug's efficacy.

By law, FDA decisions are not based on cost. But you know that the cost of these drugs can be a huge issue for children and their families. In the last year, two drugs used to manage, not to cure rare diseases, were priced at $300,000 and $750,000 per patient per year. As I noted, insurance companies are making sure these drugs are proven to work before they are willing to pay for them.

You can help the FDA make sure that the

evidence is clear. When analyzing the proposed clinical trials, we urge this committee to keep in mind the possible pitfalls associated with using biomarkers and surrogate endpoints in lieu of outcomes that are most meaningful for patients such as overall survival and quality of life.

A study published in JAMA found that only 14 percent of cancer drugs approved using surrogate endpoints were later determined to improve patients' overall survival. Our center found that only one of these drugs was proven to improve quality of life, and yet all were still on the market, costing an average of almost $100,000 per year.

Let's make sure that cancer drugs for children are proven to provide meaningful improvement in patients' health or quality of life if not both. Additionally, there are clearly subpopulations of patients who respond better to treatment than others. We encourage the sponsors to further characterize the positive responders in order to target the population of patients who are

most likely to benefit and least likely to be harmed by adverse events from their treatment.

Drug efficacy is a complex issue for children with chronic and/or rare diseases like the cancers discussed here. We commend the FDA and this committee for providing an open discussion focused on the best ways to test these five new drugs in pediatric populations.

This marks a positive effort to help ensure that drugs are safe and effective for everyone for whom they are prescribed, particularly when the cost of these drugs can be so high. Thank you for the opportunity to express our views.

Questions to the Subcommittee and Discussion

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

We will 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. We should start with the first question.

DR. DREZNER: Please comment on the unique safety concerns that arise from the use of immune-activator agents, in particular with CD40 agonistic antibodies in pediatric patients and known methods to mitigate these safety issues in clinical trials.

DR. PAPPO: If there are no questions or comments concerning the wording or the question, we will now open the question for discussion. Yes?

DR. GORE: Lia Gore, University of Colorado. So it's not clear from the presentation today the mitigation strategies for any immune-activating side effects that have been experienced. I think there were data presented regarding particular cytokines, for instance, that had been measured particularly in pre-clinical models.

Certainly, the focus on central nervous

system tumors in children mean that we have a number of biologic issues to address. Dr. MacDonald mentioned whether or not these agents actually get into the brain. This is an antibody. Antibodies are typically large in size.

Patients with brain tumors often don't have an intact blood-brain barrier, but it's not clear that the immune-mediated effects of activating T cells depend on something actually getting into the brain. However, it's not really clear from data that were presented or a lack of data that were presented regarding what that mechanism may be in the patients they intend to study, so I would certainly want to understand the strategies that they hope to evaluate better.

It's also not clear, again, and further clarification I think would be needed regarding the mitigation strategies, how they would approach this analysis. I heard one mention that there's a peak activation period of around 24 hours that would be important.

Typically, these patients might be treated

as outpatients. And so it would be important to have a strategy there that I'm not clear on from the presentation.

DR. MASCARENHAS: Leo Mascarenhas, Los Angeles. I didn't see this on the exclusion criteria and they may be written in, but again, the rare in this group of patients, previous allogenic transplant, solid organ transplant, and the role of immunizations while on this therapy should be potentially kept in mind.

DR. WEIGEL: Again, it wasn't very clearly delineated in the inclusion/exclusion criteria or in the presentation the following management, both short- and long-term, of autoimmune diseases and potential sequelae of these types of therapies, of activation of the immune system, both short- and long-term.

I think that would need to be carefully evaluated in the development of these trials and that data carefully collected so that we understand if there is an increased risk of other endocrinopathies or other autoimmune diseases.

DR. RAETZ: Elizabeth Raetz, University of Utah. I know that you mentioned that corticosteroid use would be an exclusion, but if patients are on the trial and they develop a need for steroids, I think that would be an important point to address, what would happen in that situation.

DR. MacDONALD: I also have concern that this is a unique population recovering from brain radiation, and the effect of this drug and how it may interact with healing was not addressed and how we would be able to, again, mitigate risk in this patient population in case there was an unknown adverse effect with that combination.

DR. PAPPO: Any other comments or questions before I summarize the discussion to the first question?

(No response.)

DR. PAPPO: So if I get this correctly, it is really not very clear how they are planning on using strategies to mitigate the possible side effects of this molecule, specifically cytokine

release syndrome. It is also known that the vast majority of the side effects occur within the first 24 hours, and it would be very helpful to know exactly what they plan to do within those first 24 hours, is it safe to treat these patients outpatient? Should they be observed inpatient?

The other question is whether this molecule gets into the brain and what are the potential consequences of that. It is important to clarify the exclusion criteria, particularly if a patient has been the recipient of a previous solid organ transplant and whether they are getting immunizations while in treatment or if they have received any immunizations recently.

Also, it is important to develop a strategy to monitor the short- and long-term toxicities and sequelae of this agent since very little is known, and only 30 adult patients have been treated to date. And the longest patient that has received this drug, if I remember correctly, was also 10 cycles.

Also, we once again need to clarify the

possible use of steroids while in trial if a patient develops a significant toxicity and also strategies to mitigate unknown adverse events that occur during the treatment with this drug.

Did I leave anything out?

DR. GORE: I think you mentioned prior solid organ transplant, and Dr. Mascarenhas was talking about prior stem cell transplant.

DR. MASCARENHAS: Both.

DR. GORE: Six, [inaudible - off mic].

DR. PAPPO: Thank you very much.

We will now proceed with -- let's go to the next question.

DR. DREZNER: Please consider the way in which CD40 agonistic antibodies can be used synergistically with current pediatric cancer treatment modalities, including cancer vaccines given their immunomodulatory effects.

DR. DuBOIS: Steve DuBois, Dana-Farber, Boston Children's. I was really struck by the pre-clinical data showing the combination, the significant enhancement of efficacy in pre-clinical

models with combination approaches and would really echo what others have said about trying to design a trial that more nimbly moves to a combination approach.

This is a population that often only can pursue one novel therapy at relapse or for DIPG at frontline. So I think hearing prolonged stable disease with monotherapy really and together with the pre-clinical data really argued to move very quickly to combo within the first trial, I would argue.

DR. WEIGEL: I would encourage the leveraging of the data that already exists with checkpoint inhibition and anti-CTLA for therapy in children, to leverage that, to quickly move to the combination strategy, as I think the data as presented suggests limited probably potential benefit of single-agent activity and the real potential, at least if the pre-clinical data is leveraged as combos.

DR. ARNDT: Again, I echo the recommendation to proceed with combination therapy soon. That

being said, one of the concerns with that would be what we've seen with checkpoint inhibitors, specifically pseudo-progression. And in patients with DIPG or other areas that are quite sensitive to tumor progression, to ask the sponsors to develop a plan of how to deal with that because it might sink a potentially useful combination therapy if these patients get into critical situations with pseudo-progression and brain swelling.

DR. MASCARENHAS: Just a comment on the strategy of DIPGs over here, that it's going to be used post-radiation is I think unique and novel, and actually might be potentially beneficial rather than waiting for them to progress and need steroid therapy; and again, to urge movement to combination trials.

The example data in the adult populations who have benefitted particularly in melanoma, those who respond actually tend to respond better. Even single agents respond better to multi-agent therapy. So even with a potential of stable disease, moving ahead to combination therapy based

on this really impressive pre-clinical data is something which should be kept in mind.

DR. TRIFAN: Yes. I'm usually not a proponent of moving rapidly to combinations without having some demonstrated single-agent efficacy. However, I do agree in this case, given the pre-clinical data, that really does demonstrate significant synergy. But I would just caution about moving too rapidly when we still don't know what the optimum dose and schedule is.

So we just have to keep that in mind before jumping on a combination bandwagon.

DR. WEIGEL: Greg just got back to the point I was going to clarify. I think all of the combination enthusiasm for me is predicated on knowing what we are taking forward in the pediatric population is likely to be the optimal dose and schedule. And I think that question remains for me based on the data presented today.

DR. PAPPO: Greg?

DR. REAMAN: I'll just make one more or ask -- maybe it's too late to ask a question. But

I think one other therapy that we ought to be thinking about here would be cell-based therapies which are in fact being developed for primary CNS tumors. So is there an opportunity for combination of CD40 agonists with cell-based therapies also?

DR. PAPPO: Any other questions or comments?

(No response.)

DR. PAPPO: So I will try to summarize the comments. The overwhelming majority of the comments revolved around moving relatively quickly with a trial that uses combination therapy, but also we need to be cautious. We need to identify the optimal dose and schedule of this single agent prior to jumping into combinations, but everybody feels that it's important to combine it with checkpoint inhibitors, given the very dramatic data presented in pre-clinical models.

Also, there is a concern about the possibility of developing pseudo-progressions in patients with DIPG and to develop a mitigating strategy in the event this were to happen; how is this going to be handled.

As an example, also there is a concern, although this was not raised by the committee, of the development of radionecrosis. There were several abstracts or ASCOs showing that patients with metastatic melanoma who were treated with radiation therapy and received checkpoint inhibitor therapy , about 30 to 35 percent of them developed radionecrosis at a median time of about 9 months, so that is something that also we need to be very aware of.

Then the last comment was also to consider also the use of cell-based therapies in combination with this agent. The last comment I wanted to make is perhaps also to consider if you're going to use this agent in combination to consider other histologies. I still think that it would be worthwhile doing.

Are there any other comments or did I leave anything out?

(No response.)

DR. PAPPO: We will now move to question number 3.

DR. DREZNER: Please consider the importance of evaluating the correlation of tumor cells, CD40 expression, and antigen burden in various pediatric solid tumors with the activity of CD40 agonistic antibodies and whether the combined use of CD40 agonistic antibodies with immune checkpoint inhibitors may prove to be useful in tumors with lower CD40 expression and/or antigen burden.

DR. PAPPO: Lia?

DR. GORE: I think the ultimate success or failure of this attempted pediatric exploration is the strength of your biologic correlative studies, which is hard to do in patients with DIPG certainly. But the data are really going to hinge on whether or not you understand why this does or doesn't work.

So it would be critical to evaluate cell expression, circulating tumor DNA, a variety of other sources, and what the activity level is potentially on peripheral blood mononuclear cells, on T cell populations, B cell aplasia as a surrogate marker.

There are a number of ways to approach this, but this to me is the critical question whether or not you have prolongation of survival in these patients; whether or not you understand the abscopal effect.

What the outcome of this trial will be really hinges to me on the strength of your correlative studies, and I would certainly not underestimate the importance of that to the sponsor.

DR. PAPPO: Greg?

DR. REAMAN: I would just say that this reinforces Dr. Pappo's last comment because, whereas I think we're all in complete agreement that the unmet clinical need in DIPG is real and the approach to novel interventions is laudatory, I think there are real opportunities for other pediatric solid tumors in which the biology and evaluation of the tumor microenvironment could really be more easily explored to really understand what's happening here, both as single monotherapy as well as combination therapy.

So I would strongly consider or strongly recommend that there be consideration of other pediatric solid tumors.

DR. PAPPO: Tobey?

DR. MacDONALD: Just to mention the other side, again, of the coin, very encouraged and enthusiastic by the pre-clinical data, especially the combination. However, as a pediatric neurooncologist, I'd feel much better about it should they show similar data in a pediatric brain tumor relevant model which exists. Then also, if these models are used, these afford a better chance of exploring the surrogate markers and what's going on in terms of efficacy, or lack thereof, before exploring.

So I would flip it the other way. Rather than focus on the brain tumor population, maybe focus on the non-brain tumor population to start with unless there's pediatric brain tumor model data similar for the solid tumors.

DR. PAPPO: Carola?

DR. ARNDT: In terms of the pediatric solid

tumors, I would agree with that. And I would be very interested to learn whether a tumor that actually is CD40 positive -- and I think Tobey or somebody mentioned that earlier.

Is that going to be a sync that absorbs this molecule and therefore decreases its efficacy? Is this molecule going to be a tumor promoter or a tumor antagonist? And what's the correlation between response and CD40 positivity of the target tumor?

DR. GORLICK: Richard Gorlick. Although they don't have a responder hypothesis, the use of solid tumors in pediatrics, other than CNS tumors, will permit the type of studies that are already likely happening in the context of the other malignancies they're studying.

So in the context of melanoma, we already know there's extensive literature supporting immune checkpoint expression has relevance to the response of that category. Obviously, if you were looking for combination studies, you'd start using those type of things to tease out efficacy.

We know in the context of pediatric solid tumors that some of the immune checkpoint inhibitors, even without this agent, are approaching some sort of efficacy signal, so presumably this may be able to get it over the threshold in combination.

I strongly support that correlative studies outside of the context of the CNS may allow us getting additional information to understand how to move this forward.

MS. LUDWINSKI: Donna Ludwinski, Solving Kids' Cancer. I also would be interested to see if this combination approach would work in other pediatric solid tumors like neuroblastoma, where there is an anti-GP2 antibody that's known to be effective, in addition to the checkpoint inhibitors. Thanks.

DR. WEIGEL: Brenda Weigel. In addition, I think to the biology and efficacy questions that exploring this in other solid tumors affords, it also affords a much more detailed exploration of toxicities. Especially given some of the special

toxicity considerations we've already mentioned in the CNS tumor population, we would be able to have a much greater understanding of that in a non-CNS population.

DR. PAPPO: Any other questions or comments regarding this question?

(No response.)

DR. PAPPO: I'm going to try to summarize what we discussed. So overwhelmingly, everybody believes that we need to have a strategy to have robust biological correlative studies to identify the responders and non-responders.

For example, other surrogate markers could be circulating tumor DNA, cell expression assays, peripheral mononuclear cells, T cells, the significance of B cell aplasia in these patients, perhaps the correlation with CD40 positivity in tumors.

The second point is also to try to expand the use of this drug or this drug with combination checkpoint inhibitors in other pediatric solid tumors. And that would allow expanding the

exploration of those biological correlative studies, which might be much easier, for example, in a PDX or in an osteosarcoma during biopsy in a patient with a DIPG. This would also allow us to better define the toxicity profile of these agents.

There is also interest perhaps in looking at specific subtypes of solid tumors, for example neuroblastoma, in which there's already immunotherapy with GD2, and whether there would be some kind of potential combination with this agent or other checkpoint inhibitors.

The final question that I wanted to add to this is whether this could be also an opportunity to try to better define the role of T cell exhaustion when you're using this CD40 agonist, and what is the role of adding the checkpoint inhibitors and how do you reverse that; because it's unclear to me, if the T cells are already exhausted, if you just keep producing more with the CD40 and PD-L1 is already being expressed, I'm not sure exactly how effective they're going to be. Perhaps that is the reason why you're only seeing

stable diseases here because in the pre-clinical models you didn't see a very robust response.

Did I miss anything or do you want to add anything?

(No response.)

Adjournment

DR. PAPPO: So we will now take about a 30-minute break. We're going to reconvene at 10:10. So thank you very much, and we'll see you in a little bit.

(Whereupon, at 9:41 a.m., the session was adjourned.)