FOOD AND DRUG ADMINISTRATION

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PEDIATRIC ONCOLOGY SUBCOMMITTEE OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

(pedsODAC)

Virtual Meeting

Wednesday, May 22, 2024

10:00 a.m. to 3:31 p.m.

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

P R O C E E D I N G S

(10:00 a.m.)

Call to Order

DR. PAPPO: Good morning, and welcome. It's hard to believe that it's been a year since we last met, and it's great to see all of you. I would first like to remind everyone to please mute your line when you are not speaking. For media and press, the FDA press contact is Lauren-Jei McCarthy. Her e-mail is currently displayed.

My name is Dr. Alberto Pappo, and I will be chairing this meeting. I will now call the May 22, 2024 Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee meeting to order. Dr. Jessica Seo is the acting designated federal officer for this meeting and will begin with introductions.

Introduction of Subcommittee

DR. SEO: Thank you, Dr. Pappo.

Good morning. My name is Jessica Seo, and I am the acting designated federal officer for this meeting. When I call your name, please introduce

yourself by stating your name and affiliation. We'll first begin with the standing members of the ODAC, starting with Dr. Pappo.

DR. PAPPO: Good morning. I'm Alberto Pappo. I'm a pediatric oncologist, and I'm the chair of the Pediatric Oncology Subcommittee of the Oncologic Drug Advisory Committee.

DR. SEO: Thank you.

Next is our non-voting ODAC member, Dr. Frenkl.

DR. FRENKL: Hello. Tara Frenkl. I'm the Head of Oncology Development at Bayer.

DR. SEO: Thank you. We'll now move to introduce our temporary voting members, starting with Dr. Desai.

DR. DESAI: Hello. My name is Ami Desai, and I'm a pediatric oncologist at the University of Chicago.

DR. SEO: Thank you.

Next is Dr. Gore. Dr. Gore, please unmute.

DR. GORE: Good morning. I'm Lia Gore. I'm a pediatric oncologist at University of Colorado

and Children's Hospital in Denver.

DR. SEO: Thank you.

Next, we have Dr. Gorlick.

DR. GORLICK: Hello. I'm Rich Gorlick. I'm a pediatric oncologist. I'm at MD Anderson Cancer Center in Houston, Texas.

DR. SEO: Thank you.

And we have Dr. Laetsch.

DR. LAETSCH: Hi. Good morning. I'm Ted Laetsch, a pediatric oncologist at the Children's Hospital of Philadelphia and University of Pennsylvania.

DR. SEO: Thank you.

Next is Ms. Ludwinski.

MS. LUDWINSKI: Hi. I'm Donna Ludwinski. I'm a patient representative with Solving Kids' Cancer in New York and London.

DR. SEO: Thank you.

Next is Dr. Mody.

DR. MODY: Good morning, everybody. My name is Rajen Mody. I'm a pediatric oncologist at Mott Children's Hospital and University of Michigan.

DR. SEO: Thank you.

And we have Dr. Parsons.

DR. PARSONS: Good morning. My name is Donald Will Parsons. I'm a pediatric oncologist at Texas Children's Hospital and Baylor College of Medicine in Houston, Texas.

DR. SEO: Thank you.

Next is Dr. Raetz.

DR. RAETZ: Good morning. I'm Elizabeth Raetz, a pediatric oncologist at NYU.

DR. SEO: Thank you.

We also have Dr. Seibel.

DR. SEIBEL: Good morning. I'm Nita Seibel, a pediatric oncologist here at the Clinical Investigations Branch of the NCI.

DR. SEO: Thank you.

Next is Dr. Shah.

DR. SHAH: Hi. I'm Nirali Shah, a pediatric oncologist in the Pediatric Oncology Branch of the National Cancer Institute.

DR. SEO: Thank you.

And Dr. Smith?

DR. SMITH: Yes. Good morning. Good afternoon to those participating from Europe. I'm Malcolm Smith. I'm a pediatric oncologist in the Clinical Investigations Branch, Cancer Therapy Evaluation Program of the National Cancer Institute.

DR. SEO: Thank you.

And we have Dr. Unguru.

DR. UNGURU: Good morning. Yoram Unguru. I'm a pediatric oncologist at Sinai Hospital in Baltimore and also Bioethics.

DR. SEO: Thank you.

We'll now move to introduce our FDA participants, beginning with Dr. Pazdur.

DR. PAZDUR: Hi. Rick Pazdur. I am a medical oncologist, and I am the Director of the Oncology Center of Excellence at the FDA.

DR. SEO: Thank you.

We also have Dr. Donoghue.

DR. DONOGHUE: Good morning, and good afternoon, everyone. My name is Martha Donoghue. I'm a pediatric oncologist, and I am the Associate

Director for Pediatric Oncology and Rare Cancers in the Oncology Center of Excellence at the FDA.

DR. SEO: Thank you.

Next is Dr. Drezner.

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

DR. SEO: Thank you.

And Dr. Seddiq.

DR. SEDDIQ: Good morning, everyone. My name is Marjilla Seddiq. I'm a pediatric oncologist and clinical reviewer in the Division of Oncology 2 at the FDA.

DR. SEO: Thank you.

And finally, Dr. Vatsan.

DR. VATSAN: Good morning. I'm Ramjay Vatsan. I'm an associate director in the CMC Office of Gene Therapy in CBER.

DR. SEO: Thank you, all, and I'll return the floor to you, Dr. Pappo.

DR. PAPPO: Thank you very much, Jessica.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of those 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 meetings. We are aware that members of the media are anxious to speak with FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you

very much.

Dr. Seo will read the Conflict of Interest Statement for this meeting.

Conflict of Interest Statement

DR. SEO: Thank you, Dr. Pappo.

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 subcommittee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and

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

Related to the discussions of today's meeting, members and temporary voting members of this subcommittee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants,

CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves amendments made by Section 504 of the 2017 FDA Reauthorization Act to Section 505B of the Federal Food, Drug, and Cosmetics Act, 21 U.S.C. Section 355c, which required, for original applications submitted on or after August 18, 2020, pediatric investigations of certain targeted cancer drugs with new active ingredients, based on molecular mechanism of action rather than clinical indication. The subcommittee will discuss perspectives relating to implementation of this legislation and its impact on pediatric cancer drug development to date. This is a particular matters meeting during which general issues will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the subcommittee members and temporary voting numbers, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing

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

With respect to FDA's invited industry representative, we would like to disclose that Dr. Tara Frenkl is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Frenkl's role at this meeting is to represent industry in general and not any particular company. Dr. Frenkl is employed by Bayer Pharmaceuticals.

With regard to FDA's guest speakers, the agency has determined that the information to be provided by these speakers is essential. The following guest speaker has reported an interest, which is being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speaker. Ms. Ruchi Gupta has acknowledged that as a full-time employee of Roche-Genentech, she has Roche stocks. As guest speakers, Ms. Gupta and Drs. Dominik Karres; Pamela Kearns; Maria Sheean; and Brenda Weigel will not

participate in subcommittee deliberations, nor will they vote.

We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the subcommittee of any financial relationships that they may have regarding the topic that could be affected by the subcommittee's discussion.

Thank you, and I'll return the floor to you, Dr. Pappo.

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

We will now proceed with FDA introductory remarks from Dr. Nicole Drezner.

Introductory Remarks - Nicole Drezner

DR. DREZNER: Thank you, and good morning. My name is Nicole Drezner. I'm a pediatric oncologist and the Deputy Director of the Division

of Oncology 2 at the FDA. I would like to welcome you and thank you for your participation in today's discussion of the impact of the 2017 FDA Reauthorization Act, or FDARA, amendments to the Pediatric Research Equity Act, or PREA, on the field of pediatric oncology to date. I would like to especially acknowledge and welcome our guest speakers, including our colleagues at the Paediatric Medicines Office at the European Medicines Agency, as well as pediatric oncology representative from academic medicine and industry, whom you will hear from later this morning.

We are eager to hear discussion on the impact of the 2017 FDARA legislation to date for new molecularly targeted drugs and biological products for pediatric patients; the role of proof-of-concept studies using relevant pediatric preclinical models; the role of international collaboration; and how coordinated approaches to the design and conduct of molecularly targeted pediatric cancer investigations can be best achieved.

You will first hear from my FDA colleagues Dr. Seddiq and Vatsan, followed by presentations from the EMA's Dr. Karres and Dr. Sheean. After you have the opportunity to ask clarifying questions, Dr. Weigel, Ms. Gupta, and Dr. Kearns will provide their assessments of FDARA's impact from the perspectives of U.S. cooperative groups, industry, and European academic pediatric oncology, respectively. These speakers will answer clarifying questions, and then you will have the opportunity to discuss the topics as a committee.

The intent of the pediatric study plan as required under PREA is to identify necessary pediatric studies early in drug development and to begin planning for these studies. Under the 2017 FDARA amendments to PREA, the FDA can require evaluation of certain novel targeted therapies that may potentially address an unmet medical need in pediatric patients with cancer.

Specifically, as you will hear about in greater detail in the main FDA presentation, if an initial NDA or BLA is for a new active ingredient

that is intended for the treatment of an adult cancer and directed at a molecular target FDA determines to be substantially relevant to the growth or progression of a pediatric cancer, reports on the molecularly targeted pediatric cancer investigation must be submitted with the marketing application, unless the required investigations are waived or deferred.

Given this mandate, initial pediatric study plans, or IPSPs, preparation often requires collaboration between the FDA and drug sponsors, as well as with relevant stakeholders, to ensure that the pediatric studies outlined in IPSPs are feasible with respect to patient selection, and dose, and trial design. Early consideration should be given to preclinical proof-of-concept studies in pediatric nonclinical investigations for new molecularly targeted drugs.

When evaluating the sponsor's proposed pediatric study plan, the FDA considers all the presented scientific support for the specific pediatric investigations, including applicable

adult clinical and nonclinical data and nonclinical proof-of-concept data in relevant pediatric models that should be described within the IPSP. Information provided by sponsors on input they have received from thought leaders is also valuable. FDA reviewers make an independent assessment of the potential for benefit of the targeted drug in the context of the pediatric oncology drug development landscape.

Through pediatric study plan development, discussions and input from all stakeholders are vital to optimize the use of existing resources and to promote efficient, timely development of new drugs for pediatric patients with cancer. This slide lists several means through which regulators, industry and academia, and patient advocates regularly interact to ensure that FDA decisions for drug development, for rare molecularly defined subgroups of pediatric patients with cancer, reflects community input and the available science. Your participation in this pediatric oncology subcommittee of the ODAC provides one valuable

opportunity for collaboration through today's discussion and conclusions.

Today, we will ask you to focus your discussion on three main questions: the first, describing your perspectives on how the 2017 FDARA amendments to PREA are impacting the pediatric oncology ecosystem to date; the second on considerations related to conduct of nonclinical proof-of-concept studies prior to initiating a molecularly targeted pediatric cancer investigation; and the third, on the role of international collaboration in the efficient development of new therapies for pediatric patients with cancer.

As you will hear in the FDA presentation to follow my remarks, early indicators suggest that FDARA is making a positive impact on pediatric oncology drug development; however, we are still faced with challenges to optimally leverage this legislation to enhance efficiency and reduce duplication of studies. To achieve this end, effective and consistent communication among

stakeholders is critical. Thank you, and I look forward to the discussion.

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

Now, we will proceed with the FDA presentation, starting with Dr. Marjilla Seddiq.

FDA Presentation - Marjilla Seddiq

DR. SEDDIQ: Good morning. My name is Marjilla Seddiq, and I'm a pediatric oncologist and clinical reviewer in the Division of Oncology 2. Today, my colleague, Dr. Ramjay Vatsan, and I will be discussing perspectives on implementation of the 2017 FDARA amendments to the Pediatric Research Equity Act.

I will lead off with the high-level overview of the legislative and regulatory landscape impacting pediatric drug development. Next, I will discuss which drug and biological products are subject to FDARA amended PREA requirements, which I will refer to as FDARA for brevity during much of the talk. Dr. Vatsan will then present our current thinking with respect to identifying which cellular

and gene therapy products are considered targeted therapies, and therefore potentially subject to FDARA requirements.

I will describe the factors we consider when determining whether to require pediatric studies of targeted therapies under FDARA and the information and stakeholder interactions that are crucial to our decision-making process. Lastly, I will present some results of analyses attempting to provide an early assessment of FDARA's impact to date and discuss future steps to better optimize our use of FDARA to promote development of new safe and effective drugs for pediatric patients with cancer.

As summarized on the slide, over time, there have been several key legislative acts implemented to encourage and increase investigation of drugs and biological products in children. For brevity, I will refer to drugs and biologics as drugs.

Much of the early legislation was passed in response to products that were found to cause harm to children, and therefore were primarily designed

to protect children from potential risks of clinical trials. In contrast, later legislation was implemented to encourage or require pediatric investigations to help inform products labeling with the ultimate goal of making more new treatments available to pediatric patients.

In this talk, I will primarily focus upon the last two pieces of legislation highlighted in red that are relevant to FDA's authority to require studies to be conducted in pediatric patients, the Pediatric Research Equity Act, or PREA, and the FDA Reauthorization Act or FDARA. I will also briefly discuss the incentive program for pediatric development under the Best Pharmaceuticals for Children Act or BPCA.

Our legislation provides two primary mechanisms, a voluntary incentive program under the BPCA and requirements for pediatric studies under PREA, to promote development of drugs that are being developed for treatment of adult cancers in pediatric patients as well.

BPCA is a voluntary program that provides

financial incentives to sponsors who conduct pediatric studies under a pediatric written request. First, sponsors complete a proposed pediatric study request, or PPSR, which includes a rationale for pediatric studies to be included or conducted, detailed study designs, and a plan for age-appropriate formulation development.

The FDA reviews the PPSR and may issue a written request, which formally requests conduct and submission of reports from these pediatric studies, along with proposed changes to product labeling based on these studies. FDA can also issue a written request for pediatric studies without a PPSR. Applicants who fulfill requirements of the written request are eligible to receive an additional six months of exclusivity, which attaches to any outstanding marketing intent and exclusivity for the drug.

I will next turn to the provisions under the Pediatric Research Equity Act, or PREA, which was enacted to complement the incentive mechanisms provided by BPCA by requiring sponsors to assess

the safety and efficacy of new drugs in pediatric patients prior to the submission of a marketing application seeking a new indication, new active ingredient, new dosage form, new dose regimen, or new route of administration, unless the requirement is waived or deferred.

An initial pediatric study plan, or IPSP, must be submitted early in development, in general, no later than 60 days from the end of a phase 2 meeting. It should include a description of the planned pediatric studies, pediatric formulations if needed, and a timeline for development. The intent of the pediatric study plan is to encourage sponsors to identify pediatric studies as early as possible in product development.

Although both BPCA and PREA initiatives have promoted drug development for pediatric patients overall, PREA had little to no effect in pediatric oncology because the mandate was linked to the adult indication being sought, and pediatrics are largely distinct from adult cancers. Additionally, the original legislation provided for exemption of

the requirement for drugs that received orphan designation.

However, in 2017, the FDA Reauthorization Act, or FDARA, amendments to PREA, also commonly referred to as the Research to Accelerate Cures and Equity Act, also known as the RACE Act, was passed. This gave FDA the authority to require evaluation of new molecularly targeted drugs and biologics intended for the treatment of adult cancers and directed at a molecular target substantially relevant to the growth or progression of a pediatric cancer.

After August 18, 2022, sponsors submitting an original NDA or BLA containing a new active ingredient that is directed against a target, that is substantially relevant to one or more pediatric cancers, need to have an agreed IPSP that addresses the requirement for an investigation in pediatric patients.

To summarize, FDARA created a mechanism to require evaluation of certain novel targeted therapies in pediatric patients with cancer and to

submit the reports of these investigations to the FDA. The FDARA requirements for cancer drugs directed at relevant molecular targets apply even if the drug is for an adult indication that has received orphan designation. Additionally, FDARA mandated the FDA to establish, publish, and regularly update a list of molecular targets considered to be relevant and a separate list of molecular targets that are considered non-relevant to pediatric cancers.

Next, I will give an overview of how we determine which products are subject to FDARA requirements and how the FDARA provisions of PREA are applied to molecularly targeted drugs and biologics. Dr. Vatsan will also describe the more complex considerations for cell and gene therapy products.

If an initial NDA or BLA is for a new active ingredient, and the product that is the subject of the application is intended for treatment of an adult cancer and directed at a molecular target FDA determines to be substantially relevant to the

growth or progression of the pediatric cancer, reports on the molecularly targeted pediatric cancer investigation must be submitted with the marketing application, unless the required investigations are waived or deferred.

FDA in consultation with the National Cancer Institute and members of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee maintains a publicly accessible list of molecular targets that are considered substantially relevant to the growth or progression of a pediatric cancer and that may trigger the requirements for pediatric investigations. Of note, a molecular target to which a specific drug is directed is not required to be on the relevant molecular target list in order for FDA to require a clinical evaluation of the drug in the pediatric population.

There is also a separate list of molecular targets that are considered non-relevant to the growth or progression of pediatric cancers, such as androgen and estrogen receptors. You may recall

from the last slide that one of the criteria that are used to determine whether an application is subject to FDARA amendments to PREA is that the product has to be directed at a molecular target that FDA has determined is substantially relevant to the growth or progression of pediatric cancers.

Therefore, therapies directed against molecular targets that are on the non-relevant list are not subject to FDARA and would, therefore, either be exempt from PREA requirements due to orphan designation or would qualify for a full waiver of the requirement for a pediatric assessment. As part of the requirements of FDARA, FDA periodically updates the list of relevant and non-relevant molecular targets and encourages public comments on the published list.

So what exactly is the molecular target? FDA generally interprets a molecular target in cancer drug development as a molecule in human cells, either normal or cancer cells, that is intrinsically associated with a particular malignant disease process such as etiology,

progression, and/or drug resistance. For a molecule to be considered a molecular target, there should be evidence that addressing the molecule with a drug produces a measurable effect on a cancer in vivo or in vitro, which may translate clinically to a favorable objective change in the disease process.

Some examples of oncology products regulated by the Center for Drug Evaluation and Research, or CDER, include small molecules such as kinase inhibitors and biological products, including monoclonal antibodies. Generally, molecularly targeted therapy determinations for these types of products are relatively straightforward; however, products regulated by the Center for Biologics Evaluation and Research, or CBER, can be more complex. To provide a better understanding on the considerations related to the implementation of FDARA for cell and gene therapy products, I will now turn the presentation over to Dr. Vatsan.

FDA Presentation - Ramjay Vatsan

DR. VATSAN: Thank you, Dr. Seddiq.

Good morning. I'm Jay Vatsan. I'm a biologist-immunologist with expertise in antigen and gene delivery systems. I serve as an associate director in the CMC Office of Gene Therapy in CBER. We will now discuss the implications of molecularly targeted therapy determinations for cell and gene therapy, or CGT, products.

Determining which cell and gene therapy products address a molecular target -- that is, determining which products can be considered molecularly targeted therapies that may be subject to FDARA requirements -- can be more difficult than it is for a small molecule and antibody-based therapies.

As you can see from this slide, there is a wide array of cell and gene therapy products under development in oncology, and these products are often quite complex in terms of their composition and mode of action. The products range from nucleic acid-based therapies, to adeno-associated, virus-based therapies used in in vivo genome editing, to complex patient-specific new

antigen-based vector therapeutics, to cell and gene therapy-based therapies such as tumor-infiltrating lymphocyte therapies.

As Dr. Seddiq discussed, part of the decision-making process in determining which FDARA applies to a specific product development program is whether the product exerts its effect due to interaction with the molecular target. The complexity of determining which cell and gene therapy products are directed against molecular targets stems from the complexity of mechanism of action for many cellular and gene therapy products. In some cases, there may be incomplete knowledge of targets responsible for their anticancer activity or anticancer activity may result from multiple different pathways that are not well elucidated.

For example, oncolytic viruses can also induce immune responses through antigen spreading. Additionally, unlike a small molecule or monoclonal antibodies more direct interaction with the target that results in tumor cell killing, cell and gene therapy products may not directly interact with a

specific target or group of targets on a cancer cell, or on components of cancer microenvironment. As an example, some cancer vaccines work through generalized stimulation of host immune system, and tumor-infiltrating lymphocyte products, or TILs, may work through targets that have yet to be identified. Thus, decisions regarding cell and gene therapy products, molecular targeted therapies designation are often made on a case-by-case basis.

This slide provides examples of two cell and gene therapy products, one which is clearly a molecular targeted therapy, and therefore subject to FDARA provisions of PREA, and one which is not. The CAR T cell product depicted on the left has a clear target on cancer cell CD19, in this case, and the interaction between CAR T cell product, and the CD19 target is directly responsible for the anticancer effect of the product.

In contrast, the oncolytic viral product on the right side of the screen is not a molecularly targeted therapy because it may enter a cell through multiple pathways and cause tumor cell

lysis through a non-specific process of viral replication.

In the next few slides, I will provide some examples of cell and gene therapy products that are either, one, generally considered to be molecularly targeted therapies, or MTTs, generally not considered to be MTTs, and some cell and gene therapy products for which decisions regarding whether they are molecularly targeted therapies need to be made on a case-by-case basis.

Some cell and gene therapy products have a mechanism of action that involves binding to or interaction with one or more specific known or identifiable targets, and this specific interaction correlates with the product's activity or measurable effect on the cancer cell. Therefore, these types of cell and gene therapy products are generally considered molecularly targeted therapies.

Examples of such products are CAR T cells, or chimeric antigen receptor T cells; genome edited cells where specific genetic deletions in vivo or

in vitro can be introduced into tumor cells or cell-based products to induce a therapeutic effect; cancer vaccines against specific targets such as tumor-associated antigens, or TAAs, where the presence of a TAA is sufficient to infer potential therapeutic effect; and T cells that are directed at specific targeted antigens such as tumor-associated antigens.

Some cellular and gene therapy products are generally not considered to be molecular targeted therapies. Examples of such products include mesenchymal stromal cells, or MSCs; induced pluripotent stem cells; tissue engineered products, et cetera. These products, the postulated activity is not mediated through a specific molecular target, or targets, in either cancer or normal cells. New antigen vaccines also fall under this category, as they are patient specific and not an homogeneous product.

Tumor-associated, antigen-based vaccines are considered to be molecular targeted therapies because their mechanism of action relies on a fixed

set of antigens and the vaccine's antitumor activity results from the induction of immune responses to these TAAs that would be expected to have an antitumor effect on a population of patients with a targeted antigen on the tumor cells. On the other hand, new antigen-based cancer vaccines are not generally considered molecular targeted therapies because new antigens are produced by individual patient tumor cells, which are typically identified through extensive genomic analysis using bioinformatic computation.

Since the new antigen targets are different in each patient and the immunity induced to different new antigens are governed by the patient's immune system, the presence or absence of a new antigen identified in one patient's tumor and targeted by one vaccine may not be active in another patient. However, it's important to acknowledge that this field of science is still in its infancy, and as additional information is gathered, we may need to reevaluate our approach.

Some cell and gene therapy products whose

mechanism of action may depend on the manufacturing process or the proteins they express will require a case-by-case determination on whether the particular product is a molecularly targeted therapy. Examples of this category of products include oncolytics, tumor infiltrating lymphocytes, or TILS, new antigen-specific T cells.

In summary, determining which cell and gene therapy products are MTTs is not always straightforward. CGTs may work through mechanisms of action that are independent of specific targets on tumor cells. The mechanism of action may vary depending on the manufacturing process.

Importantly, when the MOA is not dependent on a specified target on cancer cells, the molecularly targeted therapy determinations are made on a case-by-case basis. When the mechanism of action is well understood and the function is attributable to specific target molecules on cancer cells, the MTT determination and assessment of potential relevance to pediatric cancers is less complicated. Early interactions with FDA can help

sponsors design their IPSPs for cellular and gene therapy products.

Now, Dr. Seddiq will give the rest of FDA's presentation. Thank you.

FDA Presentation - Marjilla Seddiq

DR. SEDDIQ: Thank you, Dr. Vatsan.

I will now move on to discuss implementation of FDARA requirements for new drugs with targets that are substantially relevant to pediatric cancers and how this process occurs through FDA's review of IPSPs.

Typically, pediatric cancer investigations, described in IPSPs for a new drug or combination, with a substantially relevant target are non-hypothesis testing, single-arm studies. These studies should evaluate dosing in all relevant pediatric age groups based on the pharmacokinetics, safety, and provide an assessment of preliminary efficacy. If the required study, or studies, demonstrate sufficient early evidence of anticancer activity, the FDA may consider issuing a pediatric written request under the Best Pharmaceuticals for

Children Act, or BPCA, for more definitive evaluation.

There are circumstances when a plan for deferral of a molecularly targeted pediatric cancer investigation may be appropriate. FDA may agree to a sponsor's planned request for deferral if the product is ready for approval for use in adults before pediatric studies are completed, or if the pediatric study, or studies, should be delayed until additional safety or effectiveness data have been collected; for example, until sufficient preclinical data is generated to support proof of concept and the design of the pediatric study.

Just as there are certain circumstances where a deferral may be appropriate, it is also possible for FDA to grant a full or partial waiver, as appropriate, of the requirement to submit reports on the pediatric investigation of a molecularly targeted therapy even when the drug is directed against a relevant target.

Waivers may be requested if there is evidence that strongly suggests that necessary

studies are impossible or highly impracticable if the product would be ineffective or unsafe in children; if the product does not represent a meaningful benefit over existing therapies for pediatric patients and is not likely to be used by a substantial number of patients in that age group; or if reasonable attempts to make a pediatric formulation for that age group have failed. It is important to note that final decisions and agreement to plans for waiver and deferrals are made at the time of the NDA or BLA approval.

In adult oncology drug development, it is not uncommon for there to be multiple drugs belonging to the same class and directed against the same molecular target. This often happens in a pattern where after the innovator product shows success in the treatment of a particular adult cancer, subsequent products follow that often have activity that is comparable to the innovator product.

Recognizing that the rarity of pediatric cancers may preclude the feasibility of

investigation of multiple same-in-class products, FDA may consider granting a waiver for a same-in-class product under specific circumstances as outlined on this slide. Examples of same-in-class products for which we have typically agreed to plans for waivers include PD1 and PD-L1 axis inhibitors, EGFR inhibitors, and anti-CD20 antibody directed agents.

In May 2022, a pediatric ODAC meeting was held in which the subcommittee discussed the development of a conceptual framework that would inform FDA decision making regarding FDARA requirements for pediatric investigations of molecularly targeted cancer drugs and biologics, when multiple same-in-class products are approved and/or in development.

Members of the subcommittee opined that studies of additional same-in-class agents may be warranted under certain circumstances and that several factors should be considered by FDA when deciding whether to require studies or waive the requirement. These factors include comparative

nonclinical and clinical data assessing safety and efficacy, cancer rarity and feasibility of investigations, the ability to address an unmet medical need, and other considerations such as availability of age-appropriate dosage formulations. The committee agreed that pediatric investigation of more than one product in the same class may be appropriate when specific product characteristics predict an improved benefit-risk profile over previously investigated drugs in that class.

Next, I will discuss the information FDA considers when making decisions regarding whether or not to require studies of molecularly targeted drugs and describe the FDA IPSP review process. As recommended in the FDA guidance on FDARA implementation, sponsors should make efforts to initiate planning and engage with pediatric oncology stakeholders early in the development timeline of a new molecularly targeted drug. Part of this planning is investigating proof of concept using appropriate pediatric nonclinical models

whenever possible.

Sponsors are encouraged to collaborate with academic and other investigators in pediatric nonclinical testing consortia such as the NCI-supported pediatric preclinical in vivo testing program, or PIVOT, and related activities and groups. Additionally, early advice meetings known as Type F meetings are a method for sponsors to receive FDA advice on the development of an IPSP for CDER products.

FDA also recommends collaboration with recognized subject matter experts, including those involved in clinical trial networks, academic investigators, and patient advocates early in the development of the IPSP, to develop an appropriate clinical rationale and scientifically rigorous study design.

Given the rarity of pediatric cancers, it is imperative that FDA's decisions on whether to require pediatric cancer investigations reflect the needs and interests of the stakeholder community as much as possible and that required studies be

supported by sufficient scientific rationale. FDA carefully considers the totality of information submitted by the sponsor, and examples of the types of information that FDA considers important for decision making are listed on the slide.

These include a systematic review of available evidence supporting target relevance to pediatric cancers, such as through public genomic databases or literature; clinical and nonclinical data for the drug in adults; available proof-of-concept information in relevant pediatric cell lines and in vivo models; a summary of the current landscape of clinical development pertinent to the drug class or proposed pediatric patient population for investigation; and last but not least, a summary of stakeholder perspectives regarding potential development of their drug, based on sponsor interactions with pediatric oncology thought leaders.

FDA review of IPSPs is a collaborative effort. The Oncology Center of Excellence, or OCE, has a subcommittee of the FDA Pediatric Review

Committee, which makes decisions on the plans described in IPSPs in conjunction with the Oncology Review Division that overseas development of the oncology product under review. This multidisciplinary committee consists of experts in pediatric oncology and general pediatrics; clinical pharmacology; genomics; nonclinical pharmacology/ toxicology; legal, ethics, and pediatric regulations.

The IPSP review process also includes discussion with representatives of the EMA and other health authorities during cluster calls if requested by the sponsor or at the initiative of either agency. In communication with the sponsor, FDA can amend agreed IPSPs based on evolving scientific, nonclinical, and clinical information.

FDA recognizes the importance of an international approach to pediatric cancer drug development. The next few slides will highlight some of FDA's international multi-stakeholder collaborative efforts as they relate to FDARA implementation. A multipronged approach is needed

to successfully address the challenges associated with drug development for pediatric cancers.

Because of the limited number of patients diagnosed with pediatric malignancies who may be eligible to enroll in clinical trials, particularly with the subdivision of pediatric cancers into smaller subsets based on tumor molecular characteristics, international multi-stakeholder collaboration, including with patient advocates, to facilitate the conduct of global pediatric clinical trials has become increasingly important. Prioritization of drugs of interest, in general, especially for drugs of the same class, requires global collaboration to prevent duplication of studies and competition for scarce patients.

EMA and FDA collaborate in many ways to facilitate alignment, whenever possible, in pediatric programs in oncology. With FDARA, timelines for IPSPs and pediatric investigation plans, or PIPs, from the EMA are more closely aligned. To the extent possible, new PIPs and IPSPs should be submitted simultaneously, or at

least as contemporaneously as possible, in order to facilitate alignment, and approaches, and advice between the two agencies.

Pediatric cluster meetings are conducted under a confidentiality agreement and generally involve information exchange and discussion of pediatric clinical development of specific products, safety concerns, or general scientific issues with participating countries. Following a cluster call regarding a specific product, FDA often issues a common commentary to the sponsor for that product, which summarizes the discussion.

The FDA also hosts mini symposia with external constituents, often including international regulators to discuss disease-specific research strategies without discussing individual drug development programs. Lastly, representatives of the FDA and EMA are often included in pediatric oncology-related discussions coordinated by the other agency, with permission of the participating sponsor.

In addition to the efforts already

mentioned, FDA encourages participation in international multi-stakeholder meetings such as the pediatric strategy forums organized by the ACCELERATE platform, where academic investigators, industry, patient advocates, and regulatory agencies share and discuss non-proprietary information and to inform pediatric drug development strategies. FDA also hosts listening sessions with patient advocates and representatives.

Project Community is a public health outreach initiative established by the FDA Oncology Center of Excellence for patients living with cancer, survivors, advocates, families, and people living in underserved urban and rural communities who are at greater cancer risk.

Additionally, over the past few years, the Foundation for the National Institutes of Health, FNIH, has organized and hosted quarterly international multi-stakeholder meetings comprising of patient advocates, investigator scientists, pharmaceutical representatives, and members of the

FDA and EMA to identify pediatric oncology targets that should be prioritized for additional comprehensive preclinical testing. FNIH publishes publicly accessible summaries of that analysis that provided the foundation for discussion at these meetings and the level of stakeholder interest in dedicating resources to conducting additional preclinical studies of drugs directed at each target discussed.

In the final portion of the presentation, I will provide an early assessment of the impact of FDARA implementation to date, and then provide some final thoughts regarding how we can continue to work together to maximize the positive impacts of the FDARA legislation in pediatric oncology.

In 2023, the U.S. Government Accountability Office, or GAO, published a review of data provided by FDA, based on an analysis of 85 IPSPs for new molecularly targeted adult cancer drugs that FDA received, reviewed, and agreed to during the period from August 18, 2020, when FDARA was first implemented, through August 18, 2022. These data

were largely used to determine the number of pediatric cancer studies sponsors plan to conduct and the number expected to receive waivers, and how these would have compared with the number of pediatric studies required prior to FDARA implementation.

Of the 85 IPSPs that FDA agreed to during this time period, there were 32 agreed IPSPs that contained a plan for pediatric cancer investigation. As depicted on the left-hand side of the slide in pink, of the 32 agreed IPSPs during that time period that contained a plan for a pediatric cancer investigation, 25 would likely not have had a plan for pediatric study if FDARA had not been implemented due to orphan status or because the development program would have qualified for a waiver because the adult cancer for which the targeted drug was being developed occurs rarely, if ever, in pediatric patients. As seen on the right-hand side of the screen in green, only seven of the 32 IPSPs, or a little over 20 percent, would have contained a plan for a pediatric study

in the absence of FDARA amendments to PREA.

Based on the data analyzed in stakeholder interviews, the GAO concluded that early results indicate that the FDARA amendments to PREA under the RACE Act have contributed to an increase in the number of planned studies to test certain molecularly targeted drugs in pediatric patients, but that it was too soon to determine whether the RACE Act will increase the number of drugs approved to treat pediatric cancers.

In an updated FDA analysis, spanning from August 2020 to April 18th of this year, there were a total of 96 agreed IPSPs for new drugs that were directed at a substantially relevant target. FDA agreed to a planned request for a full waiver for 44 percent of these agreed IPSPs, and 56 percent contained a plan to conduct a new molecularly targeted pediatric cancer investigation.

Among the 54 agreed IPSPs that included a plan for a pediatric cancer investigation, the majority included a plan to request a partial waiver of the requirement to conduct a study in one

or more pediatric age groups, or a deferral submission of the reports of the molecularly targeted pediatric cancer investigation until after the adult marketing application was submitted, or both.

In the cases in which FDA agreed to a plan to request a partial waiver, it was generally because the pediatric cancer proposed for investigation did not occur in the very youngest subset of the population; for example, because the study would be conducted in a refractory population. In the cases in which a plan for deferral was agreed upon, the primary reasons were because data from the planned pediatric investigation would not be available when the adult application would be submitted or because additional clinical or nonclinical proof-of-concept information was needed to inform the future pediatric development program.

In summary, although FDA frequently agreed to initial pediatric study plans, that included a plan to request a partial waiver in one or more

pediatric age groups or deferral of submission of reports of a molecularly targeted pediatric investigation, over half of the agreed IPSPs for new drugs directed at a relevant target since FDARA implementation included plans to study the drug in pediatric patients.

Another way to assess the early impact of FDARA is by looking at the number of targeted drugs in oncology that were approved during the same time period and contained a requirement for conduct of a pediatric clinical trial. You will recall that prior to FDARA, there were very few PREA required studies. Between August 18, 2020 and April 18, 2024, the Office of Oncological Diseases approved 17 molecularly targeted therapies that included requirements for conduct of a clinical trial in pediatric patients with cancer. The majority of these 17 approved applications, or a little over 80 percent, had requirements for pediatric studies under FDARA. In most cases, FDA would not have had the authority to require a pediatric investigation in the absence of FDARA.

In contrast, three of the drug approvals were for applications that were subject to the original PREA provisions. Molecularly targeted pediatric cancer investigations are deferred pending availability of additional clinical data or data from proof-of-concept studies in relevant pediatric models for three targeted drugs that have postmarketing requirements, and 11 of the 17 targeted drugs have a partial waiver for the required study in one or more pediatric age group.

This figure provides additional details on the molecular targets and cancer types that postmarketing requirements, or PMRs, shown on the prior slide, have been issued for. As shown on the slide, PMRs for studies have been issued for both pediatric hematologic and solid tumor malignancies, and for drugs directed against a variety of targets. Of the pediatric studies required by a PMR to date, the majority have been in pediatric solid tumors or lymphomas.

Based on the FDA and GAO's analysis examining very early measures of the impact of

FDARA in pediatric oncology, it appears that since the implementation of FDARA in August 2020, there has been an increase in the number of planned studies to test certain molecularly targeted drugs in pediatric patients with cancer compared to what would have been expected prior to FDARA. However, given the amount of time needed to design and conduct clinical trials evaluating new drugs for the treatment of pediatric cancers, it is too early to determine the extent to which implementation of the FDARA provisions of PREA will advance the development of new treatments for pediatric cancers.

Continued focus on multi-stakeholder engagement and international collaboration is necessary to thoughtfully and fully leverage the potential of this legislation and facilitate timely investigation of the molecular targeted drugs that hold the most potential to result in a meaningful improvement over current standard of care for pediatric patients with cancer. FDA is committed to monitoring progress at pediatric investigations

required under FDARA.

Continued early and frequent stakeholder engagement and international collaboration is needed to maximize the positive impact of FDARA by ensuring the investigation of drugs that hold the most promise to improve the outcomes of pediatric patients with cancer is prioritized and to ensure that these drugs are studied in a timely and efficient manner. Additionally, as we gain more experience with FDARA and as scientific knowledge evolves, decision making should be continually reassessed to refine the implementation of FDARA and maximize the benefit of this legislation to pediatric patients with cancer.

This slide contains various links to resources such as the Oncology Center of Excellence; Pediatric Oncology Program webpage; FDA guidances; a database of approved drugs for pediatric cancers; molecular target list; and a database listing pediatric requests that have been issued. This slide contains important contact information for CBER.

Thank you for your attention today, and I would like to acknowledge all individuals on this slide who have contributed to this pediatric subcommittee of ODAC meeting. We are especially grateful to all the patients, family members, and caregivers for their participation in clinical trials and to all patient advocates and other stakeholders who work to improve care for pediatric patients with cancer.

DR. PAPPO: Thank you very much, Dr. Seddiq and Dr. Vatsan, for your excellent presentations.

We will now proceed with the first guest speaker presentation from Dr. Dominik Karres and Dr. Maria Sheean.

Guest Speaker Presentation - Dominik Karres

DR. KARRES: Thank you very much, Chair.

Good morning. Good afternoon. Thank you very much to FDA for the very kind invitation, giving us the opportunity to provide a European perspective on the complementary nature of U.S. and European regulations facilitating global pediatric drug development. This is a joint presentation

together with my colleague, Dr. Sheean, who will introduce herself later. My name is Dominik Karres, and I'm a scientific officer at the Pediatric Medicines Office in the evidence generation department at the EMA.

This is our usual disclaimer. Our presentation will have three parts. I will start with some background and general considerations and also looking into the future, then handing over to my colleague who will present additional reflections on approaches initiated at EMA towards more action development and anticipation of potential legislative changes in Europe before concluding.

I'm sure many of you are aware and familiar with the EU pediatric regulation, but to briefly recap, it's a system of obligations and rewards with the pediatric investigation plan being the research and development program consisting of the necessary quality, nonclinical -- including proof of concept as necessary -- and clinical development outlines needed to ensure evidence generation

sufficient for a marketing authorization.

The PIP is framed around the concept of the condition, taking the adult indication under development as the starting point; however, and Dr. Sheean will touch on that later, there's a proposal under the new pharmaceutical legislation currently under discussion in the European Union to take the product's modern mechanism of action into account.

Tools like deferrals, modifications, and waivers are in place, ensuring that those treatments that offer clinically meaningful benefits are developed and authorized for the right patients without unnecessary delay, with a PIP life-cycle approach to evidence supporting our decision making using our regulatory toolbox, allowing to refocus development efforts, based on emerging evidence and potential changing needs over time; and requiring context-specific discussions in an international multi-stakeholder setting, and we heard about that from our FDA colleagues, and I will come to that later tool.

The schematic circular overview on the left side of the slide really shows the challenges and context of an ecosystem with the requirement to develop addressing the clearly identified public health need, and addressing these challenges requires international regulatory collaboration between EMA and FDA, and other regulatory agencies. We continue to have this as a clear objective in mind to further strengthen these collaborations, also with the focus on the potential regulatory changes to come in Europe.

As mentioned on the previous slide, to allow refocusing development efforts based on emerging evidence over time, it needs international multi-stakeholder interactions, but also without regulators being part of such discussions. With what are now important cornerstones moving successfully through research and development to pivotal evidence, it's an enabling regulatory framework, appreciating the additional challenges when it comes to development discussions based on mode of actions, particularly related to what

constitutes sufficient proof of concept, but also in terms of moving forward certain products if there are other competing development efforts ongoing within the same population.

This requires an ability to using all evidence generated independent of who the sponsor is or was, and that is preclinical proof of concept, but also clinical trial data so that these data can inform regulatory decision making and serve regulatory requirements without the need to repeat certain studies; but that requires continuous exchange, and relevant capacities, and capabilities being in place, which is the case across all stakeholders, including regulators, and my colleague, Dr. Sheean, will touch on that part later.

The pediatric oncology drug development is and has to be conducted globally. This is widely acknowledged. It requires strong international regulatory collaboration also relating to what constitutes a relevant mode or mechanism of action. And despite the differences in regulations between

the U.S. and the European Union, given the grown and well-established regulatory collaboration between EMA and FDA -- and we heard from the FDA colleagues on that -- since implementation of the new U.S. legislation, we have observed an increase in voluntary PIPs, and that is indeed PIPs that take the molecular mechanism of action rather than the adult clinical indication as a starting point into account. We see this really as a very positive impact, indicating the complementary nature of both regulatory systems to build on.

From a European perspective, now and in the future, a regulatory framework should be predictable by fostering a research and development environment, allowing for evolution of scientific knowledge, and also in the context of the relevance of a product's mode and mechanism of action, a situation which most likely leads to growing a pipeline of products for consideration.

In order to identify and support completion of development efforts towards an indication for products likely to address existing unmet medical

needs and offering significant therapeutic benefit, there's the need to move from product to population-focused discussions, which is of particular relevance for multi-stakeholder interactions, and such population-focused discussions could be guided and framed by the following question, which is in line with wordings in the current European pediatric regulation, and that is, based on a product's mode of action, what is the target population for which the product is able to offer significant therapeutic benefits in the context of existing treatments and the wider research and development landscape such that development is feasible and generates meaningful evidence timely?

Such focus is important, particularly in context of modern mechanism of action based developments, as it really supports and underpins the understanding that choices must be made within the drug development ecosystem based on evidence, choices which we have mandated to facilitate, for example, which product, based on adequate

preclinical proof of concept, to move into an early phase development, but also which product in a given population to move forward into pivotal evidence generation, appreciating that all products with an identified mode of action will conclude successfully, leading to an indication, and emphasizing, really, the need for international cooperation and collaboration across all stakeholders, towards generating the necessary evidence to support adequate go/no-go decisions such that resources can be preserved, but mostly patients only enrolled in clinical trials with a high possibility of success.

I would like to conclude my part by emphasizing, again, the importance of multi-stakeholder interactions and internationally supporting facilitating meaningful development efforts now and in the future regulatory framework in Europe, potentially focused on mode of action based development, which needs moving from product to population-based and population-focused discussions, to really facilitating and enabling

choices to prioritize, supported by evidence with early regulatory interactions remaining key.

Also, to highlight in this context the importance of being able to utilize all the data evidence generated by academia -- that is preclinical data and data from academic-sponsored clinical trials -- such that these data can inform regulatory decision making and serve fulfilling regulatory requirements equally as possible, avoiding necessitating to repeat certain studies or not being able to conclude on benefit-risk at all; and challenging implementation of an authorized product into clinical care such that all patients, now and future ones, can benefit, but pointing also towards the need to establish regular transparent mechanisms of interaction between academia and regulators to be able to exchange; and sharing relevant information, something which we have started to initiate and are keen to further develop from our side, including and involving also FDA, while clearly acknowledging the necessary capacities and capabilities needing to be in place

here, too, as mentioned earlier.

With that said, I'm handing over to my colleague, Dr. Sheean, who will talk now about regulatory preparedness, including capacity and capability building in the context of potential upcoming European regulatory changes. Thank you very much.

Guest Speaker Presentation - Maria Sheean

DR. SHEEAN: Thank you very much, Dr. Karres.

My name is Maria Sheean. I'm a pediatric officer at the Pediatric Medicines Office at EMA, and I would like to add to what has been said, to our reflections, reflecting on future developments in the EU and to share our perspective, and also as scientific support to the nonclinical working party at EMA, and experts, delegates, from all over the EU and national competent authorities, dedicated to facilitating the assessment of nonclinical safety and efficacy of novel pediatric drugs, among other classes.

As mentioned before, we began reflecting on

the mode of action developments because of voluntary mode of action driven VIP applications that we have seen, but also in anticipation of the new pharmaceutical legislation in the EU, which is currently in preparation. The final wording of the legislation is not yet known, but as you can see from this excerpt from the explanatory memorandum of the EC legislative proposal, we anticipate that mode of action driven assessments will become more common, and that this will affect primarily the oncology space.

Although this was maybe not necessarily intentional, the regulatory landscape in Europe will mirror and complements the current situation in the U.S. In this more favorable regulatory landscape, the European regulators will be in a position to guide data generation, including proof-of-concept data and the overall development plan, which would be necessary to support marketing authorization applications.

The impact of these legislative changes is already felt, and we hope that it will result in an

increase in science-driven pediatric development and [indiscernible - 1:39:56] drugs. There is correspondingly a heightened need for thorough preclinical data, using better predictive models to develop drugs targeting mechanisms specific to pediatric malignancies.

Standard methodologies for the development of preclinical data packages necessary to inform clinical decisions do not exist, so discussions around the methodology are needed to allow for informed go/no-go decisions, and in pediatric oncology, they may be needed based largely on nonclinical data; hence, the need for better understanding of target relevance and proper proof-of-concept data. However, for the decision about the progression into clinical development and interdisciplinary discussion involving clinicians' insights into the disease in children, the unmet needs, and the flexibility of studies will be necessary.

In view of this need for nonclinical expertise, we began horizon scanning the space of

proof-of-concept research, and it's clear that the economic community already started building this capacity to address the need for nonclinical proof-of-concept data. For example, ITCC-P4 project, which was previously mentioned in one of FDA slides, was initiated as a public-private partnership in 2017 as part of the EU IMI2, with the goal to develop patient-specific clinical laboratory models for the most common high-risk childhood cancers that are currently undertreated.

Upon request, academic institutions, biotech, and pharmaceutical companies can access the comprehensive repertoire of over 400 fully-characterized pediatric tumor models for systematic efficacy testing, and we have recently engaged in discussions with P4 in order to exchange information on the actionability and relevance of molecular targets, and to help regulate and stay up to date with the current developments in the field. We are also pursuing other avenues and have involved other academics groups in our discussions.

So although there's a lack of standardized

methodology or development of nonclinical data packages necessary to evolve clinical development, the academic community has started building such standards, and this is one of the examples. The publication from 2021 shows an interest in the guidance on the minimal preclinical testing requirements, and we received such signals from industry asking for similar guidance. However, it is not our intention to come up with guideline documents and running the risk of becoming too rigid or quickly outdated in this fast-paced, scientific field, but to build our capacity and to reflect on the methodology necessary for a case-by-case, weight-of-evidence assessment and considering existing proof-of-concept data.

We also take note and observe the academic activities overseas. The NCI-supported Pediatric Preclinical In Vivo Testing program evaluates novel agents as well against genomically characterized childhood cancer models and builds upon more than 15 years of experience with the Pediatric Preclinical Testing program and the Pediatric

Preclinical Testing consortium, and has shown over the years that many agents that are effective for adult cancers have limited activity against pediatric preclinical models. To draw from this wealth of information, we are currently also making efforts to initiate interaction with pivotal programs, as well as to exchange learnings and involve them in the future, as needed.

So from this horizon scanning exercise, we have moved into our first steps to build the regulatory capacity in preparation for the mode of action driven PIP assessments, which will become more common in the future within the pharmaceutical legislation. Therefore, we organized a session during the nonclinical working party monthly meetings dedicated to proof-of-concept discussions, with a presence of a multidisciplinary group of colleagues, including also FDA observers, and we are hoping that we can use this opportunity of having observers to exchange and harmonize our approaches, given the global nature of these drug developments.

Our activities involving mode of action assessments will be also included in the nonclinical working party plan for 2025-2027, and this workplan will be sent for consultation with our stakeholders in the summer [indiscernible - 1:44:56] of this year. We have reached out to the industry on this topic, and we had initial discussion during the preclinical assessor meeting with FDA in February of this year, and it was met with interest, but also with scientific expectation for guidance documents.

Instead, we tried to encourage early interactions and cooperation on this, and what needs to be multi-stakeholder dialect, since everybody seems to be developing their own strategy for handling their go/no-go decisions, so we would like to converge here. We are therefore expecting that mode of action driven developments will be included as a topic in our future meetings for the stakeholders.

We have also initiated a dialogue with academics in dedicated meetings, and would

encourage any interested parties to get in touch with us directly or through an innovation task force meeting. Innovation task force, or ITF for short, is a very good platform to make your activities visible across the EU regulatory network and to engage in discussions about meeting scientific development with regulatory needs.

Finally, but not least, we have started attracting nonclinical and clinical experts from the European assessors network to create a drafting group of the nonclinical working party. The group has just been proposed and will be in charge of drafting a reflection paper on the mode of action driven assessments of pediatric oncology. We would like to work out a model for an improved process by which routine multi-stakeholder engagement and discussion will be encouraged. We would hope to include FDA and academics, as appropriate, in the preparation of this paper, and we would also cover in the same publication the methodology necessary for the mode of action driven assessments, which would likely utilize a weight-of-evidence approach

and involve nonclinical and clinical perspectives.

So with this, I've arrived at the conclusion in which I would like to reiterate that we've already seen cases of mode of action based developments in the EU, and we are also used to seeing interactions with the FDA, which inform us about what is happening overseas in this field, and we are highly motivated to build regulatory capacity to achieve consistency and high scientific value of our go and no-go decisions with regards to new pediatric drugs.

We are aware that the relative weight of nonclinical proof-of-concept data will be of greater importance, where extrapolation from adult data may be impossible because of distinct features of pediatric cancers or where we're typically dealing with very small populations. And hence, we're interested in building a network with academics who seem to be ahead of us in building capacity at the moment. We receive messages indicating an expectation of some form of guidance or minimum data requirement statements, but we see

this rather more as collaborative efforts in building weight-of-evidence methodology.

So we are intending to build capacity, and develop a dialogue, and retain dialogue with stakeholders, industry, regulators, academia, or partnerships such as ITCC-P4, so we are starting to routinely also involve colleagues with diverse expertise in our assessment meetings, colleagues with nonclinical and clinical expertise. And to reiterate, we have no plans for guidelines or minimum nonclinical requirements, but we do intend to work on a reflection paper to explain our collaborative approach further.

We also are looking forward to further our collaboration with FDA in view of the global nature of the developments in this space. And with these notes, I will end this presentation, and maybe we can go back to the next slide here that lists our acknowledgements.

We'd like to thank Karen van Malderen, who is the nonclinical working party vice-chair and the Belgian delegate to the pediatric committee; to

Ralph Bax, who's our head of the Pediatric Medicines Office; and to Franca Ligas and Giovanni Lesa, our colleagues and pediatric team who are involved in oncology product assessment and also facilitating FDA interactions to date. Thank you very much.

Clarifying Questions

DR. PAPPO: Thank you very much, Dr. Karres and Dr. Sheean, for your excellent presentation.

We will now take clarifying questions for the FDA and guest speakers who have presented thus far. Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again after you have asked your question.

When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank

you and end of your follow-up question with, "That is all for my questions," so we can move on for the next panel member.

We will start with questions, and so far, we will start with Dr. Seibel.

DR. SEIBEL: Hi. This is Nita Seibel from NCI, and I have a question directed at Dr. Seddiq. I was hoping that you could give us further information for follow-up on deferrals, and if there's a standard approach to how you follow up on those that have been granted a deferral, those drugs that have been granted a deferral.

DR. SEDDIQ: Thank you, Dr. Seibel, for that question. So plans for deferral, generally we follow up with the sponsors after the initial deferral was granted. I'm not sure if Dr. Donoghue or Dr. Drezner would like to add any additional information that's more specific to follow-up time period when a deferral is granted.

DR. DREZNER: Yes, sure. This is Nicole Drezner, the Deputy Director of Division of Oncology 2. Just to build on that, as you know,

there are a substantial number of plans for deferrals within the agreed IPSPs for molecularly targeted pediatric investigations, and generally, probably the most common reason or justification for many of the deferrals is that the design of the pediatric studies needs to be informed by additional proof-of-concept data from clinical trials in adults, or proof-of-concept data that may be taken from additional pediatric nonclinical studies in relevant pediatric cancer models. So that information is often needed to help to further refine the approach to the pediatric studies, such as which tumor types, which patient populations are going to benefit from the investigational targeted drug.

That's the most common reason that we issue or that we agree to a plan for a deferral. The intent of FDARA is not to delay the adult development, so often companies will be ready to indicate the application for the adult indication before they have completed the required proof-of-concept studies to determine which tumor

type or which pediatric tumor type they're going to be studying. So in that case, we issue a deferral and a postmarketing requirement.

DR. SEIBEL: So is there a follow-up, like a year later you go back to the company, or it's deferred, and you just wait for them to come back and respond? Is there any follow-up at a period of time later as to what's happening?

DR. DREZNER: Yes. So through postmarketing requirements, there's a mechanism for us to follow up on the status of the studies. And as part of IPSP, we have a timeline for when the studies are going to be completed. And I see that Dr. Donoghue also has her hand raised, so I will let you take that part of the question, but that is one of the ways that we follow up on postmarketing requirements.

DR. PAPPO: Dr. Donoghue, please go ahead.

DR. DONOGHUE: Hi, Dr. Seibel. Thank you so much for the question because it's actually a really important question that I think should be on the back of many of our minds, and is.

There are two parts to this question, I think. One part is thinking about plans for deferral that are in the IPSPs that we've agreed to, that we know contain a plan for pediatric study, but we've agreed with the planned request for a deferral of submission of the reports, of the pediatric study, to a certain time. So I think it's important to know that during the IPSP review and agreement process, these are the ultimate plans to request a deferral, but that actual request for deferral doesn't come in until the marketing application is submitted. So that's the first point.

I want to emphasize that -- although it's related to your question but not directly answering your question, which I'll get to -- during part of our IPSP review process, part of that is looking at a standard section of the IPSP that outlines the timeline, the estimated timeline, that it's going to take a sponsor to submit their protocol, initiate their study, complete the study, and submit a report for that molecularly targeted

investigation outlined in their IPSP. When we're reviewing IPSPs, we're looking at those timelines, and we're thinking carefully and conferring with the sponsor about what we think is a reasonable time frame for each of those milestones. So that even happens before the adult marketing application.

Switching gears, once the application is submitted, we agree upon a postmarketing requirement if the applicant hasn't submitted the reports of their pediatric investigation with that first marketing application in adults. So at that point in time, we have more definitive discussions if they haven't yet completed the study as to where that study is, and then following, we establish milestones for when they have to submit those study results. And then after that PMR is established, or the postmarketing requirement is established, we have a yearly review of the status of every single postmarketing requirement, not just the pediatric one, but part of our review includes the review of the progress of that PMR.

Having said that, I think you might be also asking about, if we agree upon an IPSP and the application hasn't been yet submitted for an adult program, what are we doing to monitor the progress of the pediatric studies if they're planned to start before the adult application? And I have to say that at this point in time, we don't have a standardized approach to that. That is something we're actively working on, however. We're creating a database that hopefully will be done by the end of this summer that will enable us to track these milestone dates so that we can, on a quarterly or six-month basis, review for all of the agreed IPSPs, have we hit upon a milestone date that should have already taken place; has that taken place; and if not, it will give us a mechanism to reach out to sponsors and track in more real time how the progress of that plan study is going.

So that's where things stand, and we're working on it, and I hope we can implement it before the end of the fiscal year.

DR. SEIBEL: Thank you.

DR. PAPPO: Thank you.

I'm going to allow three more questions. That will be Dr. Gorlick, myself, and Dr. Smith, in an attempt to try to keep us on time. And remember that we're going to have time to come back and circle back and ask additional questions after the open public hearing session before beginning the committee discussions.

Dr. Gorlick, you're next.

DR. GORLICK: Richard Gorlick at MD Anderson Cancer Center. I'm not sure who my question is directed to. It's whoever has the data.

The question I have is, is there any data that can be brought to bear on the extent to which harmonization between the EMA and the FDA is working thus far? And what I'm getting at specifically is, is there a sense that first-in-pediatric oncology trials are happening predominantly in Europe, or predominantly in North America, or predominantly as international studies? Thank you.

DR. DONOGHUE: Is it ok, Dr. Pappo, if I

start off with this?

DR. PAPPO: Yes, please do. Please do.

DR. DONOGHUE: Another excellent question. Thank you, Dr. Gorlick, for that.

I think the short answer to your question is that we don't have a formal established mechanism to do all of this tracking of clinical trials, and I think that is a very big, I hate to say the word "problem," but I think it's an issue, and I think we need to work on that.

We are working on it, through a variety of mechanisms, to try to make sure, at least when we're talking about our approach to pediatric studies that are under the PIP or IPSP process. We are actively working on a monthly basis, if not more often, with EMA to discuss individual development programs and make sure that we're aligning and promoting an international approach, frankly, to conducting studies intended to fulfill a requirement, because we should be thinking about pediatric patients with cancer throughout the world, not just in the U.S., not just in the EMA.

We've had some interesting discussions with other stakeholders outside of those two areas to try to figure out how we can leverage and help address the needs of all patients with cancer as we're thinking about these studies.

Having said that, we do have an obligation to be sure that the results are applicable to our patients in the U.S. as well, being a U.S. regulatory agency, so you're touching upon a very important topic. We get thinking about these issues and try to work more toward a better understanding of what's happening through a lot of these multi-stakeholder meetings, such as the ones that take place in ACCELERATE, but I think when we go back and think about the past, I don't think we as a community have done a great job at knowing what everybody's doing, thinking about it from a 20,000-foot view instead of our own individual country basis.

So that is something that I think we will be tracking as we're thinking about pediatric requirements here. And often, I will say, that

when we confer with sponsors about their programs, we are often asking, well, is this an international trial; is this going to be primarily in the U.S.? And encouraging whenever possible, opening up and casting a wide net because we have a very rare population that's getting even more rare, and equally important, though, is that we're not doing redundant trials and that we understand.

So I think we're certainly open to ideas and opinions, and I think that we'll get to that hopefully in the discussion section, things that you think that we, FDA, could do differently or better to work with the community and ways to try to track this better. Part of it's just too much information coming from different sources, and it's hard to figure out how to best aggregate it.

Sorry for the long-winded answer that didn't really answer your question totally, satisfactorily, probably, but that's my view of things at this point.

DR. PAPPO: We'll discuss it further.

DR. GORLICK: It did. Thank you, very

responsive.

DR. PAPPO: I had a question for Dr. Seddiq and a question for Dr. Sheean.

For Dr. Seddiq, is there any preliminary data from the RACE Act on the timeline for initiating a pediatric clinical trial when compared with when the first clinical trial was initiating adults? I mean, is there any data to suggest that we're shortening that time frame that Dr. Steve DuBois published several years ago; that it takes 6 and a half years for a first-in-pediatric clinical trial to open after the first adult trial, or is it too early to know?

DR. SEDDIQ: Thank you, Dr. Pappo, for that question. At this time, it's too early for us to be able to have that data, but it is also something that we'll start tracking with the database that we're working on, but it's too early at this time.

DR. PAPPO: Thank you very much.

And the question for Dr. Sheean is, can you give us a little more clarity on the interactions between the ITCC and the PIVOT? Do you all have

something similar to like cluster calls to know which agents are being investigated by each of the groups to be sure that there's not a lot of duplicative efforts, or this is just starting to happen?

DR. SHEEAN: Yes. Thank you very much for the question. It is indeed first steps we are taking at the moment in establishing the context. We are going to have an ITF meeting with P4 very shortly, so there we will discuss the first set of questions and discuss how to enhance our relationship. But indeed, we don't want to duplicate effort. It's more about establishing good channels of communication and access to information that may be helpful for both parties.

DR. PAPPO: Thank you very much.

Dr. Smith, you're next.

DR. SMITH: Okay. Thank you.

My question is for FDA. The question is, part of the task today is how do we think the IPSP process is going and the FDARA implementation? The kind of questions that I would want to know to say

it's going really well or has some issues are looking at IPSPs and what are the agents? What are the patient populations targeted? For IPSPs, are there competing agents being studied for that population? And then making assessments for, well, the trial that's requested can probably enroll well, and then being able to look at what trials have already been started based on IPSPs. How many are there? How are they enrolling? For the ones that aren't enrolling well, are they ever likely to succeed part of the issues?

And my question is, are we going to be able to get access to these types of data to evaluate how the IPSP process is being implemented and how it's going.

DR. DREZNER: Thanks, Dr. Smith. I can start off with that. I think that's a very important point, that it is important to know, when studies get off the ground, how they're enrolling and whether they are ultimately even bearing out. And I don't know that we have that type of information yet, but I think that that is certainly

something that we can begin to capture as pediatric studies move beyond preclinical data into the clinic and begin enrolling.

I think we provided some granularity in terms of the cancer types that have postmarketing requirements associated with them. In some cases, it's a little bit difficult to make that sort of determination because a lot of the early studies are for general solid tumors or something like that. But I do think that you've asked an important question, and one that we will think about.

Dr. Donoghue, did you want to address this as well?

DR. DONOGHUE: Sure. I'll attempt. I think, Dr. Smith, you are bringing up a lot of pieces of information that I think we would like to have as well. We won't have some of those pieces of information, I think, for a little bit more time, at least in a meaningful way, given the relatively small number of, I think, trials that have been initiated. At this point in time, it's

probably certainly fewer than 30 or 40, I think right now, as a result of FDARA; although I won't know for sure what those numbers are until we track this database that I mentioned in a more granular way.

To give a little bit more flavor for things -- and, again, it won't be as specific as I think we'd all like, and part of this is because, as you know, the initial pediatric study planned agreements are not public information. So, in many cases, these IPSPs are for targeted therapies, where there may only be a few, one or two, maybe even three, in a space that it's a little bit more difficult to get to that level without risking divulging some proprietary information. I think maybe in a different forum, we might be able to get to more granularity with the permission of sponsors, so that's something that we'll certainly be able to look into.

But I will mention, just to kind of give a little bit more granularity compared to what we've already given you, when thinking about our agreed

planned requests for full waivers, I would say over a quarter of them are for the PD-1- or PD-L1-directed agents, given the number of agents in that space. So a good proportion of those full waivers are for drugs for which we've seen an explosion of drugs in the same class, maybe not to the same extent, but at least more than one or two full waivers have been given to EGFR, HER2, VEGF, AKT, PI3K, c-MET directed agents, partly because of the discussions that we've had in the ACCELERATE platform, partly because of the data that has been accumulated over time, and partly due to maybe the extreme rarity of some pediatric patients that could benefit from certain of these classes of drugs.

I will say that in terms of the IPSPs that we've agreed to, roughly there's been a pretty even split between hematological cancers and solid tumors, and in general, as one would expect, the cancer types that are being studied in the hematological realm are more closely resembling the adult cancers under study, as one might expect.

For the solid tumors, there's much more heterogeneity in that looking at the targets for which there are planned studies, there's a lot of heterogeneity in those targets. There are like 54-ish agreed IPSPs that contain a plan for a study. They reflect about 50, or maybe even a little bit more than 50, different targets or target combinations.

So there is some redundancy among the targets that are being studied, but not a lot. And I do think that we'll over time be able to track, and I think it's very important for us to track, actually, the progress of the studies that we're requiring or planning, or the studies for which there are firm plans under IPSP so that we can monitor the progress of the studies if we're having accrual problems; because the last thing I think we would really want to do is have an unintended consequence of spurring too much activity in an inefficient way that ultimately might result in the abandoning of clinical trials and wasted resources.

I hope a little bit of what I've said has

provided a little bit more granularity. But we, again, would be interested in the types of information that the community's interested in hearing about in a future meeting, and we can think about maybe in the next couple years, when we have a little bit more experience, revisiting and thinking about that.

DR. SMITH: Thank you for that explanation. Can you clarify if we would ever know when a particular trial was done as a result of an IPSP --

DR. DONOGHUE: Yes. Yes.

DR. SMITH: -- or if it's forever confidential?

DR. DONOGHUE: Yes. Well, once an application is submitted, then the approval letter will contain a postmarketing requirement, or not, or acknowledgement of a waiver exemption from the pediatric requirement. Those are public. Those letters are public. The postmarketing required studies are public. And once the information comes in as a result of the postmarketing study, then

part of the requirement is to include the information from that study and product labeling.

So there is a very clear mechanism for that kind of information to be provided. Given the nature of pediatric oncology and, again, based upon the importance of trying to make sure that we're making decisions that really are reflective of community needs and that are appropriate, thinking about rare resources and wanting to be sure we're dedicating and only requiring, or agreeing to require, a study in those cases that we think there's a real potential for pediatrics and not have too many redundant studies, I do think, even before the adult application comes in and the postmarketing requirement is set, that we have a way of tracking what's happening more contemporaneously with the plan itself, because there are plans in place where the studies are already well underway in pediatrics, and that's well before you would get the approval and the postmarketing requirement.

So yes, there are ways that will be tracked.

I'd like to try to track things a little bit more closely before the adult marketing application comes in.

Did that help, a little?

DR. SMITH: It helps. Not having access to what agents have IPSPs, it makes it harder to plan for clinical trials when there could be one or two IPSPs that aren't yet public and another group is trying to develop a clinical trial.

DR. DONOGHUE: I agree. I agree.

DR. SMITH: So that is a concern.

My last follow-up question is --

DR. PAPPO: We're going to have to -- okay.

DR. SMITH: -- there could be IPSPs for which agents don't go on to approval, correct?

DR. DONOGHUE: Correct. Yes, because these are plans for studies during end of phase 2 development in adults, generally speaking, post end of phase.

DR. SMITH: Do those become public or is that forever confidential?

DR. DONOGHUE: At this point in time, the

IPSP status is not public, no, up until then. That's something that I think is maybe outside of our purview, out of our area of control at this point, but it is acknowledging that you're in a situation where there's a bit of a blinder happening --

DR. SMITH: That's correct.

DR. DONOGHUE: -- but that's not unique necessarily, even to these regulations. I think there are many instances where there are ongoing studies happening that others are not aware of until a publication occurs or something like that. So I do think it goes beyond this issue, but it's still an important --

DR. PAPPO: We can come back --

DR. DONOGHUE: -- I acknowledge that for FDARA as well, yes.

DR. PAPPO: We can come back and circle back on this. We're a little bit behind on schedule, but thank you.

So now we will proceed to our next speaker presentation, Dr. Brenda Weigel, and sorry for the

delay, Dr. Weigel.

Guest Speaker Presentation - Brenda Weigel

DR. WEIGEL: Thank you very much, Dr. Pappo, and it is my pleasure to present the COG perspective. And I wish to thank the FDA and all participants for the opportunity to really, I think, raise more questions and reflections; that anything data-driven, as we've just heard from the perspectives of the questions, is that we really are looking at collecting data to really understand the impact moving forward. I hope to give you some of the things that we consider in the COG, and some of the questions I think at the end will lend themselves to further discussion later today.

We really, over the last several decades, have seen a real explosion in the number and types of agents that are targeting cancers, and this evolution has really been accelerated in the last decade with the advent of targeted therapies. As was alluded to this morning, the legislation has been implemented to try to increase and shorten the time frames for studying potentially effective

targeted agents in pediatric cancers.

As exemplified in this slide with the development of crizotinib, the ALK-targeted agent was really, if you think about it, in 1994 discovered, ALK in anaplastic large-cell lymphoma, and that if you put in today's context, that would potentially have been something that was of pediatric relevance. But it really was 12 years later when it was discovered in connection with lung carcinoma that it really developed into an anti-cancer therapy, and then further than that, the discovery that it was associated with neuroblastoma and the development of this in the pediatric oncology space.

So the time frames were incredibly long, but one would suggest that once it was actually recognized that ALK was of relevance in pediatric cancer, even before FDARA, there was a movement into the pediatric oncology space that was really driven from pediatric academic investigators.

As Dr. Pappo mentioned, Dr. DuBois and colleagues really provided the benchmark for us for

pediatric cancer drug development, with the median being 6.5 years from the time of first in human to first in pediatrics, and this benchmark, one would suggest, gives us a comparator for what hopefully will be data collected, as has been already mentioned, to say that we really are making a difference with the current RACE for Children Act in shortening this time frame. So historically, there is really this delay in moving into pediatric drug development, and one would hope that the RACE for Children Act is moving that bar.

We have heard the requirements of the RACE for Children Act, and we really have seen that, as was mentioned earlier, there has been an increase in the number of IPSPs, but we still are unclear as to whether that is changing the bar for moving trials and/or approvals in pediatric oncology forward.

Some of the things that we really consider, and I think a lot of the discussions that we have with our pharma partners and within pediatric academics, are really the factors related to

relevance, and the molecular targets list has helped with this, and there are very few exceptions on the molecular targets list. So this really does become a big topic of conversation of how do we define relevance, and I think this continues to evolve, as we also heard this morning, with other types of targets and biologic effects.

We also heard that there really needs to be that preclinical data to help determine relevance. We heard reference to the NCI-supported PIVOT program and the ITCC-P4 programs, all of which are contributing information into the preclinical space. We also know that, historically, many targets have been evaluated late, as exemplified by ALK, even though the initial findings were in a pediatric relevant tumor, and we do have limited human tumor data in pediatric oncology to help define some of the most interesting and most promising data. So really, the access to the preclinical data, the data coming out of these assessments, is critical to our understanding of relevance and in advising what moves into the

pediatric clinical trial space.

Drug formulation is really part of the RACE Act, and I would say that formulation, by and large, in IV is easy. Oral, we really have seen, so far, that what is coming into the pediatric space is really what is currently in the adult space with plans to develop pediatric formulations, but not necessarily a clear movement to actually move into formulations at the time of starting a pediatric trial that are pediatric relevant and friendly.

Some of the key considerations, especially in the formulation area, are the timing of the development of these formulations. We saw, as exemplified by larotrectinib in the rare NTRK fusion-positive infantile fibrosarcomas that Dr. Laetsch led and published, that knowing that this patient population was in the pediatric space and in very young children, a pediatric friendly formulation was developed very early, and these types of considerations really make a difference in moving an agent that is effective forward in the

pediatric space.

We do not delay moving into the pediatric space and try to move into the smallest children possible with existing formulations, recognizing that that may limit the lower age limit and size of individual that can be enrolled on a pediatric trial, and try to move forward as data emerges into a pediatric friendly formulation.

Key considerations, I think when we look at safety and toxicity, is really balancing risk and benefit, and really, a lot of this toxicity data is coming out of the adult experience. How do we move that so that we can have a better idea of the safety profile and not have to delay for significant amounts of data in adults in an agent that we feel may be of real potential benefit for children?

So key considerations I think play into some of the meetings of the requests to move trials into pediatrics that we have to recognize, really, in dealing with rare patient populations. And as will be discussed later, and has already been mentioned,

international trial collaboration is critical and key as we move into rarer and rarer populations.

It has been mentioned, the coordination of regulatory requirements. I think we heard earlier today, from representatives of the FDA and the EMA, several efforts, intangible steps, to try to coordinate regulatory requirements on a more international scale. This is really going to be required as we move into more and more defined subpopulations of pediatric patients.

Adequate safety and dosing in children and adolescents, I've mentioned the formulations. We also have seen many, many trials now following the FDA recommendations for adolescent cohorts, and it is really unclear what is the enrollment of the adolescent patient population and how is that impacting some of the decisions for moving into younger patients.

Another issue that I think really needs to be considered is how do we implement novel trial designs that both minimize patient numbers needed for trials, and are there ways that we can more

effectively utilize master or platform protocols such has occurred with the pediatric NCI-supported MATCH protocol and efforts, or the European e-SMART efforts, or similar types of platforms where potentially multiple companies and multiple sponsor entities could utilize a more centralized platform? Minimizing patient numbers I think is really key, especially as we're moving into rare diseases, and minimizing dose finding in the pediatric space to try to, as quickly as possible, move agents forward into combination strategies.

The Children's Oncology Group really can partner in three different ways with sponsors to study drugs in the pediatric space. One is through the NCI-sponsored trials mechanisms, and that would be an NCI-held IND. We function in what we call a hybrid model, which is that we utilize our NCI-funded mechanism and really look to the pharma partner or industry partner to supply drug and additional potential resources to conduct the trial, and the IND is held by the company or by the Children's Oncology Group.

Some industry-sponsored trials also look to cooperative groups, including the Children's Oncology Group, to do what is traditionally an industry-sponsored study, and this is a fully-funded study without utilizing NCI resources to conduct the trial, typically at selected sites, and the company holds the IND.

So how do we as a consortium begin discussions with an industry partner? It is bidirectional. It can come from an investigator, an academic investigator who has an idea, who has generated preliminary data in their academic lab, or we can be approached by an industry partner for collaboration in developing a clinical trial. This is typically driven out of discussions and recognition of the RACE for Children Act and the need, potentially, for a pediatric study plan.

Key considerations in these initial conversations include what is the business and regulatory strategy for that pharma partner, and this gets to where they are in their development stages for the entity. Are they very early? Have

they dosed in adults or are they in the preclinical space, and what is their strategy? And sometimes that strategy includes the discussion, as has been brought up earlier, with regards to waivers or deferrals as part of that strategy.

What do we know about the drug's mechanism of action? Formulations, again, is part of that discussion. And importantly, what studies are underway in the adult and/or pediatric populations that inform some of our thinking about how to move this entity into the pediatric space, and what are any drug safety concerns?

One of the things that increasingly comes up and is not addressed, really, by FDARA or by the discussions today, but is for us I think a really critically important thing to consider is, where do we go in combination, and how do we look at single-agent information and data when we may be wanting to move into a combination strategy as quickly as possible? Several things should be considered in the selection of combination regimens, including the activity in advanced

disease, cross-resistance, the mechanism of action, be it additive or synergistic, and toxicities.

As was mentioned, ACCELERATE is a multi-stakeholder group that holds as part of their annual meeting stakeholder working groups, and one of the working groups was addressing combination strategies. This was published in the Journal of Clinical Oncology last year, really looking at recommendations to how do we move some of these combination strategies forward, and can we look at this in the context of more platform type approaches as well? These can include combinations with novel drugs and standard chemotherapy, novel drugs and novel agents that are novel-novel within a single sponsor, or potentially and more complicated is across entities.

So it's hard to make conclusions to date. I think it's too soon to truly understand the impact of the RACE Act, and this point has been brought up a few times today, and I think what is going to be critical is what data do we need to collect to really make that decision. We certainly have

noticed a shift in the industry pendulum to earlier discussions regarding potential pediatric trials for targeted therapies, but it's not clear that this has yet translated into more clinical trials or ultimately more approvals.

As we heard earlier, the RACE for Children Act is really focused on molecular targets, and it doesn't take into account, really, cellular therapy or combination therapy, and we really need to think about how do some of these requirements affect our ability to move some of the most promising agents forward.

I think also that was mentioned and really needs, I think, to be emphasized is a no-go decision in the pediatric oncology space, and that we then can utilize our most precious resources, that being our patients, for the most promising agents or do as minimal assessment as possible in the pediatric space if we really feel that it is not an agent or a target to move forward.

I think in my last few slides, raising some points of things to consider and I think things for

further discussion moving forward is how to engage the pediatric oncology experts as early as possible in the regulatory process. We heard many comments made earlier about wanting early engagement, and we also heard that the IPSP is required at the end of phase 2 testing in adults. Is there a way to move that earlier, and is there a way to not only encourage, but facilitate the involvement of multi-stakeholders in these earlier conversations?

As we heard, the Type F meetings typically are occurring prior to the engagement of the pediatric oncology experts and multi-stakeholder meetings, and they are being very encouraged, but I would suggest, is there a way that there could be a process implemented to encourage and codify involvement? We did hear a little bit earlier about addressing cellular therapy, and I think this is something that we will need to consider moving forward; and as we heard, some of that is still on a case-by-case basis.

How do we move forward agents that are not molecularly targeted but may have relevance in

pediatric oncology space? We heard a little bit about that earlier today, but I think this is something that we really need to consider moving forward, and then how do we address combinations I think is key.

We really need to think about impacts on trial design, and the vast majority of the data required for regulatory approval is single-agent data for single-agent safety and pharmacokinetics, and how much do we need before moving into combination strategies? It's very difficult to set preclinical data requirements. A lot of combinations in the adult space are not combinations that would be of interest in the pediatric oncology space, and how do we generate that data to move forward in pediatrics?

The real challenges of novel-novel combinations versus standard or more classic chemotherapy combinations with a novel agent, again, are things that need to be thought about as we're developing the pediatric study plans and what circumstances require demonstration of a single

agent prior to incorporation into a clinical trial -- i.e., adult data versus preclinical data -- and how do we set that bar of what needs to be learned prior to moving into a pediatric clinical trial.

It was brought up earlier as to how do we address multiple agents in class in a limited patient population. The example of PD-1/PD-L1, and then the number of waivers given in class, is an example of multiple agents in class, to use Dr. Donoghue's words, of an area that has exploded. But in the ACCELERATE forum dedicated to PD-1/PD-L1 targeting, that was at a time in that decision when over 1,000 children had been enrolled on clinical trials looking at that agent, and how do we look at when there's maybe two, three agents, and how do we coordinate that and make those decisions?

As was mentioned, the pediatric ODAC made recommendations with regards to how to strategize in that context, but it does get to the issue of what is publicly available information when there are multiple agents in class. How do we minimize

the number of patients in looking at multiple agents in class, and is there a way to ensure that we are not having redundancy in this area?

Another key, and we will talk more about this in this session, is international collaboration is key. I think we've heard that, and I think we really need to think about how can we utilize some of the requirements that FDARA puts forward in the RACE for Children Act to strategically look at meeting these needs through international collaboration.

So as I stated at the beginning, we do not have a lot of data to bear. We definitely, I think, are engaged in a lot of conversations, and I think there's a lot of opportunity for us to, as a community, try to build a more efficient way of moving drugs forward in pediatric oncology. So I thank you, and I look forward to the discussion later today, as I think there are many, many important questions. Thank you very much.

DR. PAPPO: Thank you very much, Dr. Weigel, for your excellent presentation.

We will now proceed with the next speaker presentation, Ms. Ruchi Gupta.

MS. GUPTA: Thank you, Dr. Pappo. Can you hear me clearly?

DR. PAPPO: Yes, we can.

Guest Speaker Presentation - Ruchi Gupta

MS. GUPTA: Thank you.

Good morning. Good afternoon, everybody. My name is Ruchi Gupta. I am a program director in Regulatory Affairs at Genentech. I've been working in the field of pediatric oncology drug development within the industry for the last 10 years, and I'm here today to provide an industry, especially Roche and Genentech, perspective towards pediatric drug development and the impact of Research to Accelerate Cures and Equity for Children Act, also known as the RACE Act under the FDA Reauthorization Act 2017.

Before I start with my presentation, I would like to thank the FDA for inviting Genentech to this forum to share our views. This is the disclosure slide. As mentioned earlier, I'm an

employee of Genentech, Inc. and a stockholder of Hoffman-La Roche, Inc.

A quick look at the agenda, I'll be briefly discussing the PREA requirements pre-implementation of FDARA 2017 and challenges associated with it. I will then go over the various aspects of the RACE Act under FDARA 2017, including how it changed the landscape and how it shifted the paradigm of pediatric oncology drug development; how it impacted the industry and what are the challenges associated with it; what we are doing at Roche and Genentech to address requirements and challenges associated with FDARA 2017; and what's the industry perspective on how FDARA 2017 can be made more effective, ultimately concluding with key messages.

I will not go into the details of the first few slides, as they have already been covered by other presenters but would like to reiterate that PREA, as pre-enactment of FDARA 2017, provides exemption for drugs and biologics for adult indications not found in pediatrics, and so is the case with indications granted orphan drug

designations. As alluded earlier, PREA was not really impactful in the oncology therapeutic area due to various factors, including the fact that adult oncology indications do not occur in children and oncology indications with orphan designation by default exempt sponsors of any pediatric obligations. It is also not perceived as an exciting opportunity to the limited patient pool, waiting for the challenges, and limited commercial drivers.

So moving forward to 2020 post-implementation of FDARA 2017, introduction of this revision was applicable to both drugs and biologics in oncology. Revision to PREA tried to address the two big challenges in pediatric drug development. Firstly, it required a mechanism of action based pediatric cancer investigation for drugs intended for adult cancer treatment, but it also aims towards molecular targets for relevance in growth and progression of pediatric tumors. Secondly, the revision took away the default PREA exemption granted based on orphan drug designations.

So what does it mean for industry? Sponsors of new marketing applications for new molecular entities were required now to submit initial pediatric study plans based on the mechanism of action of the drug if the drug aimed towards the molecular target relevant to pediatric cancers.

Sponsors were required to provide a high-level study design to evaluate dose, safety, and preliminary efficacy of the drug; and in order to work on the details of the clinical study, they are now required to understand the overall profile of the molecule based on adult data addressing pediatric formulation issues, starting dose, and more importantly, the selection of pediatric patient population.

So as alluded earlier in various presentations, FDARA 2017 definitely shifted the paradigm on how pediatric drug development is now done and thought about. Here, I would also like to refer to the Government Accountability Office report issued in January 2023, which reviewed the effectiveness of the pediatric study requirements

enacted by the RACE Act and in one of the provisions of FDARA 2017. This report included the views of FDA, industry sponsors, patient advocacy groups, industry groups, researchers, et cetera.

According to this report, there has potentially been an increased interest in pediatric cancer drug development with large academic institutions and consortiums now that the drug development for most oncology drugs became mandatory. The Act has increased visibility to unmet medical needs in pediatric cancer, as it pushed the companies to look into ways to develop studies in pediatrics. This ultimately led to potential for increased treatment options for the pediatric population due to the increase in pediatric oncology clinical trials being initiated across the United States, although the GAO report indicates that since the implementation of FDARA 2017, between 2020 and 2022, there have been 32 initial pediatric study plans submitted to FDA with intentions to conduct a pediatric study.

However, it is too soon to know if this

increase in the number of pediatric studies will lead to an increase in the number of drugs approved to treat pediatric cancers. This is because these planned studies are still in the only phases or have not yet begun, and will take years to complete given the long timelines associated with pediatric drug development. Given the changes were implemented approximately four years back, it is also too soon to say how it impacts adult drug development, and it is yet to be assessing to account the totality of the data.

Now, I'll be speaking to the common challenges across industry with obligatory pediatric drug development. One of the biggest challenges, what we have acknowledged or what we have observed so far, is for global alignment discrepancies, feedback, and expectations between various health authorities, including FDA, EMA, MHRA, and various others. Through the RACE Act, the common commentary process was introduced as a way for sponsors to request that their pediatric programs can be evaluated at these health

authorities' cluster calls. Unfortunately, the common commentary process is not very well defined, and across programs, we have had different experiences with feedback received, or the process outright denied, or received cluster call feedback ad hoc without requesting the aligned health authority feedback. It would be very helpful if there was clearer guidance available on the common commentary process and how we can streamline the feedback on critical aspects of the pediatric programs.

Coming to the study design challenges, oftentimes agreeing on the study design, including the proposed cancer types, the starting dose and the overall sample size of number of patients to be evaluated in the proposed pediatric studies have been challenging. In most cases, we have experienced, as we expressed, that the pediatric studies are statistically robust to demonstrate benefit-risk with requests for fully powered, randomized studies for registration purposes.

This point, it can be extremely difficult to

create large randomized confirmatory studies when the population is extremely rare, or when they are completing trials for this rare pediatric population, or when randomization is not feasible given there is no standard of care to control or compare the investigation drug to. Again, as it was also mentioned earlier, it would be helpful if the FDA could provide more guidance for pediatric requirements for drugs studied in combinations.

Coming to the operational challenges, one of the major challenges with the implementation of the RACE Act is the prioritization of molecules, either same in class with the same or similar mechanism of action or prioritization of molecules with different mechanism of actions but within the same disease area. Oftentimes, the areas of unmet medical need in pediatric cancers are quite rare. With limited patient numbers, with multiple industry partners investigating same-in-class molecules with similar mechanisms of action, it is not always feasible to conduct comprehensive pediatric studies due to competition. Even

internally, Genentech-Roche has prioritized molecules for pediatric development and deferred molecules of the same class and MoA, which has led to complex scientific discussions.

Aligning on this rationale and the timing of when it may be feasible to investigate the deferred molecules have been very time consuming and challenging, and ultimately, in an ideal world, it would be helpful to have a streamlined process and timelines for review for various pediatric documents, and it is burdensome for the industry sponsors to manage all at once.

Now, I'll be speaking about the Roche best practices and what Roche does to implement and direct requirements and challenges that are under revised legislation. As a sponsor, Genentech-Roche evaluates the therapeutic areas that could derive the most benefit of an investigational drug based not only on the mechanism of action, but also on the availability of preclinical data, literature review of relevant and feasible pediatric cancers, any available safety, pharmacokinetic, and efficacy

data in adult trials, along with the consideration around unmet medical need. But obviously, reference is also made to these published list of molecular targets for the growth and development of pediatric cancers, as it plays an important role in defining the clinical and regulatory strategy to move forward.

Some of the considerations on how FDARA 2017 can be made more effective, overall, when a drug's MoA is brought in adults and pediatrics, development is a multifactorial company decision that may lead to developing a specific molecule in a specific disease area to avoid competition. It would be helpful for FDA to develop a process for prioritization across industry either through multi-stakeholder meetings, and more transparency and flexibility when engaging with sponsors.

In addition, it would be helpful to have specific PSP procedures that will streamline the review of PSPs that are competing with same-in-class molecules and a more defined approach and timelines for different processes. Similarly,

it would be helpful to take the holistic approach to set realistic targets for the minimum patient numbers required for conducting pediatric studies and number of pediatric indications to be studied.

What could also help is to understand FDA's expectations around evidence collection or willingness to accept alternatives in lieu of appropriate animal models to establish safety, efficacy, and dose in rare pediatric indications.

This is my last slide. In conclusion, I would just like to say that, nevertheless, the requirement of mechanism of action based pediatric development under FDARA 2017 has enforced the proactive and early consideration of integrating pediatric development as part of the overall clinical development plan for the molecule. It has encouraged collaboration among regulators, sponsors, and academic partners to share best practices and has presented the opportunity for additional global harmonization of study designs. However, we still need more guidance on implementation of innovative trial designs like

extrapolation, basket trials, et cetera.

I understand that the FDA guidance from 2021 briefly speaks about six such approaches, but they come with their own set of challenges, and there is very little information on the successful implementation of these approaches. Overall, we need to shift mindsets across to take a portfolio approach internally and externally and find the path for prioritization to address some of the major challenges posed by the changes in regulation, and benefit the children in need.

With that, I conclude my presentation, and in the end, I would like to acknowledge my colleagues at Genentech who helped prepare me for this presentation. Thank you.

DR. PAPPO: Thank you very much, Ms. Gupta, for your excellent presentation.

We will now proceed with the last guest speaker presentation from Dr. Pamela Kearns.

Guest Speaker Presentation - Pamela Kearns

DR. KEARNS: Thank you very much. My name is Pam Kearns. I'm a pediatric oncologist from

Birmingham in the UK, and I'm the current President of ITCC, and I'd like to say a big thank you to the FDA for inviting me to participate in what has been a really interesting meeting, and I look forward to the discussions. I'm going to perhaps shift gear and move a little bit away from some of the direct discussions about FDARA, but talk more specifically about the international collaborations, and what that means in reality, and really get down to the nitty-gritty of what works and what doesn't work.

I think the first thing to say is that, in Europe, we are very familiar with international collaboration because unlike North America, we don't have enough patients in any one country to run pediatric oncology trials, so we always have collaborated across Europe. And what I want to do is outline how this works in Europe, and then some of the challenges we've had in trying to collaborate transatlantically, and how we might move that forward in the future.

So just to set the scene, in Europe, we have the European Society for Paediatric Oncology, which

brings together all the European clinical trial groups, but they are independent groups. SIOP Europe is not like the Children's Oncology Group. It doesn't have independent funding. It's a member society. Each of the European clinical trial groups is disease based and has multiple academics and patient representatives from different countries working on particular disease areas, and we all come together under what's called the SIOP Europe Clinical Research Council. The particular clinical trial group I'm going to focus on, which is most relevant to the discussions today, is ITCC, because this is concerned with the early-phase trials and drug development.

The ITCC comprises 62 pediatric centers across 17 countries in Europe. All have been accredited to have the expertise to conduct early-phase trials in children and adolescents, and we're also recognized by EMA as part of EnprEMA, which is a European Medicines Agency network for pediatric research. The ITCC is not just a deliverer of clinical trials; we bring together

expertise across both the preclinical and the clinical aspects of clinical trial development.

In the green box in the center here, you'll see we have an academic sponsors network because within Europe, we don't have a single sponsor like the NCI running our clinical trials in partnership with the Children's Oncology Group. We have academic institutions of which there are only a handful in Europe that have the expertise to run international early-phase trials, who do this on behalf of ITCC. ITCC-P4 has been mentioned several times today, and ITCC-P4 started as a project within ITCC and is now spun out as an independent company, obviously retaining the ITCC name to show its origins.

Moving on to the next slide, please, within ITCC, we deliver everything from academic through to industry trials, and the academic trials are slightly typical of academic-sponsored trials, where they're entirely government or charity funded by grants, and the output of that would be publications and maybe a clinical practice guidance

change, and there's no industry involvement. They are becoming less so now in drug development as we move into partnerships with industry, and some of the trials delivered within ITCC are fully-sponsored industry studies, where the industry takes complete responsibility for the trial, and ITCC's role is in recommending the sites that would have the right expertise and patients to deliver the study, and we review the studies to make sure that they're designed and relevant to our patient population.

Then there was a lot of what were called IITs or ISTs, where there's a mixed model of an academically-sponsored study, where the company might give the drug and a little bit of funding, but they weren't desperately different from the traditional academic trial. But what I want to focus on is our new paradigm, which is the Academic Industry Collaborative Study.

This is the type of trial where it's sponsored by an academic organization, but the purpose of the trial is very much towards providing

a package of data that, if it's a positive trial, could influence a label of a drug so it would be used for filing. But there's been a lot, I think, described from industry to say that academic consortia can't deliver these sorts of trials; we don't have the right expertise to do it.

So within ACCELERATE, we set up a working group with contributions from both FDA and EMA, the pharmaceutical industry and academia, and patient representation to say what's the delta between an academic study and an industry study if we're both trying to do it for filing? It was a very interesting discussion which resulted in a paper, but we came up with this phrase, "fit for filing." What this encompasses is a paradigm shift in how we can deliver academic and industry collaborative trials, and I'm going to give you an example of this.

After one of the ACCELERATE forums, the Pediatric Strategy Forum for B-non-Hodgkin's lymphoma -- which is a disease which, as you all know, has really good outcomes at frontline, but

when children relapse, the outcomes are devastating. In the adult hematology malignancy world, there are a plethora of new drugs, but we don't have the patient group to investigate which ones are good for children if we did it sequentially in individual industry-sponsored studies.

The recommendation for the strategy forum was it would be good to evaluate these drugs and academic-sponsored studies, with industry support, with compounds and different companies being investigated in a platform forum with an adaptive design, but the academic study would have to be conducted so at the end of the study, the data could be used for filing.

Out of this was born Glo-BNHL, which is exactly what was described on the previous slide. It's an academic platform trial intended to be run internationally, with a design that is based on the Bayesian statistical approach to get the answer from the smallest number of patients possible. I put these boxes on because it's too small to really

read it properly, but the principle of the study is that any child that's relapsed or is refractory being on Hodgkin's lymphoma can enter the trial, and then be allocated, depending on where they are in their disease pathway, to one of three arms, looking at the three classes of drugs that were identified in the strategy forum as most relevant for children being on Hodgkin's lymphoma, and that's the bi-specific antibodies, the ADCs and the CAR T cells.

The platform is funded by charity. We've got charity funding from Fight Kids Cancer and Cancer Research UK, but each arm, when a company comes on board to have their drug evaluated, is fully funded by industry. How do we select the drugs to take into this? Well, we have a steering committee that looks at the assets put forward by the company, and they present an entire package under a confidentiality agreement. And we've got a very systematic scoring system to say, is this drug relevant to our patient population; is the evidence already available sufficient; and where does it sit

in the priority list? And we now have two companies fully signed up and on board, and the trial has just opened in the UK, and we're just signing the contract for the third one.

What was really important about this study is we took the design of the platform and the statistical design to EMA for qualification advice, and we had a long and very detailed discussion with them to make sure that our design was of sufficient robustness for the risk assessment, that should it be a positive result, the data could be used for filing. Because this is a global study, we also wanted to take this to the FDA, and it's been through a pre-IND support evaluation, and we're now in the full IND process. So this will be an academic study with a fit-for-filing capability.

As mentioned by the previous speaker, the importance of statistical design being efficient and what has been really important about this study is that we do not evaluate the drug to the point of a fixed number where we're treating children with a useless drug. So each arm is based on the priors

of what we know about the patients going into the arm and the clinically relevant target response rate, which we've determined using a panel of experts.

Each arm has its own statistical design, and there's a rapid no-go decision after 15 or 30 patients, but the complex base in statistical modeling means it's being continuously evaluated, and we can stop the trial at any time if it's futile, so we're not putting patients onto the study or wasting the time to recruit patients with what is already known to be a futile drug.

Now, although it's an efficient study, we still need global collaboration to get enough patients onto this study. And obviously, we're running in Europe and Australasia, but the big challenge is being able to run it in America, and this is being co-developed with our colleagues in America, but we've run into a big challenge. The challenges are the operational challenges of running trials, academic trials, transatlantically. So the second part of my presentation, I want to

just go through what those challenges are.

Working with ITCC, and the Children's Oncology Group, and the NCI, we realized that one of the biggest frustrations we had was the delays in achieving these collaborations, and we have trials that have been trying to be set up transatlantically for well over a year, if not longer, because of these obstacles. One of the biggest problems is we really don't understand each other's processes, but there are also some regulatory challenges.

So we brought together experts from all three groups to say, can we understand each other's differences in how we run international trials? Can we compare the systems, and can we develop a framework that we're not reinventing the wheel each time we try to do one of these trials so that anybody in the Children's Oncology Group or in Europe could say this is how we run a transatlantic study? This is a high aspiration.

Just to put this in context first, the way we run studies in Europe is that the academic

sponsor identifies national coordinating centers in each of the participating countries, and the academic sponsor takes all the responsibility for the trial, the legal responsibility for the trial, but delegates certain activities to the national coordinating center, who is then responsible for the sites in their own country.

Just to put a bit more granularity on this, the sponsor deals with all the design aspects of the trial, the database, pharmacovigilance, and monitoring, et cetera, et cetera, and delegates some very specific tasks to the national coordinating center around patient information and consent, which in different countries have slightly different regulations, the regulatory submissions in their own country, but specifically the set-up and oversight of the the sites in their own hospital, in their own country. And as an academic sponsor, we audit the national coordinating center. So that's how we run all our studies in ITCC, and indeed in most European clinical collaborative groups.

We thought, naively, we could just apply this in America. We'd take the Children's Oncology Group, make it a national coordinating center and run our studies in the U.S., and that's where we were unbelievably naive because that just doesn't work in the simplistic way that it sounds. Equally, we thought, well, we can participate in U.S. studies by simply having the Children's Oncology Group or the NCI designating one of our ITCC sponsors as the international or the European delegated sponsor, and we would be responsible for running the trial in Europe; and in principle, both of those models could work, but we hit barriers.

So what we did, we took three case studies of different scenarios, two of which were run from the U.S. but we wanted to participate in Europe, and one where we were running it in Europe and we wanted the U.S. to participate. What we identified were four main roadblocks. One was just a complete transatlantic misunderstanding about each other's processes; and although we speak the common language as in English or American, we were using

different words to describe what we were doing, and we really hadn't understood how each other's regulatory processes worked. The other problem we had was database access, and when we dug down into it, it was more than that. It was access to the clinical trial infrastructure on both sides of the Atlantic.

There were two regulatory problems. One was around data protection and one was around pharmacovigilance. So we set up four working groups to propose solutions, and from it, the Einstein principle that we have to think outside the box. We have to have creative thinking to find out how we can solve these problems. I'm going to go through four slides for each of the working groups, what we did and what we found out.

The lack of understanding of each other's processes, that was relatively simple. We've done some process mapping in a huge amount of detail of everything that happens, from the idea coming into the Children's Oncology Group, to having a trial ready to set up, and we've done the same on the

European side. And now we're writing a document which is a complete guidance document so that it would be transparent to anybody who's going to run the trials transatlantically and this is how the two processes work across the Atlantic. So that was one of the easier problems.

The second one was the databases. One of the trials of the three that we had to look at, the solution, which had been a workaround, was to have two databases, one based in Europe and one based in the U.S. on a single trial. And on every look at that, there were too many flaws and risks to running two separate databases, that we felt that the ideal scenario was to have a single database where there is a European study or a U.S. study, and it would be one database, one or other continent, and we would work out how to access that database on either side of the continent.

So if we take it from the point of view that COG is running the study and we want to participate from Europe, there were two barriers. I'll go from the bottom of the slide first, because that was the

one that was solvable; that just the whole logging into the NCI RCR system from Europe and registering our trials and our patients was really challenging, and it was simply a matter of terminology. Working with some really fantastic people at the NCI, we identified what those blocks were, and that has been largely resolved.

Just to give you an example of the sort of problem, when you went into the database, you had to put down your IRB. European centers don't have IRBs; we have national research ethics committees, but the way we designate those just didn't fit into the database. That has been relaxed, it's much easier now, so that problem has been solved simply by collaboration.

The bigger problem we have is federal-wide assurance, and we deep dived this as to why this is a problem. In Europe, we don't have to have federal-wide assurance, obviously, but the way we assess a site is able to deliver clinical trials to GCP with total compliance is the responsibility of the sponsor, and it's all part of the documentation

that we collect about the investigators and the site, and that's kind of what federal-wide assurance is looking for in a nutshell.

So we proposed, well, given that it's the coordinating center that has that responsibility, a workable model would be if it was just the coordinating center that had to have federal-wide assurance, and they dealt with the rest of the site responsibility. That was not rejected as a bad idea, but that takes quite a lot of changes within U.S. legislation within the NIH, that we haven't quite cracked it yet. So at the moment, we're still waiting to see if we can overcome the problem of federal-wide assurance, but it is impractical to ask lots of sites in Europe with different countries to get federal-wide assurance to run the trial in Europe.

The other way around in terms of accessing databases is actually considerably easier. There's no problem; we've got a database in our university in Birmingham for our clinical trials unit, and any U.S. site can put data into it if they've been

set up and activated as a site in the trial. There's no issue. We don't need any particular special permissions.

However, the challenge we had was being able to activate sites in the U.S., which we needed the Children's Oncology Group to act as our national coordinating center. But because we've moved into these new collaborative industry studies, they don't quite fit into the lovely slide that Brenda showed of any of the models that are run at the moment within the Children's Oncology Group. They're not really hybrid studies, they're not completely industry studies, and they're not completely academic studies.

So there needs to be an almost reinvention of how this can be done within the Children's Oncology Group and working with the leadership of the Children's Oncology Group -- hugely grateful to Doug Hawkins and Lia Gore in this -- and we're looking to actually set up that capacity and expertise within the Children's Oncology Group; that these types of studies would have the capacity

to have that oversight that we need them to have to be a national coordinating center in the U.S., and we're going to pilot this with Glo-BNHL.

The next two problems were regulatory, and I think anybody who's been dealing with clinical research in Europe knows that we are bound by something called GDPR, which is our data protection legislation. Unfortunately, the U.S. doesn't come under what is referred to as "adequacy status" under GDPR, which means that we cannot transfer any identifiable data -- and that includes pseudo-anonymized data or data like dates of birth -- over to the U.S. under GDPR, except without very specific permissions. And of course, a clinical trial cannot be anonymized. It has to be identifiable data in some way or another, so we had to find a way around it, and one route was Article 49 of the GDPR, which is called the Derogations for Specific Situations.

So we thought we found this as a potential way around how we could be able to set up a trial with a contract arrangement with the Children's

Oncology Group to be able to send the data over; however, GDPR is not implemented equally across Europe, and every country and almost every institution has its own interpretation of GDPR. At the moment, we're going through a process of assessing whether, within the ITCC network, the sites will accept the concept of Article 49 exemption language, in which case, problem solved.

If it isn't, there are a couple of other workarounds that the NCI identified, having worked with other cooperative groups, which we are exploring, so there should be a way around this. But what we really need, and it's already ongoing, is the NCI talking to the European Commission to see if there can be a policy change, particularly in the clinical research arena, to make the ability to send data to the U.S. when it is pseudo-anonymized, if not completely anonymized, permissible under data protection regulations.

The final problem, which is again regulatory, is pharmacovigilance. We had a working group that did a fantastic job of analyzing the

pharmacovigilance legislation in the UK, in the EU, and in the U.S., to see what the differences were, specifically looking around phase 2-plus types of trials. To summarize this on the next slide, we had the key differences, and the key problem is that we don't even name the investigational products in trials in the same way in the U.S., and UK, and Europe. You have what's called an IND, an investigational new drug definition. We have a definition for an investigational medicinal product, and they don't map onto each other.

Just to put it simply, if we're doing a trial, for example, of vincristine and carbaplatin versus vincristine and carbaplatin and X new drug, the IND is the X new drug. In Europe, they are all IMPs, and that has implications on the safety data that we collect and the reporting requirements. And it's that discrepancy which is causing us our biggest problems in terms of compliance because, as you know, most academic trials are not of a single agent, but they have combination drugs, so we often have normal cytotoxic drugs or other combination

drugs alongside which wouldn't be considered INDs.

So we've gone around in all sorts of circles around this workaround. We've talked to our competent authority to see what minimum requirement reporting we could get from the U.S., based on the data that you normally collect. We've been talking to our U.S. colleagues, going into more granularity about the data you collect to see if there's some way that we could marry the two processes, even the discrepancy in what we use as our reference safety information and what protocol exclusions are allowed in the U.S. compared to Europe; so even writing the protocol pharmacovigilance sections is really challenging. So this is not yet resolved, and the outcome is something that we need to understand how we can be compliant with the reporting requirements on both sides of the Atlantic.

This slide just summarizes where we got to with the four roadblocks that we identified and the solutions we proposed. I think the three things we need to focus on now is overcoming the issues of

federal-wide assurance, overcoming some of the data protection issues, and finding a solution for pharmacovigilance. Then on my final slide, we've said the academic international collaboration is important and it is possible. And I hope I've convinced you that it is possible for academic consortia to design trials and deliver data to the quality that is required by filing, but if we're going to do it transatlantically, we do need to take into account some of these obstacles that we've hit.

It is resource intensive. We need some very specific guidance documents to develop, which we need to develop, and we're going to use some of these exemplars of trials that are ongoing at the moment to try and run through these solutions and see if they work. We've talked about the alignment between the FDA and EMA, but they're actually some more fundamental alignments between the actual things, like pharmacovigilance transatlantically, that would make life a lot easier for us.

My final slide is just an acknowledgement of

all the people, and some of them who are on this call, who helped in the piece of work to understand the differences between Europe, the UK, and the U.S., to deliver international trials. Thank you very much.

DR. PAPPO: Thank you very much, Dr. Kearns. That was amazing, and thank you for your hard work trying to bridge this big gap.

We're going to change the schedule a little bit because of the time, so we will now break for lunch, and we will reconvene at 1:30 pm Eastern Time. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to reconvene at around 1:20 Eastern Time to ensure you are connected before we restart at 1:30 pm. At that time, we will go back to clarifying questions both from our guest speakers and also from the FDA and the EMA. Enjoy your lunch. Thank you.

(Whereupon, at 12:48 p.m., a lunch recess was taken, and meeting resumed at 1:30 p.m.)

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

(1:31 p.m.)

Clarifying Questions (continued)

DR. PAPPO: Welcome back, and I hope you all enjoyed your lunch.

Next on the agenda was the open public hearing session; however, I would like to state into the record that there are no speakers registered for this open public hearing session, so we will now go back to clarifying questions for our guest speakers, Ms. Gupta, Dr. Kearns, and Dr. Weigel.

Please use the raise-hand icon to indicate that you have a question, and remember to lower your hand by clicking the raise-hand icon again after you have asked your questions. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end

of your question with a thank you and end of your follow-up questions with, "That is all for my questions," so that we can move on to the next panel member.

We will now start the clarifying question portion, first for guest speakers, and then we can always go back to our FDA and EMA representatives. So the first question is from the FDA from Haleh Saber.

DR. SABER: Hi. This is Haleh Saber. I'm the Acting Director in the Pharmacology and Toxicology Division in the Office of Oncologic Diseases at CDER, FDA. I have a question for Ms. Gupta. There was no numbering on this slide, so I'm just going to mention it.

Thank you, Ms. Gupta, for your presentation. You mentioned the requirements for nonclinical data, pointing to juvenile animal toxicology studies. We generally don't ask for juvenile tox studies. We'd rather rely on other data for safety evaluation in children. We rely on the clinical data in adults and on any clinical experience in

related products, as well as data from animal toxicology studies that were conducted previously in support of adult indications, as well as pharmacology data, and these have been sufficient to inform safety of the product for pediatric development.

So could you please explain and elaborate, do you believe that juvenile animal toxicology studies are needed or did the FDA ask you to conduct a study in support of an IPSP?

MS. GUPTA: Thank you, Dr. Saber, for your question. Can you hear me?

DR. SABER: Yes, I can.

MS. GUPTA: Thank you for your question, again. It's been, I think, a long standard practice to include the juvenile data, the preclinical data for the PSPs in the past. With the RACE Act, definitely that has been diminishing a little bit in our perspective. I think the biggest challenge that I wanted to allude to was the fact that there are no real preclinical animal models for pediatrics to mimic, and thereby, it was

asked if we can look for alternate solutions, which I believe in your question you have indicated that there are other aspects from the data that can be translated to design a pediatric study. So if that's the understanding, that moving forward, this is not like a critical requirement in designing the pediatric studies, that's very helpful.

Does that help clarify?

DR. SABER: Thank you, Ms. Gupta. I want to also clarify that the animal toxicology studies are for safety evaluation, and proof-of-concept studies are separate. They are pharmacology studies and they're different. My question was on juvenile animal toxicology studies, and we have not been asking these studies for IPSP, in support of IPSPs.

That's all from me. Thank you very much.

MS. GUPTA: Thank you so much.

DR. PAPPO: Thank you.

Next, Dr. Tara Frenkl.

DR. FRENKL: Hi. Thanks, Dr. Pappo.

I actually have two questions. One is left over from this morning, and the second one is for

Dr. Kearns. Sorry, everybody. I'm Tara Frenkl. I am the industry rep. So maybe I'll start with Dr. Kearns, if possible.

I'd just like to start saying, I'm super impressed with what ITCC has established in the international collaboration and the real problem-solving approach to make the studies fit for filing, and then of course the medicines available to children, so congratulations on that impactful work that you're doing.

From an industry perspective, one of the common problems that we face when we're working with cooperative groups or academic sponsors is really the degree and the frequency of data monitoring for quality of data, not looking at the results, but actually looking at missing data where the question's answered as intended and that kind of stuff. And we as industry usually have no access to that data quality monitoring as the study goes on. We only get access to the data after the study has been unblinded and the results are available, and then that quality aspect is really

not addressable. Then of course, if there are quality issues, then it's really not fileable, and we haven't reached the outcome that we wanted.

So I'm wondering if you could share whether this came up in your discussions in the gap assessment between industry and academic sponsors, and how ITCC has addressed this so we could all learn and maybe use it with other groups.

DR. KEARNS: Thank you very much for your kind words. It's a lot of work in progress, and I think that the point that you raise about data quality was a major part of our discussion, and the fact that personal experience of initial collaborations with industry on these types of studies was the lack of academic understanding of what you would call a data management plan and everything that you put in place in terms of quality and monitoring.

We detailed that as one of the critical areas that need to be addressed, that if an academic sponsor is taking on a fit-for-filing study, then there should be a co-development of

that data management plan so it's completely understood by the academic group what they need to do, but importantly, that the industry partner is comfortable that what's being put in place is what they would expect as well.

I genuinely believe that we've learned a lot in academia in terms of how you do this type of study. I think the difficulty sometimes is industry doesn't quite trust us yet because you've had the bad experience previously. But I think that with co-development, it shouldn't be halfway through the study going, "Oh, we've got to give the data to industry," and that's retrofitted. It should be from day one when you're planning the study to put everything in place; that from the industry side, you're comfortable with the way the study is going to be run, but then it's the academic sponsor's legal responsibility. So it isn't a matter of the industry dipping in and out to see what's going as the study is being run, but that it's planned that way.

What we've done in our studies is we don't

let the industry partners be part of our independent committee, such as our steering committee or the data monitoring committee, but we have a separate oversight committee, and that we just touch base as the study's going on to see if there are any concerns as the study's going on. So I think working properly in partnership makes the difference.

The other thing is, one of the reasons that I would say academia, in our non-collaborative studies, doesn't do the level of quality control is about resources. When we do these collaborative studies, because industry is investing in the study, they're paying for it, it allows us to up our game and be able to do much more source data verification and much more on-site monitoring, as well as checking of the data as it comes in because we get a bigger team around it.

DR. FRENKL: Yes, that's great. I think that proactive attitude and ability to flex for we need is super important. Thanks so much.

Dr. Pappo, I had another question for

Dr. Seddiq. Would you like me to ask it now or --

DR. PAPPO: Let's just wait until we're done with our guest speakers, and then I'll bring you back on.

DR. FRENKL: Okay. Thank you.

DR. PAPPO: You've been waiting for a long time. I'm sorry.

DR. FRENKL: No worries. No worries.

DR. PAPPO: Okay. Dr. Laetsch, you're next.

DR. LAETSCH: Thank you, Dr. Pappo, and thank you to the speakers. I think excellent presentations for everyone.

I had a question to follow up what was just raised by Dr. Frenkl, maybe for Dr. Weigel to comment, and really that is the impact of RACE on how early-phase clinical trials in children are conducted, and whether this has resulted in more industry-sponsored trials, and potentially challenges with cooperative trials due to what was raised by Dr. Frenkl around industry feeling the need to have more control over the data for fit-for-filing studies or studies that are intended

for FDA submission, given the requirements of RACE.

I don't know, Dr. Weigel, if you have thoughts on that.

DR. WEIGEL: Thank you, Dr. Laetsch, and I appreciate the kind comments as well. Again, this is my experiential anecdotal opinion. I do think that over the last couple years, as Dr. Kearns indicated, we certainly have, I think, a greater perception of the concept of fit for filing and the need for regulatory submission for these pediatric studies much more so than certainly if you go back 5-10 years. I think there's a real recognition that from the get-go, we in the academic and consortium side need to have a mindset that any and all data that we are generating could be used, and potentially should be used, for regulatory purposes.

So I do think it has changed some of those initial conversations. As I presented on the one slide, it's that business and regulatory strategy that I think we enter into discussions much earlier. I do think what I have seen is that

companies and industry are being very thoughtful of how they are thinking of conducting that pediatric trial, and as Dr. Kearns so beautifully demonstrated, I think we have to be able to provide fit-for-filing data through consortia. I think we have to, and we have to be able to do it in any of the three mechanisms.

My perception is that our industry partners -- and, Dr. Laetsch, to use your words, from a control, and I think using Dr. Kearn's words of trust -- I think we still have to really convince our industry partners, for that true regulatory filing trial, that the data and the lens on the data is what they actually need. And I think key, as exactly as Dr. Kearns said, is you have those conversations from the minute-go of what data do you need, what are your expectations, and how can we best partner to bring that forward.

I think we have to be able to do it on the COG side and any of the three mechanisms that we can conduct a trial, but to your point, I think there's a lot more discussion about that now, and I

think there's a lot more thought put into how to execute that on the pharma-partner side.

DR. LAETSCH: Thank you.

DR. PAPPO: Dr. Smith?

DR. SMITH: Yes. Thank you. This is a question and a bit of a comment for Dr. Kearns. And first, I thank Dr. Kearns for really an excellent presentation in outlining the challenges in international trials for academic teams and how teams on both sides of the Atlantic are trying to address them.

This was slide 59 in the PDF file that was circulated to us, but it's the slide about different types of clinical trials in academic versus industry, and there were four types shown. The implication from the slide was that academic trials would seldom be used for regulatory purposes unless they were fully industry funded. The comment is it doesn't really incorporate the way COG works, and Dr. Weigel described the hybrid model where COG or the PEP-CTN are using NCI funds to support the trials that are getting additional

industry funds to collect additional data or do other things, and those kind of trials are submitted for regulatory filing.

Dr. Gore and Dr. Hawkins published a paper last year, 2023, that listed the 12 agents that have been approved by FDA, based on COG clinical trials, NCI-supported COG clinical trials, since 2003 from imatinib, crizotinib, nelarabine, all the way up through brentuximab vedotin for first-line Hodgkin's lymphoma. So I just wanted to clarify that in that slide that Dr. Kearns showed, COG is kind of an additional model with a hybrid industry NCI support, where clinical trials have been used successfully for regulatory filing.

DR. KEARNS: Thank you, Malcolm. I agree with your point. I think I still would say that that would fall under the industry collaborative study. It may be a different model because you've got NCI holding the IND, but I still think that it would be more under that than the traditional IST, but I take your point. It does also emphasize the differences that we don't recognize sometimes.

When we were talking with COG, the concept of a hybrid trial came up in how does that fit in with what we're doing, because that's one of your models, and it wasn't a language and understanding that we even have in Europe because we don't have the NCI in Europe, unfortunately. I wish we did, but we don't.

DR. SMITH: Yes, and it does get to the language because when we see full funded, that means that it's not a COG trial sponsored by NCI per se, it's a COG independent trial that is being done strictly with industry without use of NCI resources, so there is that difference in language.

DR. KEARNS: Yes.

DR. PAPPO: The next question is me, and it's for Dr. Weigel. You mentioned in one of your slides that the COG has three different models for industry collaborations, NCI, versus hybrid, versus industry. Do you have an idea of what is the breakdown of each of those, and if there is obvious differences in the activation timeline, the completion of those protocols, accruals, and how

many of those in each of those categories are for fit for filing?

DR. WEIGEL: Yes. Thank you, Dr. Pappo, for your question. I will frame this in the context of early-phase trials and not for all COG trials.

For early-phase trials, over the last decade or so, the greatest number of studies are in the hybrid model, where -- as Dr. Smith and Dr. Kearns were just saying -- really we look at it as a collaborative partnership between an industry partner, and COG, and the pediatric Early Phase Clinical Trials Network utilizing NCI support and NCI infrastructure to conduct those trials. That is definitely our most common model to work in.

To answer your next question on timelines, over the NCI held ones that are done under a creative mechanism and then the hybrid ones, our goal for our early-phase trials from concept approval to study activation, our goal timeline is roughly around nine months. So I would say, typically, we're in the 9-to-12-month ballpark for an early-phase trial.

The fully-funded industry trials, where that is done independent of the NCI resources, those timelines are really controlled by the industry partner because it is their trial. They write the trial. The databases, the company's trial, it is really a pharma study in collaboration with COG because they'll utilize COG sites and a single contract. So the timelines are really theirs, and those are highly variable because it goes through their processes.

I would also say every hybrid contract is different, depending on what the pharma partner wants in addition to what would be standard of care. And also getting to some of the things that have been mentioned, for some fit-for-filing studies, pharma partners may want additional monitoring because we do auditing and central monitoring, which has been utilized for regulatory purposes. Having said that, every contract is a little different in that regard, depending on what the [inaudible - 4:20:05].

As far as -- [inaudible], I would say --

DR. PAPPO: Brenda, you're breaking up.

DR. WEIGEL: -- we've seen the shift is to more hybrid models.

DR. PAPPO: Thank you very much.

Then it's Dr. Shah.

DR. SHAH: Thank you so much. This might be a more general question and maybe not so much for our specific guests, but I can see if they have an opinion on it. I wanted to go back to the issue for the fit for filing.

For the adult registration studies, what is the guidance provided on the IPSPs, and does that typically include a mindset that it's going to be a path towards registration or simply just to have a pediatric plan to facilitate the testing in children? Because I think where some of the pediatric development has halted is that that larger goal of accessibility commercialization is not there, and that's why I think some of these hybrid model discussions have to be taken into account because there's such a heavy reliance on investigational-only use.

So the specific question is, is there specific guidance on the IPSPs for pediatric registration?

DR. PAPPO: Is this directed to our FDA and EMA speakers or to our guest speakers?

DR. SHAH: I think it might be more the FDA-EMA, if that's ok.

DR. PAPPO: Let's go for it. Martha?

DR. DONOGHUE: Dr. Pappo, is it ok? Okay. Thank you so much.

Dr. Shah, thanks for the question, and if I'm hearing you correctly, I think you're asking whether we provide advice during the IPSP review process with respect to registrational trials. In general, the answer to that is no because the scope of the IPSP, the initial pediatric study plan, is really limited under FDARA to an early dose-finding PK and preliminary efficacy and safety evaluating trial, in general, in pediatric patients. So at that point, it's a little premature to start thinking about registration, most of the time, although not always, because sometimes in certain

populations and for certain drugs, and depending upon other factors, sometimes those very early studies can actually result in a registrational potential study.

So, in general, that's not part of the formal advice we're providing during the IPSP process, but if we do know that there is a potential for that initial trial to result in a potential indication, then we will provide advice and also would more than welcome, actually, industry and others seeking a meeting with us to talk specifics related to that. But due to the nature of the document itself, it tends to be relatively high level. It doesn't generally get into the weeds in the same degree as you might want when we're really thinking about the nuts and bolts of fit for filing.

Having said that, of course, because the data arising from an IPSP requires a study we are going to require, it has to be of sufficient quality to submit to us once the study is conducted so that it can inform labeling. There's a balance

there, and I think it's incumbent upon us to try to figure out ways together to have those discussions so that we're not expending undue resources to ensure that the quality is sufficient for the purposes of an early phase 1-2 trial, so certainly we'd be agreeable to those discussions.

DR. SHAH: Great. Thank you.

May I ask one more question of our Genentech representative?

DR. PAPPO: Sure, of course.

DR. SHAH: The specific question there, as you know, we talk a lot about the pediatric plan, and my question is how can pediatric development be introduced early; and can any of your ad boards, especially if it may cover a disease that does include pediatric patients -- could you find a path forward that would have pediatric oncologists at the ad board providing additional opinions or inputs so that that notion can be introduced earlier as opposed to at a later phase?

MS. GUPTA: Thank you, Dr. Shah. This is Ruchi Gupta. Yes, you raise a very important

point, and I think this is one of the visions that we go with within Roche-Genentech with regards to our pediatric group, and how we try to integrate pediatric drug development early on within this clinical development plan of the molecule.

I cannot speak for the broader industry in terms of what practices there are, but I can tell you that within Roche-Genentech, we try to look from the portfolio perspective and see when the molecules are coming in from the pipeline, how early we can assess in terms of the available data, or what studies need to be performed based on the mechanism of action of the drug, and to then start those conversations either through ad boards or we have in the past conducted the portfolio meetings with FDA to get that early feedback, not just for one molecule but molecules that are coming through the portfolio.

And just to add to that, yes, we do have a requirement in the legislation that the pediatric study plan should be filed within 60 days of end of phase 2 meeting, but you cannot actually develop

the pediatric study plan in those 60 days. So the conversations and the discussions around what that clinical study design might look like, or what that strategy might look like, happens much earlier than the end of phase 2 meeting for the adults. So this is just to give a little bit of flavor in terms of how early those discussions usually get started.

Does that answer your question?

DR. SHAH: Yes. Thank you.

MS. GUPTA: Thanks.

DR. PAPPO: Dr. Raetz?

DR. RAETZ: Thank you to all the speakers for, really, the excellent presentations. I had a question or just was wondering if I could ask Dr. Weigel to share her experience and her perspective on an issue.

I really enjoyed your slide where you were talking at the very beginning when there are investigators that have ideas for trials or industry members who are looking for potential trial partners, and that bidirectionality of that exchange in the very beginning. I've found

sometimes that can be challenging. I just wondered in those very early phases, from your perspective, are there things that you've seen that have worked well or any comments on that?

DR. WEIGEL: Thank you, Dr. Raetz, for your kind comments and for your question. I really do appreciate it. I think one of the challenges is essentially knowing what is out there and knowing when to engage in the conversation. I think a couple lessons learned -- and I think it gets back to engaging early and often -- is the challenge for us if there's been a lot of conversations and actually planning and even designing of pediatric trials. And this is particularly true on the industry side, and then they come and say, "So, this is where we are," and myself and colleagues will be like, "Oh, I'm not sure that's feasible or doable." I think it's that piece that is a bit challenging, is when we have to level set, and that's challenging.

I also feel, as well -- and we've been really working, I think, hard with academic

colleagues to say include people with disease expertise, or whatever it is, as early as you can to bring something forward; and something that people do want to bring through the cooperative group mechanism is ensuring that we have buy-in and transparency. The other thing that I think we have really worked hard on is having confidentiality agreements so that we can have a lens on data to be able to best advise as well.

I also think one thing that has been challenging is I think on the other side when we have felt that it really wasn't something that we wanted to bring forward in pediatrics, or we felt that there really just wasn't enough data, and then how best to advise moving forward. And at times, that has been in the lens of the company feeling they have a regulatory requirement, and potentially even additional discussions with regulatory authorities that they should go into pediatrics. Some of those discussions I think have been challenging of how best to do next steps.

I also think, Dr. Raetz, that one of those

challenges, as well, is the timing of when you enter those discussions, and a lot of that is knowing what's on the landscape. It gets back to that communication, and how do we track, and how do we know what's out there. So yes, I still think there are a lot of challenges in those bidirectional discussions, but I actually do feel that over the last several years -- and I do think that a direct impact of RACE and FDARA is that awareness and more of, I think, a willingness -- especially industry -- to recognize that there needs to be discussion about pediatrics.

So I do think that has changed, and I do think that has increased the number of conversations we're having, which I think is a good thing. I still am not convinced they're early enough, but I do think that is a direct change.

DR. RAETZ: Thank you so much.

DR. PAPPO: Thank you.

Dr. Laetsch?

DR. LAETSCH: Thank you, Dr. Pappo. I had a related question to what Dr. Weigel was just

commenting on for Dr. Gupta. I noticed in her slides, and agree completely, that she talked about the need to prioritize across different pharmaceutical companies within an industry, and wondered if she had additional thoughts on how to do that, because I personally agree that that's a critical need, but of course it's challenging.

Sometimes those discussions are, as have been highlighted, happening fairly early within the company before there may be much public data that could be shared, those challenges about deciding which companies are going to have the regulatory obligation to conduct the pediatric study and what happens if that chosen agent then doesn't proceed to regulatory approval for adults, but others in the class do, for example.

So I wondered if she had additional thoughts about how to bridge some of those gaps. I think it was also highlighted by Dr. Weigel just a minute ago; that we think it's really important to have early involvement in these discussions, but how do we do that and make sure that there's awareness of

these different efforts across companies in the setting of confidential disclosure agreements and other things?

MS. GUPTA: Thank you, Dr. Theodore. I personally don't have any insights or ideas around how the prioritization can be made more effective. I know that internally we do practice prioritization, obviously because we have more transparency and visibility among our own data and pipelines coming through the portfolio. As I mentioned also in my slides, sometimes even going through the exercise of privatization for those molecules which are internal can be very time consuming, and it takes a lot of effort to not just get internal agreement but also external agreements in terms of which molecules to be prioritized.

So all I can ask for is that I think it's a more collaborative effort that we need externally, not just between the industry partners, but also from the health authorities, to increase more transparency and flexibility around some of these discussions moving forward. I know that this

doesn't answer, really, your question, but this is the best I can do at this time.

DR. LAETSCH: Thank you.

And if it's ok, Dr. Pappo, I also had a question for Dr. Kearns.

DR. PAPPO: Of course.

DR. LAETSCH: Dr. Kearns, I really appreciated your talk. I noticed one thing you didn't mention was alignment around funding. And we've discussed NCI funding for COG trials and industry-sponsored models run through cooperative groups, but I didn't know if that was also a barrier to some of these international trials that may not have a pharmaceutical partner that could fund the trial on both sides of the Atlantic, and how you think about overcoming those barriers.

DR. KEARNS: And that's a really important point, and thanks for your question. If it's just an academic study, we struggle with getting international funding, and most funding is on a national level. So even in Europe, if I were to run a trial from the UK, I could get funding from

Cancer Research UK to do the central administration and the per-patient cost within the UK, but I can't get a per-patient cost in any other country. So each country is going through a review process in their own country, and that just delays the set-up because all the different usually charitable funders do not recognize review of another country or another organization, so the same protocol gets reviewed over and over again.

We've not tried to do a pure academic study in ITCC with the U.S., but I suspect it would be the same issue. We'd have to wait for it to go through the NCI-NC type approval and whether it would be taken onto the portfolio, and aligning that in terms of timing is really challenging. It's not without challenges even if it's a fully industry-funded study because the costs of delivering a study to industry level is different in every country.

So whilst I could do a complex spreadsheet on all the research costs in my country within the healthcare system, I need that from every country

because the cost of MRIs, for example, or other investigations and what gets charged to research is different in every country, so you're right to raise the funding issue. It's slightly easier with industry because we have a little bit more flex in being able to run the study, but I think it would be fair to say that they are very rarely completely economically funded.

I think we subsidize a lot of research even when it's industry funded within our healthcare service. However much, we try to put the budgets out there because it's surprising that funders don't understand how much clinical trials cost to deliver. They push back on the cost. And when you're working in the rare disease space, when you calculate the total cost of the trial and divide it by the number of patients that are going into the trial, they say, "Well that's a lot of money for a small number of patients," but the set-up, and the organization, and the quality control all cost money whether it's one patient or a thousand patients.

DR. LAETSCH: Thank you.

DR. PAPPO: I believe Dr. Drezner had some clarifying statements or to answer some of the comments of Dr. Saber.

Dr. Drezner?

DR. DREZNER: Yes. Thanks. It was really great to hear the presentations and so important for us to hear the perspectives from the people whose opinions we really value when we're making decisions, particularly around IPSP structure and content.

I thought that there may have at one point been implication that through the IPSP process, we require randomized trials in pediatrics with statistical analysis plans, and I just wanted to clarify that the FDARA amendments to PREA are really with respect to the conduct of earlier studies within the IPSP. The intent of the IPSP study plan is to layout early dosing, PK, safety information, and preliminary antitumor activity information, but are not required to be an entire development plan or certainly to culminate in a

randomized trial.

As the committee knows, there have been many drug approvals of pediatric therapies based on single-arm data, so that's what they're evaluated on, sort of a case-by-case basis, depending on the tumor type and the specific development program. So I just wanted to clarify if there were any questions around a requirement for randomized trials within the IPSP, which is not the case. Thanks.

DR. PAPPO: Thank you very much.

Any comments around Dr. Drezner's statement?

(No response.)

DR. PAPPO: We have still 20 minutes left if you want to have additional questions, and this can go back either to our FDA and EMA representatives or to our guest speakers. I had a question for Dr. Drezner, and perhaps to Dr. Seddiq also, regarding the issuing of waivers.

If you have several IPSPs of a same-in-class product, and there are still ongoing trials in adults where you do not have all of the

information, how do you prioritize or how do you say this drug will get a partial waiver or a waiver will proceed with your investigational plan to further explore this in pediatrics?

DR. DREZNER: Sure. I can take that. Some of it has to do with -- because, generally, the studies when we're evaluating IPSPs, generally the adult studies, as you say, are ongoing, not complete, and typically, usually, we're discussing an IPSP before a marketing application has been submitted, or is close to being submitted, for the adult indication.

So typically, when we're looking at same-in-class products, our decision will largely revolve around whether or not the company has made an argument, whether the product could meet a specific need in pediatrics that is unique to that particular product versus another same-in-class product, or if there's a particular pediatric cancer that, for some reason, that product would address better than other in-class agents. But typically, if the new product is considered to be

the same with no benefit to formulation, administration, that would be something that we would grant a waiver to because, as you know, sometimes these are fifth, sixth, even more, in-class products, particularly in one of the examples we gave for the PD-L1 class.

If there is consideration that perhaps the particular product could provide a benefit to pediatric patients, we will sometimes consider issuing a deferral rather than a waiver while additional work is being done to determine whether or not there may be a benefit.

DR. PAPPO: Thank you very much.

Donna Ludwinski?

(No response.)

DR. PAPPO: I think you're muted, Donna.

MS. LUDWINSKI: Sorry. This actually has to do with what Dr. Drezner was just talking about. I was wondering about the reverse situation. What if there's an agreed pediatric study plan, and then six months later, something that seems to be superior comes along. Is it possible to go back to

the first one -- I'm making this up, but maybe this never happens. But say it's a similar indication. Can you go back and tell the first one maybe not because this new molecule seems to be more effective or there's something better? How would that work?

DR. DREZNER: Thanks. That's a great question. Dr. Donoghue will know better if that's ever happened before. I can't remember that happening but, certainly, amendments can be made to IPSPs. And we would hope that the sponsors who are conducting the studies and drafting the IPSPs would be collaborating with key opinion leaders, and thus have a general sense of the environment. If there is another product that was in class, but for some reason had substantially more promise in pediatric patients, and the feeling is to direct development in that way, we can certainly amend an IPSP if a sponsor requests an amendment.

But I don't know if, Dr. Donoghue, you want to add anything because I can't remember an example where that has happened, but it probably will

happen at some point.

DR. DONOGHUE: Thanks, Dr. Drezner, and thank you, Dr. Ludwinski, for your question. I think it's an important one because it does go both ways; right? We should be able to, of course, correct, if we need to, following agreement for an initial pediatric study plan. And I think that speaks to the need for us to try to track what's going on a little bit more systematically than we currently are and while we're working on that so that we can monitor not only the number -- which we already are monitoring the number of IPSPs for a given target, and to some extent in those specific disease spaces, but also to be able to reassess and look at how those studies are being conducted, and keeping in mind the various information streams that we have access to, whether they be from EMA, from stakeholder groups, through programs like ACCELERATE, through published literature, et cetera, to either take the initiative ourselves to reach out to companies and have a discussion about course correction, or if the companies have

this knowledge before we do, they can always come to us.

Essentially, our decision making heavily relies on the package that we're given primarily from the company, and we've received some really well thought-out IPSPs that look not only at their product but at the overall landscape of development in pediatrics to try to help assist us with that decision making. And when that occurs, we very much appreciate it because the more people that are thinking about this, I think the better off we are.

MS. LUDWINSKI: Thank you very much. No more questions.

DR. PAPPO: Okay. We have Dr. Frenkl.

DR. FRENKL: Thanks. I have a question for the FDA, and then just first a comment. I really thank you very much for holding this ODAC on this important topic, and it's been so helpful to hear also about the international coordination of requirements and the clinical trial collaborations that are going on, and great to see the progress.

I think it's truly a clarifying question,

slide 28 of Dr. Seddiq's presentation, where you say that early nonclinical investigation is encouraged. And it's really not a hundred percent clear to me in the supporting guidances and documents whether FDA could actually require a sponsor to generate this preclinical data, especially if it's a mechanism that's not yet on the relevant or not relevant list. And if yes, will there be some framework to help guide the sponsor in generating this data?

DR. DONOGHUE: Thank you --

DR. SEDDIQ: Thank you -- oh, go ahead.

DR. DONOGHUE: Go ahead, Dr. Seddiq.

DR. SEDDIQ: No. That's ok, Dr. Donoghue.

DR. DONOGHUE: I think I can take it, maybe. I'm looking at this slide, which I think essentially does emphasize the importance of early consideration of nonclinical work.

In general, when we are thinking about whether or not to apply FDARA to a specific adult product development program, one of our decision points is whether or not the target is a

substantially relevant target to pediatric cancers, and we generally make that decision before even thinking about going in depth to the review of the IPSP. And there are cases where we receive IPSPs for pediatric development programs for which we don't consider the target substantially relevant, and in those cases, we generally inform the sponsor.

It is not always clear, if a certain target is not on either list, where that target falls in. So in those cases, we make use of all available public information, including the public genomic databases that are out there, published literature, and other information provided by the sponsor to make that determination as to whether or not we consider a target substantially relevant to pediatric cancers, and hence, subject to FDARA requirements.

So as far as we have been implementing, as far as my knowledge, we have not required companies to conduct preclinical studies to determine relevance; however, I do think it's very important

in some cases, just as is done in adult development programs for cancer products, that when we know the target is substantially relevant, when we know that there's a high unmet medical need, that part of the investigational plan for pediatrics includes thoughtful nonclinical development to help inform the design of the pediatric trial.

So that is our current thinking and advice we're providing sponsors. I'm not saying that we also need in all cases to have proof-of-concept nonclinical work done. There are cases where there's enough existing information to support a well thought-out pediatric investigation without that, but there are times when I do think it's necessary. I hope I've answered your question.

DR. FRENKL: Yes, you have. Thanks so much.

DR. PAPPO: Okay. Dr. Smith?

DR. SMITH: Yes. This is a question for FDA, and it reflects back on Dr. Weigel's comment about the importance of no-go decisions. It has to do with waivers not only when there are multiple agents in class, but just the general priority of a

particular agent. I'd first acknowledge that there is a tension between casting wide net and studying agents, and accepting that many of the agents may actually not be effective and children won't benefit, versus taking an approach of focusing on agents with stronger rationale, but you may miss something by narrowing the net.

So the question is, in terms of waivers, how you approach that tension, and if there's any perceived need to reduce the number of waivers? Is there a perception that a waiver might be a bad thing, so you need to minimize the number of waivers that are actually agreed to?

DR. DONOGHUE: Thanks, Dr. -- oh, I see Dr. Drezner came on. I'll let you go first. Sorry.

DR. DREZNER: I was going to start out with the easier part of the question, which is the last part. No, I don't think that there's a sense, at least among us, that a waiver is a bad thing. Typically, these are applied in cases where there has been general agreement that there's a

same-in-class product that would represent a benefit to pediatric patients or there's a partial waiver for a specific age group in which the disease rarely or never occurs.

But Martha, I'll let you go ahead. I was just going to address that part of the question.

DR. DONOGHUE: Sure. Thank you for the question. This is Martha Donoghue again. We, I think overall in our committee discussions, and ultimately our decisions about IPSPs, do think long and hard about is this going to be feasible and is this going to help the community. There's a part of me that worries we're not waiving enough requirements at this point -- I'll be completely frank -- and I think that goes to what Dr. Seddiq was saying towards the latter part of her presentation, that I think there is a need for us to continually refine our decision-making process, and tweak it, and improve it; and, yes, even make amendments to agreed IPSPs when needed, based upon emerging data.

That emerging data can come in several

forms, either data in the form of information for that particular drug development program that indicates a new safety signal or maybe less potential for important activity in pediatric patients; data from other drugs in the same class; information that we get from other members of the community that may signal that we need to shift gears.

So the question in my mind is how best to aggregate the information that's out there in a timely way so that we can do course corrections when needed, so I think we need to refine our process; but I do think more work needs to be done on that. We're certainly receptive to ideas from the community about how better to accomplish that. I think the ACCELERATE meetings are helpful when we talk about multiple drugs in class. Sometimes those discussions are happening in some ways later than they need to be and maybe not frequently enough, so I think we need to establish some other processes.

I think, as Dr. Karres mentioned in his

presentation, we need to think not only about the landscape of what's going on in drug development within a particular drug target. Also, the types of products that are directed against that target differ, and therefore the potential may differ for pediatric patients, and also looking at, in addition, what's happening in a particular disease subset so that we are cognizant of all the other clinical trials that are ongoing in subsets of populations with neuroblastoma, for example.

Does that answer your question?

DR. SMITH: Yes. Thank you. Sometimes I think there's a perception that a waiver is benefiting the company, they don't have to do a pediatric trial, but when a waiver is appropriately applied, it's benefiting the children who aren't exposed to an agent that's unlikely to help them. So I think they are difficult decisions, but I was just asking if there's a perceived judgmental aspect, and I'm glad to hear that there's not.

DR. DONOGHUE: Well, it's always a difficult decision either way. The decision to expose

pediatric patients to, potentially, an ineffective drug shouldn't be taken lightly by anybody. I think we all feel that we should have confidence, or at least a fairly high degree of confidence, that there's a good prospect for clinical benefit before we do that. But sometimes it is harder to make a no-decision, to grant a waiver than it is to grant a study. I understand that.

DR. SMITH: Thank you.

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

DR. SMITH: Yes. That's very good. Thank you.

DR. PAPPO: Okay. I had a question probably for Dr. Seddiq and perhaps for Dr. Drezner.

In the initial presentation, you said that the molecular targets are updated on a regular basis or updated regularly. I just wanted to know what the process for that is, and if there is also a process to eliminate or get rid of some of the targets that have already been known to be tested in pediatrics, for example, PD-1 inhibitors or mTOR

inhibitors. I just wanted to know a little bit more clarity about what the process of that is and who makes those decisions.

DR. DREZNER: I think they're pretty collaborative decisions amongst all of the decision makers within the FDA throughout the committee of people who make the decisions. We update the lists about every 4 to 6 months, and it's really a constant discussion of topics, a constant discussion of targets, that occurs in our weekly meetings, and then comes together at a larger meeting every 4 to 6 months to officially update the lists that are on the website. There is also a non-relevant list there, too, and targets will get added to that as well. As you know, the lists aren't meant to be the be-all/end-all of what is or is not substantially relevant.

So quick answer, 4 to 6 months, but we have meetings every week where there is certainly discussion about different targets and whether there's something that we're seeing where there's been a lot of IPSPs that have come in and we're

considering, and we've now read a lot about it and heard from key opinion leaders, and have decided that that's not relevant; those discussions happen frequently.

DR. PAPPO: Thank you very much.

DR. DREZNER: And I think Martha raised her hand also.

DR. PAPPO: Martha?

DR. DONOGHUE: Thank you for the question, Dr. Pappo. Just so people know, I am thinking about having another public forum where we can get input beyond our multi-discipline committee and ongoing discussions about this, and I'm trying to think of the best forum for those to take place. I know we've used subcommittee of ODAC meetings to do that in the past.

I just also wanted to acknowledge, though, and clarify that in my thought, you can still have targets that are substantially relevant to pediatric cancers for which you have studies, and sometimes multiple studies, of drugs against that target that have not been effective. It's hard to

know sometimes is that the fault of a drug, or the approach that the drug is taking to direct against that target, or the fault of there not being the appropriate combination.

So in my mind, one of the criteria should be what do we understand about that target based upon the accumulated knowledge, but I don't think necessarily that lack of activity for some, say mTOR agents -- that those targets may still be relevant, but maybe not at this time warrant additional studies unless something changes. And that's one reason why the target lists are guides but not directly used in isolation for decision making, with the exception of the non-relevant lists, which is pretty firm that if the target is non-relevant, then the application is not subject to FDARA to begin with.

DR. PAPPO: You got to the root of my question. Thank you very much.

Okay. We have time for one final question, and Dr. Frenkl will do that.

DR. FRENKL: Thanks very much. This is, I

think, just an add-on, and maybe Dr. Drezner or who was just speaking.

When you're deciding on the relevant list, are there specifics like standardization of the criteria or the evidence that's required for it to come on that list? I recognize that it's very difficult to do across all the different mechanisms, but just wondering if there is a standardized framework for that that, that could eventually be shared with industry and academia.

DR. DREZNER: Sorry. Yes. I would say there's a framework that's standardized, although there is obviously discussion that occurs on a case-by-case basis. There needs to be some evidence or biologic rationale, which can be obtained from a multitude of data sources -- gene expression, genetic alterations, nonclinical/clinical data in adult patients from either publications or peer-reviewed data or databases -- that suggest the target's relevant to the growth or progression of one or more pediatric cancers.

So I think the decisions that we make when we are deciding whether a target is relevant is based on the totality of that information. And it's hard to assign a specific threshold as to whether something's relevant or not relevant, but we would be open if there are ideas that people have about what should tip something over into being relevant versus not relevant. For now, I think we have that baseline standard that is in the guidance, and then the rest of it is based on a preponderance of the data that is provided through multiple sources provided both by the sponsor, opinion leaders, as well as our own searches in terms of whether we consider it substantially relevant; so kind of a blurry answer, but yes.

DR. FRENKL: Yes, kind of like an expert consensus still at this time --

DR. DREZNER: Exactly, expert consensus.

DR. FRENKL: -- but perhaps we can work towards having something that's like a minimum threshold or whatever.

DR. DREZNER: Yes. I think we would be

happy if people had ideas or if there's something that people with the expertise thought was of particular importance when we make these determinations.

DR. FRENKL: Thanks so much.

Questions to the Subcommittee and Discussion

DR. PAPPO: Great discussion, and now the committee will turn its attention to address the task at hand, the careful consideration of the data before the subcommittee, as well as the public comments.

We will now proceed with the questions to the subcommittee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording. We will proceed with the first question, which is a discussion question.

Question number 1. Please discuss your

perspectives on how the 2017 FDA Reauthorization Act, FDARA, is impacting pediatric oncology and development of new molecularly targeted therapies for pediatric patients with cancer. Describe positive effects or challenges associated with this legislation, and thoughts regarding how to improve its implementation.

If there are no further questions or comments concerning the wording of this question, we will now open this question for discussion.

Dr. Laetsch?

DR. LAETSCH: Thank you, Dr. Pappo.

My sense of the data from the presentations and also my anecdotal experience is that FDARA has certainly increased the attention being paid to developing these agents for pediatric patients, and my anecdotal sense, and I think some of the early data, might suggest may be increasing the number of clinical trials that are available, so I think those are clearly both positive.

I think a couple of the challenges that have been mentioned would include the need for

additional mechanisms of early collaboration across all of the stakeholders -- academia, industry, multiple industry partners, potentially, in the case of multiple drugs in the same class, and regulators -- about how to prioritize these agents for pediatric cancer, and then while not directly the subject of FDARA, how to ensure that promising agents that are identified through these early trials proceed towards regulatory-intent trials or confirmatory phase 3 trials to potentially establish a new standard of care. Thank you.

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

Dr. Shah?

DR. SHAH: Hi. My comments are quite similar. I would say that I think it absolutely serves the purpose of raising awareness and attention to the need for pediatric studies. I think that the FDA's plan to follow these up, track these, and understanding what happens with the initial IPSPs is great. I think that that will provide additional data that's needed to see how

these are being truly implemented, as well as having additional back and forth, especially when something is deferred and there's an opportunity to do more there. I do think that understanding what happens beyond this early stage, especially if some of these targeted therapies are quite promising early on, and establishing that path forward for fit for filing will be a good next step.

I would just finally say -- and this was raised earlier -- I do think the term "molecularly targeted therapies" can be a little bit confusing. I'm not sure if there's anything that actually can be done about it, but recognizing that the umbrella of molecularly targeted therapies is a little bit different, especially as we think about these antigen-targeted therapies, and it was really beautifully presented earlier.

DR. PAPPO: Thank you very much.

I had a comment. I think that one of the issues that I think some people have raised before is how do you measure this impact or if there is success or not, and I think that doing a very

thorough evaluation of all of the IPSPs; what agents have been tested; like Malcolm was saying, what protocols have been activated, the accrual of these protocols, and how many of those eventually led to a regulatory approval. In my opinion, also, the time to start a clinical trial -- if this has helped a little bit to start first-in-child clinical trials earlier, based on the fact that now we're paying particular attention to drug development in pediatrics -- is going to be important.

The next person is Dr. Gore.

DR. GORE: Yes. Thank you so much, and thanks to all of the speakers and certainly the panel members. One of the things that continues to strike me about the significance of this is that I feel like we're just starting to get a feel for the impact now. Part of that is how long it takes to get a trial up and running, how long it takes to accrue to a trial, the number of starts and stops that trials have; and particularly, as we run into amendments and things that can slow trial data, I

guess one of my biggest fears around this is that we would rush to make a decision too quickly about the impact without really having that depth and breadth of measurements, as many people have just commented on.

So I think I guess the challenge associated with this question is I'm not sure that we've had enough time to really assess the impact, and as several people have just also said, we haven't agreed on a set of metrics that will really help us determine that impact, and I think that's key.

Speaking a bit to what Dr. Shah also just mentioned, I think ensuring that we continue to understand what is being called a molecularly targeted agent is in line with the current practice and that we continue to evolve that definition to meet the intent of the impact of FDARA. Thanks.

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

Dr. Seibel?

DR. SEIBEL: Yes. I want to agree with Dr. Shah, to a certain extent, because I think one of the things that was brought up earlier was about

transparency, and I think a perfect example was the recent ACCELERATE meeting last fall, looking at CDK4/6 inhibitors and the number of trials that were very similar that were being done throughout both internationally as well as in the U.S.

So getting a better feel for the number of trials or the trials that are being done in such a small pediatric population I think is important. Dr. Donoghue touched on some of the issues, particularly not having the ability to track this necessarily, but this is one area that I think could really be improved upon. Thank you.

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

Any comments on the effects or challenges associated with this legislation and thoughts regarding how to improve this? Dr. Seibel mentioned that, as well as Dr. Gore. Any other comments from from the panel?

Dr. Smith?

DR. SMITH: Yes. I would just emphasize what Dr. Seibel and others have said about the need for more transparency, and one issue is we're

talking about childhood cancers, we're talking about small patient populations, we're talking about where a decision made in secret by one company to study childhood cancer, in collaboration with a regulatory agency, then has an impact on the ability of everyone else, all other childhood cancer researchers, potentially to study that same population. And this is so different from the adult cancer world, where for most adult cancers, there are so many patients that a decision made like that for an adult cancer doesn't have the same impact that it does for childhood cancers.

So I understand that right now a childhood cancer IPSP is a trade secret and it can't be discussed. But it would be so beneficial to the childhood cancer research community if IPSPs like PIPs could be viewed, could be understood, what the requirements were and what was already committed to, so that plans could be made in a more rational way. That's my comment. Thank you.

DR. PAPPO: Thank you, Dr. Smith.

Dr. Frenkl?

DR. FRENKL: Yes. Thank you. Tara Frenkl from industry. I'll start in with the challenges. I think we already covered how it's progressed and what the positive effects are. The biggest challenge from an industry perspective is I think recruiting the studies because they are rare diseases that we're working with. So I think that the international harmonization of EMA and FDA is fantastic and will really help us in the transparency of all of the communication, as you guys are already doing.

And it's great to see that we're building the infrastructure with ITCC and COG so that these studies can actually be conducted, because it's very difficult to do in isolation because it's so rare. And we need to work on all of those things that we were talking about before, with the data reconciliation and how can the databases be reconciled.

The other thing that's been on my mind since it came up, I think, in this conversation has been the prioritization of mechanisms. To me, it's a

very important concept so that we can enable studies with the highest possibility of success to move forward and to actually be able to recruit so we get robust, intangible data and avoid duplications, and save resources across. But it seemed to me -- and maybe I got it wrong -- like the conversation was a little bit like it was industry that needed to do this internally, but we can only prioritize our internal pipeline, and we do do that, but the PREA is a requirement for whatever we move forward, so we can't really prioritize beyond that.

So I think the first step in that would be deciding actually who is accountable for a broad landscape prioritization, and to me, it would have to be regulators like FDA, and perhaps some other groups that have great expertise like the ones that are here. Thank you very much.

DR. PAPPO: Thank you very much.

I'm going to try to summarize our discussion for question number 1. The panel feels that, indeed, the RACE Act has raised the attention about

developing specific drugs for pediatric cancer and increasing the number of clinical trials available for these patients. That was the first point. The second point is that we apparently need a little bit more transparency and a little bit more depth to measure the impact of this initiative in pediatric cancer.

There are several challenges. One of them is recruiting patients, and therefore it would be very important to focus our attention also on the prioritization of agents so we can identify the most likely leads that will lead to higher success, and therefore we could accrue patients in that specific area.

We also need to develop better metrics to assess the impact of the RACE Act, and that could also include measures such as making more available or transparent the IPSPs that are submitted to the FDA, and also look at time to completion of clinical trials, the time of initiation of a clinical trial in the pediatric population. The overall consensus of the panel was also that

perhaps it was a little bit too early to assess the full impact of the RACE Act, but I think that these are some considerations that need to be taken into the future to try to determine its impact in the coming years.

I wanted to know if anybody has any additional comments, or any suggestions, or if I missed anything, or if I summarized everything.

Dr. Laetsch?

DR. LAETSCH: A very nice summary, Dr. Pappo. The only comment I would add is I think that in addition to the IPSPs, potentially, making them public, I think finding a way to collaborate earlier before those are agreed will be important because my sense is that companies will be hesitant to renegotiate pediatric study plans with the FDA or EMA after they're established, and some of these prioritizations across different companies will have to happen before those are established if there's a way to increase multi-stakeholder involvement earlier in that process. The ACCELERATE meetings have been mentioned, but I

agree with Dr. Donoghue. I think sometimes those are occurring long after the PSP or the IPSC have been established, so if there's a way to accelerate that collaboration, I think that will be really helpful.

DR. PAPPO: Thank you.

Dr. Shah, you had your hand raised. Not anymore? You're good?

DR. SHAH: Yes. I just wanted to be sure you got the point about the term "molecularly targeted."

DR. PAPPO: Yes. I had it twice, and I missed it, yes, to better define the term "molecularly targeted therapy," yes.

DR. SHAH: Thank you.

DR. PAPPO: Thank you for bringing that up.

Okay. We will now move on to the next question, which is also a discussion question. Please discuss factors that should be considered when determining whether nonclinical proof-of-concept studies should be conducted prior to initiating a molecularly targeted pediatric

cancer investigation in pediatric patients with cancer. Also discuss the degree of preclinical antitumor activity that would be considered sufficient to warrant clinical development.

If there are no further questions or comments concerning the wording of the question, we will now open the question to discussion.

Dr. Gorlick?

DR. GORLICK: I'm Richard Gorlick at MD Anderson Cancer Center. Thank you for the opportunity to comment. Really, what I wanted to bring up is the whole topic of adolescent and young adult oncology in the context of nonclinical studies. And I know this is a topic that many are aware of, but the adolescents and young adults are a group that the needs aren't entirely met by the peds or the adult community, and the challenge is nonclinical studies usually means, in my view, toxicology studies. Adolescents and young adults, in contrast to children, children have unique toxicities related to growth, whereas that doesn't apply to adolescents. And if you looked at

adolescents and young adults, they tolerate chemotherapy generally better than older adults or younger children, with the only real question being the adequacy of dose.

So I think in that particular population, nonclinical toxicity studies are really not needed as a general principle, and I would hope that could be codified to a greater extent. Thank you.

DR. PAPPO: Thank you, Dr. Gorlick.

I was going to call on you, Malcolm, based on the paper that you published, the requirements for preclinical testing. I was wondering if you were going to be able to comment on that, and I'm glad that you raised your hand. Thank you.

DR. SMITH: Yes. I can comment on the preclinical testing, and first thank the EMA presentation for highlighting. Both the ITCC-P4 and PIVOT program are doing preclinical testing and collaborating with many different companies to do preclinical testing.

In terms to address some of the questions about preclinical testing, one is, in terms of what

you consider in success, what's the degree of activity, and we've consistently considered, in looking for activity, that we should be looking for robust regressions for the agents that we test. This is a criteria that we usually use to claim success in clinical trials both for children and adults and, of course, it's rare that a drug can be more active in patients than it is in the mice. So to claim less than what we would consider success in humans and patients doesn't seem a reasonable approach, so we use regressions.

The other part of that is when we consider what agents should we use in combinations, we also look for those agents that have been effective as single agents, both because of the history of pediatric cancer research and what have been effective successful combination therapies for pediatric cancers, and also because of the work of Adam Palmer from Chapel Hill and others recently, and looking at successful combinations, ones that have achieved FDA approval, and finding that most of these combinations depend on additivity of the

agents; that is both agents need to be active rather than synergy.

A point just to make about how reliable is the preclinical work, is it just noise or does it actually indicate some likelihood for success, we've looked back over our first 20 years of preclinical testing, and first, just to get rid of the myth that everything works in mind, when we look at our solid tumor models, only about 15 percent of the models tested against all the agents actually had an objective response. The vast majority of things don't work.

When we looked at the things that worked in the mice, they generally aligned with how they behaved in the clinic. The standard agents were active pretty much as expected. Agents like HDAC inhibitors, proteasome inhibitors, hsp90 inhibitors for solid tumors, showed little or no activity. The VEGF pathway-targeted agents slowed growth but rarely caused progressions. The molecularly targeted agents rarely caused regression, except if the genomic alteration was

there, BCR-ABL1 for dasatinib, BRAF V600E for selumetinib, KMT2A rearrangement for menin inhibitors.

Then one last example, the IGF-1 receptor-targeted antibodies, our response rates were in the 10 percent range for Ewing sarcoma and other sarcomas, and that was very similar to what was observed in the clinic, so we do think that the models can provide useful information. ADCs now are an area that we're intensely interested in, as are many companies, and we think that the preclinical testing can help with the ADCs, more in confirming what's expected, that the targets there in rhabdomyosarcoma or osteosarcoma and the ADC is, in fact, effective with whatever payload that it's using. The PDX models also provide an opportunity to look for surface antigen expression across a wide range of models and get some data about that, and you would want to confirm with clinical specimens.

So I think we -- obviously a conflict of interest here -- are supportive of preclinical

testing. We think that it can inform prioritization decisions and go/no-go decisions, that when an agent is tested preclinically and doesn't show objective responses -- and I think one needs to think very hard about whether that's an agent that you want to bring forward for testing in children -- there needs to be some really compelling biological reason to negate the lack of preclinical activity and the ability to induce regressions. So thank you, and those are my comments.

DR. PAPPO: Thank you, Dr. Smith.

Any thoughts as to who should be conducting these preclinical studies? Should it be through PIVOT, through ITCC, through independent investigators? Should the company be getting some of these PDXs and testing their own agent, and then submitting this to the FDA, and say, "Look, it's active?" And how do you validate that compared to the standards that you have with ITCC or PIVOT, for example?

DR. SMITH: Yes. I think the benefit of

centralizing testing is that you can have 100 ALL models or 50 or 60 osteosarcoma models, so there's a benefit in doing that. And it's not to say that PIVOT and ITCC-P4 are the only places that are doing testing. There are additional CROs that are doing testing. There are academic researchers that are doing high-quality testing. And I do believe that it's hard, if not impossible, to have too much preclinical testing, so we're glad to collaborate with companies when there's an interest, but we really encourage others to do preclinical testing as well and I think enhance the robustness of the results.

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

Dr. Frenkl?

DR. FRENKL: Yes. I was wondering if Dr. Smith could maybe comment from his expertise as well. My understanding is that there is a dearth of available clinical models that are applicable for the pediatric cancers. So if those models don't exist, are in vitro, or xenograft, or other kinds of models enough to then take it into the

clinic, from your perspective?

DR. SMITH: Yes. I think that's probably historically true, but it's not true now. The ITCC-P4, as was presented, has over 400 models. I think between the seven research teams that make up PIVOT, we're well into the 600s or 700s. There are a wide range of models. Just about any molecular aberration or alteration in a pediatric cancer, the vast majority of them, there are PDX models that could be tested; not all, but the vast majority.

So I think at this point, again, Richard Lock, with 100 different PDX models for ALL, you can look at all the different subtypes that he has, and maybe not everything, but there are many of the different subtypes for which one might consider a molecularly targeted treatment. They are within the group of models that he has, and the same would apply for the sarcoma models and the brain tumor models.

DR. FRENKL: Great to hear. Thanks so much.

DR. PAPPO: Dr. Shah?

DR. SHAH: Great. So in terms of the first

part of the question, which is discuss the factors, I broke it down into three key considerations. I think the first would be, is the indicated disease in pediatrics the same? So if you're simply trying to use something like inotuzumab, which is established and has preclinical data in adults and has clinical testing, I don't think that you would need to do nonclinical proof-of-concept studies in pediatric patients. Recognizing that, of course, there are some biologic differences between pediatric cancers and adult cancers, I think that the applicability would be there, so that would help to at least establish a threshold in terms of what nonclinical testing would be needed if the disease is the same.

I think the second would be if the indicated or proposed indication of the disease is similar. A good example there is are you doing the testing in B-cell non-Hodgkin's lymphoma, and would the preclinical data that supported those adult studies be comparably able to be applied in pediatric lymphoma studies, and potentially be applicable to

a leukemia study? So I think that would help to support whether the nonclinical studies that were already done are sufficient for use and to see if there's any unmet need or a gap that needed to be filled.

Then lastly, in terms of factors, I think the question is, is the proposed mechanism of action identical to what's being proposed? Do you plan to use the drug in the same way that it would be intended to be used? Because that, I think, would really help to establish whether additional studies would be needed to account for differences in the mechanism of action.

In terms of the degree of preclinical activity, I think that probably what Dr. Smith said in terms of objective response, you'd want to see that there is some activity. It does become challenging because there are clearly limitations, but I think that could set the bar to objective response.

DR. PAPPO: Thank you, Dr. Shah.

Dr. Gorlick?

DR. GORLICK: Richard Gorlick, MD Anderson. I wanted to provide an additional comment in the context of what Dr. Smith shared. I totally agree with what he stated, but I wanted to add the addition that one can envision in the future that there would be targeted therapies that may exist that require an intact immune system in order to evaluate the activity.

A flaw of the PDX system is, obviously, it's an immunocompromised animal, but there may be cases where there are specific therapies that can't be evaluated through preclinical systems, and I think those agents may still remain relevant, and alternative pathways would need to exist for those kind of agents. Thank you.

DR. PAPPO: Thank you, Dr. Gorlick.

Dr. Laetsch?

DR. LAETSCH: I just wanted to agree with both Dr. Smith and Dr. Shah and say that I think this really depends on the data that's been generated already in adults, as I think Dr. Shah highlighted. I think the best model of a pediatric

patient is an adult patient if they have the same tumor.

So if you have a histology agnostic drug that's active against adults with the same alteration occurring in pediatric cancer, my argument would be that is sufficient data to study the drug in pediatric patients without any additional nonclinical studies; but then also agree completely with Dr. Smith that for tumors where we're talking about similar targets but different potential biological effects of those targets, for which the data and adults don't necessarily support that there's a histology agnostic level of activity of the molecularly targeted therapy, I think very robust preclinical studies are really critical to help with what we talked about in response to question 1 in terms of prioritization of these agents for studies in patients, and preserving and maximizing the potential benefit for the children who enroll in these trials. Thank you.

DR. PAPPO: Thank you.

So I'm going to try to summarize our

discussion. Overall, the panel believes that preclinical testing and using the methods that we currently have, including PDXs, might be a reliable method for identifying potentially active agents in the pediatric cancer population. We would define success as robust tumor regression.

We also know that, for example, when you give certain agents in the PDX model, sometimes they mimic the same responses that you're going to see. One of the examples that Dr. Malcolm Smith gave was the IGF-1 inhibitor with a 10 percent response rate in preclinical models and 10 percent in Ewing sarcoma, for example, and rhabdomyosarcoma sarcoma.

It is also important to start thinking about how we're going to be testing newer chemotherapeutics or newer molecules such as ADCs and what amount of preclinical testing we're going to require. It's also important to know that by doing analysis of the PDXs, you can detect surface antigen expression that can guide you to a new potential therapeutic opportunity. We talked about

centralizing testing, but it is not exclusively required that PIVOT or ITCC will have to do all the preclinical testing for new and upcoming agents.

There was a lot of discussion as to what's the extent of preclinical testing or the proof-of-concept studies that you need to move on a therapy to pediatrics, and there are three possible scenarios. The first one is that there's the same disease in adults and pediatrics, and there's this agent that appears to be active, and you have enough toxicology data that in those specific events, you may not need to have continuing proof-of-concept nonclinical studies, and then you could have a similar indication in adults and in pediatrics; for example, I would like to think like a B-rhab mutant tumor. For those, you probably would not need nonclinical proof of concept, but then when you get to the mechanism of action, that's when you should dig in a little bit deeper to figure out what you're going to do further and what models you're going to use.

Also, Dr. Gorlick brought up the issue that

most of the preclinical testing that we're doing is in immunocompromised mice, and that in certain agents, we may have to start considering doing testing in mice that have intact immune systems to better define the activity of some agents.

The final issue that was brought up by Dr. Gorlick was also the AYA oncology population, which is usually neglected, and I agree with him; they don't belong to the adults and they don't belong to the pediatrics. Perhaps in that population there is no need for nonclinical studies since they can tolerate doses better than pediatrics and better than adults.

I would like to know if I missed anything or if anybody wants to add anything.

(No response.)

DR. PAPPO: Alright. We're all getting a little tired here, so let's keep going. We have one more question.

We will now move to the last question, which is also a discussion question. Please discuss the role of pediatric clinical trial networks and

international collaboration in efficient development of new medical products for pediatric patients with cancer, including identification of relevant molecular targets, specific efforts that have been most valuable, and ideas for improved collaboration. Additionally, please discuss barriers to the conduct of international trials in pediatric oncology and potential ways to address these barriers.

If there are no comments regarding the wording of this question, we will now open the question for discussion.

(No response.)

DR. PAPPO: Dr. Gorlick?

DR. GORLICK: Richard Gorlick, MD Anderson. I'm going to start off by saying this is a clinically important topic. If we take rare diseases and now start breaking them down into molecularly defined subgroups, the sizes of the population, as has been articulated previously, become prohibitively small, and large collaborations are necessary to make it happen.

I don't want to reiterate what was said by so many speakers during this call. Whether the barrier is the sharing of information, whether differences in the rules, and whether differences in the ability to share and monitor data, there are a lot of issues to be overcome in order for this to work more effectively. All of those things are critical to address in order to move pediatric oncology forward. Thank you.

DR. PAPPO: Thank you, Dr. Gorlick.

Dr. Gore?

DR. GORE: Yes. Thank you. Lia Gore, University of Colorado, Children's Hospital of Colorado. I need to agree with that, and I would actually go out a little bit farther and say that this is probably our most critical challenge and our most important problem that we have to solve. We are going to get into the N of 1 situation very soon the more we molecularly define different diseases in both pediatric and AYA patients, and until we figure out how to cross oceans and be able to do effective quick, efficient trials, we're not

going to get those trials done.

So I'm hearing from Dr. Karres, from Dr. Kearns, and I know that FDA and EMA have spent quite a bit of time trying to collaborate and break down some of those silos. I think Dr. Kearns highlighted very importantly the barriers that still exist, and this is going to have to be a critical area of our investment. We're going to have to figure out how to get through privacy rules. We're going to have to get through the challenges that we have, because otherwise, we are not going to be able to conduct clinical trials. And the standard of the burden of proof around superiority or noninferiority, this can't be done by decentralized clinical trials, real-world data, all of those kinds of things. We're going to have to get better at this, and I think that that has to be a key priority for us in the next five years; otherwise, we're really in trouble.

DR. PAPPO: Yes, and I wanted to add also, the work that Dr. Kearns is crucial for this, and I really want to congratulate her again for what

she's doing.

Dr. Shah, you're next.

DR. SHAH: I just wanted to say, the advances that have been made thus far in pediatric oncology have only been through collaborative efforts and networks, and we really need to take it to the next stage and be able to overcome this to be able to make improvements that are needed in this next era of these molecularly cell- and gene therapy-targeted therapies. I think that the barriers were really nicely presented, and trying to address those one by one really is the path forward.

DR. PAPPO: Thank you, Dr. Shah.

I think I have Dr. Mody next.

DR. MODY: Hi. I'm Rajen Mody from the University of Michigan. Thank you, Dr. Pappo. I would say the role of pediatric clinical trial networks and international collaboration in pediatric drug development is invaluable. As Dr. Shah said, all of our previous advances have been done through national multi-institutional

trials. Especially when we are trying to do trials with industry partners and specific very substratified molecular subgroups, it is very hard to do institutional trials. The structure that is required and the cost that is required is untenable for most single centers, so I would say national efforts are necessary.

At the same time, crossing the Atlantic and doing trials internationally with our European collaboratives is also exceedingly important, as the neuroblastoma community, and as a neuroblastoma researcher, they have shown certain variances and certain nuances that needs to be kept in mind. One is how you define responses. Neuroblastoma is one of those diseases where overall response is more important than [indiscernible - 5:41:34] responses.

So some of those nuances are important to have the same page and on both sides of the Atlantic, and what is the prior therapy that patients receive before coming on to trials because sometimes the induction and other previous therapies are different. So all those things are

very important before you define somebody deflecting, so I think the international trials are exceedingly important, but attention does need to be paid for those nuances.

One final point is, across various countries of Europe and in America, minority populations dose differ and their genetics are different, so I think there needs to be balance. And when we extrapolate the data and responses within this subpopulation, care needs to be paid and careful attention needs to be paid to really understand are there any racially or ethnic differences in responses. Thank you. No more questions.

DR. PAPPO: Thank you, Dr. Mody.

Dr. Frenkl?

DR. FRENKL: Hi. Tara Frenkl, industry rep. I do want to reiterate just a couple of things that we talked about because I think they're so important, and also Dr. Gorlick's comment that we need these large collaborations in order to run these sites. And I think that industry recognizes that and actually really appreciates that the

infrastructure is being built so that we can meet the requirements as well, and we want drugs to be available for pediatric patients where it's applicable.

But I think to get there -- and I think Dr. Weigel was saying -- it's really going to be based on that mutual trust and us sharing the objective, which is to get the drug registered eventually, should the data support, so it's available to everyone, and then to do that, there is the quality of the data, as we've discussed, and that trust. Dr. Laetsch said that you're trying to control the data. It's not that we're trying to control it; it's just that we're trying to ensure, again, the best quality so that we can actually use the data in the end to make the right decision.

Then the second part of it is recruitment timelines. When we're doing an IFT-SP [ph], we have timelines that we have agreed to with the agencies, and sometimes when it's done by a cooperative group, the objectives I think are different, and resourcing is different, and we're

not able to meet it, and then we're constantly needing to readjust the timelines by a lot; so if we can work together to somehow increase recruitment and maybe use additional resources in AI to help us find those patients, but to address it together because it needs to be a mutual objective.

Then the third is I think we are having issues with data protection. Even if sometimes we try, and we have sites that are interested that are part of a not-for-profit group, they're unable to actually share the data with us because we are for profit and they are not for profit, and through their policies, they can't share the data with us. So these are things, again, that we need to overcome for the common good and objective of getting drugs registered for pediatric patients. Thank you.

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

Dr. Desai?

DR. DESAI: Hi. Ami Desai, University of Chicago. I'm probably not introducing anything too

new, but just wanted to reiterate how critical international collaboration is. And there really needs to be significant efforts for data governance and harmonization, but also alignment of the regulatory needs on both sides. And I just wanted to applaud Dr. Kearns on her presentation, not just identifying the problems, but also trying to find a path with certain solutions. This will be critical to expedite some of our timelines as well.

DR. PAPPO: Thank you very much.

Dr. Smith?

DR. SMITH: Yes. Malcolm Smith, NCI. I'll reiterate the importance of international trials. As Dr. Kearns outlined, it's just really challenging for academic researchers to have the resources, to pull together the infrastructure, to do this on a regular basis. It's very challenging, but it is absolutely critical. And I think trying to work within our individual entities to get the resources to complete the task will really be important in the coming year for the studies that Dr. Kearns identified, and others, to be planned.

A second point is I would encourage us to say, yes, international trials are critical, but that not every trial has to be an international trial. If there's a drug and we need a phase 2 study in neuroblastoma, it could be an international trial, but the ITCC could do it without participation from North America and vice versa; COG could do it without participation from Europe. So I hope there's not a penalty, when the goal is to do a trial that can be done within one hemisphere, that there's a requirement that it must be done internationally.

The final point is just to make the point that we are breaking down diseases into smaller and smaller categories, and every brain cancer type seems to have four or eight or more subtypes. ALL now has 23 subtypes at least, and AML similarly. So I think the one point about that is that doesn't mean we need 23 different treatments for ALL, and just because they're biologically distinct, we need to keep in mind that the treatments may be very similar. CD19 may be present on all of them, and

that's all they need.

It was George Sledge that I give credit to here in pointing out and making the comparison that every snowflake is unique, and yet they all melt; and likewise, a cancer may have 20 different subtypes, but 15 of them may all be treated successfully with the same approach, and a smaller number require different approaches. Thank you. That's all.

DR. PAPPO: So I think you highlight a couple of the points that Dr. Gore and Dr. Gorlick brought up, and that is that numbers are important in very rare subtypes of cancers. On the other hand, as you mentioned, it's going to be very important to identify those populations that could potentially benefit from this ultra rare intervention. For example, a MYOD mutant rhabdomyosarcoma, you don't want to do a randomized trial or explore a new therapeutic possibility on a patient with low-risk rhabdomyosarcoma who has a 95 percent survival rate, so thank you for bringing that up, Malcolm.

Dr. Raetz?

DR. RAETZ: I certainly agree with everything that's been said and the critical importance. Just a comment that I had about some of the forums that bring people together internationally have been really positive in those that I've participated in. I think one consideration that was brought up by Dr. Laetsch is just the timing, and could that be a little bit earlier in the trial developmental stage to maybe have more harmony and more synergy in terms of thinking about those things earlier on.

DR. PAPPO: Thank you.

So if I can summarize this, everybody agreed that collaboration is critical for the success for moving the needle forward in pediatric cancer. I agree with some of the comments that were made, that not all of the studies have to be international, especially when it all boils down to the numbers, I think. I also agree with Dr. Smith that not all subsets of tumors need to be treated on an individual protocol because they have a

unique genomic abnormality. Many of them are going to respond to the same therapies. It's just those outliers that have a very poor outcome that behave very poorly that perhaps we should be focusing on, or the ones that do extremely well in which we could cut back a little bit of therapy. That's my own view. If you all disagree with this at the end, you can say, "No, please don't put that on the minutes."

Another important point that was brought up was recruitment timelines and how to work together to get to that final path and finally breaking down the barriers -- basically what Dr. Kearns is doing -- is a recurrent theme, and I think everybody agreed with that.

Another point that was brought up by Dr. Mody also is that international collaboration could also help identify subtle differences in minorities because of the way they metabolize some of the agents or because of the unique genomic abnormalities that they may have. And finally, it is going to be important to have mutual trust,

share data, and have good quality data in order to move this forward. So let me know if I missed anything or if anybody wants to say something different.

Richard?

DR. GORLICK: Richard Gorlick, MD Anderson. Sorry. I always have to start with my name. While I agree with a modification that not every clinical trial has to go through a large group, nor is every malignancy that's a favorable prognosis necessitating these large definitive studies, I think, generally, in the context of this meeting, unless I misunderstood it, we're talking about regulatory approval and the path to FDA approval.

I think if you add in the caveat that the file has to be robust enough to lead to FDA approval, I think more often than not, that's going to be a novel agent for a poor prognosis malignancy, which is either if it's common, going to have to be a large enough group to define statistical significance, or if it's a rare enough subset to accrue enough folks. I think that's

driving some of the sentiment towards needed collaboration. I don't know if you can encompass a concept of FDA approval frequently requiring cooperation as a modifier.

DR. PAPPO: Any additional comments on that from Dr. Gorlick's statement?

(No response.)

DR. PAPPO: Okay. We will now proceed with the FDA closing remarks from Dr. Martha Donoghue.

Closing Remarks - Martha Donoghue

DR. DONOGHUE: Thank you so much, Dr. Pappo. I would like to extend my sincere thanks to the members of the Pediatric Oncology Subcommittee of the ODAC; the speakers from EMA, Dr. Karres and Dr. Sheean; the speaker from Genentech-Roche, Ms. Gupta; as well as to Drs. Weigel and Dr. Kearns from the COG and ITCC, respectively, for their time, expertise, candor, and engaging discussion during this meeting. I'd like to assure all of you that we at the FDA will take back what we have learned and heard today, and I'll probably actually relisten to the discussion again soon, and we'll

use the discussion to help inform our processes, efforts, and future decision making.

I'll take just a few moments to reflect on some of what I have heard and taken away from today's meeting, with the note that I'm not going to be able to capture everything, but so many important points were made.

First, it appears that the overall consensus is that, so far, FDARA has resulted in an increase in dialogue among all stakeholders regarding development of new targeted therapies in pediatric patients and that there are early indicators that FDARA is likely to help address the need for earlier development of new targeted drugs in pediatric patients with cancer, based on early measures such as the number of IPSPs containing a plan for pediatric studies and the increased number of postmarketing requirements for conduct of molecularly targeted pediatric cancer investigations in the U.S.

We've also heard from our EMA colleagues that there's been an increase in voluntary

pediatric investigational plans, or PIPs, for molecularly targeted therapies since FDARA was implemented; however, we do not yet have the full picture because the implementation phase of FDARA is in its infancy, or maybe in its toddler phase, and it's incumbent upon FDA, with stakeholder input, to continually reassess its impacts and refine decision making based upon experience, and the first part of this process is agreeing on which metrics to assess and how to assess them.

Second, I heard that there's a real desire and need for more information sharing both in terms of information about studies that are required by FDA and the progress of those studies, as well as efforts by the entire community, including preclinical work and planned and ongoing clinical trials that are related to the development of new targeted therapies in pediatric cancers. There are information gaps that need continued work to fill, and perhaps to borrow a term brought up by Dr. Kearns in her talk, there's a need for "process mapping" to better understand the best way to fill

these gaps.

There is a need for improved transparency regarding molecularly targeted pediatric cancer investigations required to IPSPs, as well as a better understanding of trials that are being conducted independent of a regulatory requirement. Decision making regarding pediatric trials, which drugs should be studied and in which patient populations shouldn't be made in isolation, and the process for this should not rest solely on any one stakeholder. Industry, regulators, investigators, and the advocacy community all need to be involved, but a more structured process would be helpful.

Third, many have voiced the importance of considering the approach to pediatric development early, even prior to an end of phase 2 meeting time frame, for the adult indication being developed. And to loosely paraphrase Dr. Weigel, we need to think a bit more like Einstein and think of creative processes and solutions to ensure that there's a more consistent approach to this, including early consideration of obtaining the

necessary preclinical proof-of-concept data when needed and pediatric formulations. I think she also mentioned the importance of having conversations early and often between the investigator, community, pharma, and other stakeholders.

Fourth, I also heard that although early consideration should be given to conducting nonclinical proof-of-concept studies early in development, that toxicology studies are generally not needed because the adult experience is more predictive, except in unusual circumstances, and that several factors should be considered when deciding whether nonclinical proof of concept should be conducted, including the availability of data in adults, the similarity between the adult and pediatric cancers proposed for a study, the availability of relevant pediatric preclinical models, among other factors. We've also heard that proof-of-concept studies may not be necessary prior to investigating a targeted drug in adolescent patients, particularly if the cancer type is

similar to or the same as the adult cancer for which the product is being developed.

And finally, there was a consensus regarding the importance of international collaboration both in terms of decision making regarding regulatory requirements, as well as prioritization of which drugs to study in which patient populations among the entire stakeholder community. There are logistical barriers that need to be addressed to increase the level of international collaboration, particularly with respect to promoting more international clinical trials, both those run by industry as well as cooperative groups.

The good news is that there are several ongoing efforts to promote this, and in particular, important work is being done by the Children's Oncology Group and the ITCC to tackle and solve the logistical impediments to conducting coordinated studies. There are also important efforts underway by EMA, FDA, and other multi-stakeholder groups such as ACCELERATE. Dr. Smith made a very important point that not all trials need to be

international and that EMA and FDA need to be receptive to the use of data that may not be acquired in Europe or U.S., respectively.

I'd again like to thank everyone who participated in and logged into this meeting and to all of the FDA staff who contributed to the organization, content, and smooth conduct of this meeting. And I'd like to give a shout out to the advisory committee management team who helped make this whole process go very smoothly. I'd also like to especially thank Dr. Pappo for chairing this meeting and guiding the discussion so expertly, and keeping us on track.

My final thought is I'd like to emphasize that the discussion won't end here. I'd like to really emphasize that we at FDA have an open-door policy, so if you have suggestions or have other ideas about ways to improve our processes or forums in which we could have additional discussions to discuss potential workstreams to move things forward, we are very open to that and encourage you to reach out to us. And with that, I will turn it

back to you, Dr. Pappo.

DR. PAPPO: Thank you very much. Dr. Donoghue.

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

(No response.)

Adjournment

DR. PAPPO: If not, I would like to echo Dr. Donoghue's comments. I would like to thank all of our presenters. I would like to thank all of our panel members. I would like to specifically thank Jessica and Yvette for guiding me through this process so I wouldn't look too bad in front of you, and I also would like to thank all of the FDA staff AV for making this conference -- I'm sorry, this meeting, I'm very tired; you have to listen very carefully for 5 and a half hours -- this meeting a success. We will now adjourn the meeting, and thank you very much, and hope to see some of you at ASCO. Thank you.

(Whereupon, at 3:31 p.m., the meeting was adjourned.)